EMJ ONCOLOGY

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+ ESMO VIRTUAL CONGRESS 2020

Reviewed

+ EDITOR'S PICK

Precision Medicine in Lung Cancer

+ INTERVIEWS

Prof John B.A.G. Haanen spoke to us about future directions of ESMO, and Dr Vinay Prasad shared his thoughts on oncology research.

+ ABSTRACT REVIEWS

We are pleased to offer a range of engaging abstract summaries of research presented at ESMO 2020.

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"If you are looking for the most up-to-date content on the latest developments in the oncological field, EMJ Oncology has got you covered."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

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EMJ Oncology 8.1

Welcome

Dear Readers and Contributors,

If you are looking for the most up-to-date content on the latest developments in the oncological field, *EMJ Oncology* has got you covered. This issue is a brilliant collection of all your usual favourites, including compelling and trailblazing articles alongside our comprehensive review of the European Society for Medical Oncology (ESMO) Virtual Congress 2020. Without further ado, I cordially welcome you to *EMJ Oncology 8.1*.

"If you are looking for the most up-to-date content on the latest developments in the oncological field, EMJ Oncology has got you covered."

The unprecedented coronavirus disease (COVID-19) pandemic has resulted in the replacement of all face-to-face congresses with virtual events. Nonetheless, the quality of these online congresses, and particularly the ESMO Virtual Congress 2020, has been spectacular. Included in this year's Congress Review of ESMO is a review of the topical session 'SARS-CoV-2 and Cancer', providing essential information for oncologists about the virus. We have also included breaking news from the congress, including a first-line treatment option for metastatic kidney cancer, how COVID-19 has led to a backlog of oncology research, and more.

Further included are summaries of the top abstracts presented at the meeting, ranging from chemotherapy options in recurrent glioblastoma, to the safety of fertility treatments in breast cancer survivors; ensure you give these a read. This issue also includes two inspiring interviews, the first with the Scientific Chair of ESMO, Prof John B.A.G. Haanen, and the second with Dr Vinay Prasad, Associate Professor of Medicine at the University of California, San Francisco, California, USA.

While there have been many breakthroughs in the field, an increased prevalence of oncological disorders exists; we hope that *EMJ Oncology* can contribute to new advances by igniting new ideas. I hope that our assortment of intriguing articles and the journal in its entirety will keep you engaged, and we look forward to connecting with you in person at the next ESMO congress.

Spencer Gore

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

It is my pleasure to warmly welcome you to this issue of *EMJ Oncology*, featuring a review of the European Society of Medical Oncology (ESMO) 2020 Annual Congress. Always one of the most keenly anticipated worldwide meetings in the oncology calendar, this year's congress took on an altogether different, virtual format over a 3-day Science Weekend, due to the enormous challenges posed by the coronavirus disease (COVID-19) global pandemic. The meeting was universally considered a triumph, with over 2,000 presented abstracts and 49,000 hours of streamed content watched by an audience of over 30,000 cancer care professionals from around the world, with the appropriately apt theme of 'bringing innovation to cancer patients'.

Naturally, the pandemic, and its effects on global cancer care, were a major focus for debate at the congress. A summary of this discussion and a selection of practice-changing abstracts are highlighted within the eJournal, together with expert commentary on how these studies may shape the future for patients.

This publication also includes a number of articles celebrating recent innovation in personalised medicine, including an overview of recent developments in metastatic HER2-positive breast cancer by Rygiel. As a breast oncologist, the proof of concept to clinical confirmation story of HER2 in breast cancer has long been a hugely inspiring one, and there has been enormous progress in this field over the last 15 years since the seminal HERA trial was published. However, selected as this issue's Editor's Pick is the article 'Precision Medicine in Lung Cancer' by Joshi et al. This review comprehensively details evolving strategies in diagnosis and the importance of subtype classification, together with novel therapeutic approaches harnessing the immune system and in targeting oncogenic driver mutations and should be considered essential reading for anyone with an interest in oncology. Also on the perennially hot topic of immuno-oncology, Shang et al. analysed recent advancements in immunologically-cold solid tumours.

Like ESMO 2020, I do hope you will find this latest eJournal thought-provoking, inspiring, and informative.

Dr Caroline Michie

Consultant Medical Oncologist, Honorary Clinical Senior Lecturer & NRS Career Research Fellow, Edinburgh Cancer Centre and the University of Edinburgh, Edinburgh, UK

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EMJ Hematology 8.1

Editor's Pick

+ Pregnancy-Related Thromboembolism in Sickle Cell Disease

Articles

+ Initial Anticoagulant Management of Deep Vein Thrombosis/Venous Thromboembolism in Primary Care: Review of Current Approaches
+ Concerns Regarding the Management of β-Thalassaemia Patients in the Era of COVID-19
+ Expanding the Role of CAR-T Cell Therapy to Systemic Lupus Erythematosus

Interviews

+ Prof Margarita Guevova
+ Prof Antonio Almeida
+ Dr Noémi Roy
+ Roundtable Interview with Dr Alba Maiques-Diaz and Dr Anna Kabanova

And even more...

EMJ Hematology 8.1 provides fascinating insights, including a review of the management of thromboembolism in sickle cell disease in pregnancy.

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Congress Review

Review of the European Society for Medical Oncology (ESMO) Virtual Congress 2020

Location: ESMO Virtual Congress 2020.

Date: 19th–21st September 2020

Citation: EMJ Oncol. 2020;8[1]:12-21. Congress Review

MADRID'S stunning boulevards and awe-inspiring galleries and museums were a sorely-missed backdrop for this year's European Society for Medical Oncology (ESMO) Virtual Congress 2020. Once home to Nobel laureate Severo Ochoa, jointly awarded the prize in 1959 for his discovery of the mechanisms of synthesis of RNA and DNA, the beautiful city was unable to host this year's congress because of the ongoing impact of the coronavirus disease (COVID-19) pandemic. Undaunted, >30,000 people from 150 countries formed a community online for a virtual ESMO 2020. Despite the limitations and separations of a global pandemic, the new digital format massively increased education and access for oncologists and cancer care professionals worldwide, as 49,000 hours of streamed content were watched over the 3-day science weekend.

"This event is, and remains, the most prestigious platform in Europe on which to share the latest oncology science."

The digital format was certainly apt for the theme of ESMO 2020: 'bringing innovation to cancer patients'. In her Presidential Address at the Opening Ceremony, Prof Solange Peters, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, highlighted the innovation of the oncology field and medical community in ensuring ongoing care during the challenges of a pandemic: "It makes me proud to see how we, as a society, have been able to innovate and implement new ways of working to continue serving the global oncology community." She underscored the importance of continuing medical education and collaborative research meetings, despite the difficulties of this

"ESMO firmly believes in a world where cancer professionals grow together as a community; a community that fosters inclusion across disciplines, draws strength from people's differences, and blurs geographical borders."

year: "This event is, and remains, the most prestigious platform in Europe on which to share the latest oncology science. We owe it to our patients to uphold this annual meeting and continue driving therapeutic progress in our field."

With the impact of the COVID-19 pandemic at the forefront of most healthcare provisions for 2020, the ESMO 2020 community was provided with a direct update by world-leading infectious diseases expert Dr Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, Maryland, USA, in his Keynote Lecture at the Opening Ceremony. The impact of COVID-19 on patients with cancer was further considered in expert panel-led sessions at the congress, with the most fascinating insights summarised in our congress review 'COVID-19: Impact on Cancer Patients and Oncology Professionals'.

Beyond COVID-19, the congress was packed with clinical insights, late-breaking data, and scientific discoveries across cancer care, new therapeutics, and the oncology profession. Notable findings shared at the congress are highlighted in the following pages of our review, including results supporting a new first-line treatment for metastatic kidney cancer, insights assessing the benefit of radiotherapy in non-small cell lung

cancer, and evidence for the survival benefit of immunotherapy in gastric and oesophageal cancers. The toll of the COVID-19 pandemic on oncologists' wellbeing and provision of cancer care for patients was also studied and is summarised in our review, along with an analysis comparing healthcare spending on cancer across Europe.

Honouring the work of field-leading oncologists, the annual ESMO awards were announced ahead of the congress. Prof Hans-Joachim Schmoll, University Clinic of Martin Luther University, Halle, Germany, received the ESMO Award 2020 for his work in developing the speciality of medical oncology both in Germany and internationally, and particularly in developing treatment standards and progressing medical education. The ESMO Lifetime Achievement Award 2020 was presented to Prof Nadia Harbeck, University Hospital of Ludwig-Maximilians-University (LMU), Munich, Germany, for her work throughout her career to advance global cancer research in both supporting the development of evidence-based guidelines and in her groundbreaking research in individualising the care of patients with breast cancer. Prof Harbeck commented: "To receive this award as a gynaecologist who has spent her career individualising treatment for early breast cancer shows that ESMO is a truly interdisciplinary society."

This interdisciplinary, collegiate atmosphere was palpable throughout the congress. During the congress, the parallel European Oncology Nursing Society (EONS) highlighted clinical and research findings alongside practical considerations for the care of cancer patients and progress of oncology nursing. Insights shared throughout ESMO 2020 at proffered paper sessions, keynote lectures, colloquia, and patient advocacy sessions spanned basic science, population studies, clinical research, and healthcare policy in Europe and globally. Attendees shared in the community of the congress online, with breaking research news debated on Twitter, alongside shared photographs of oncologists and researchers tuning in to the congress from their homes and hospitals around the world.

Prof Peters celebrated the value of this education-driven community, at the congress and beyond, to further cancer care globally: "ESMO firmly believes in a world where cancer professionals grow together as a community; a community that fosters inclusion across disciplines, draws strength from people's differences, and blurs geographical borders." With field-changing innovation and research findings shared at ESMO 2020, and the fires of collaborative education and progress stoked during the meeting, we look forward to the year ahead in oncology and to sharing in ESMO 2021, planned for Paris, France in September.

ESMO 2020 REVIEWED →

Metastatic Kidney Cancer: New First-Line Treatment

RESULTS from the Phase III CheckMate 9ER trial have provided hope for patients with metastatic kidney cancer as the new first-line treatment trial has shown success. This was reported in a press release dated 19th September 2020 at the ESMO Virtual Congress 2020.

A combination of the drugs nivolumab and cabozantinib, both used as monotherapies in the second line, were compared in the trial to the standard of care, first-line treatment, sunitinib. The combination showed superiority to sunitinib for progression-free survival, overall survival, and response rate, and there were consistent benefits in subgroups of age, sex, PD-L1 expression, bone metastases, International Metastatic RCC Database Consortium (IMDC) risk group, and geographical region.

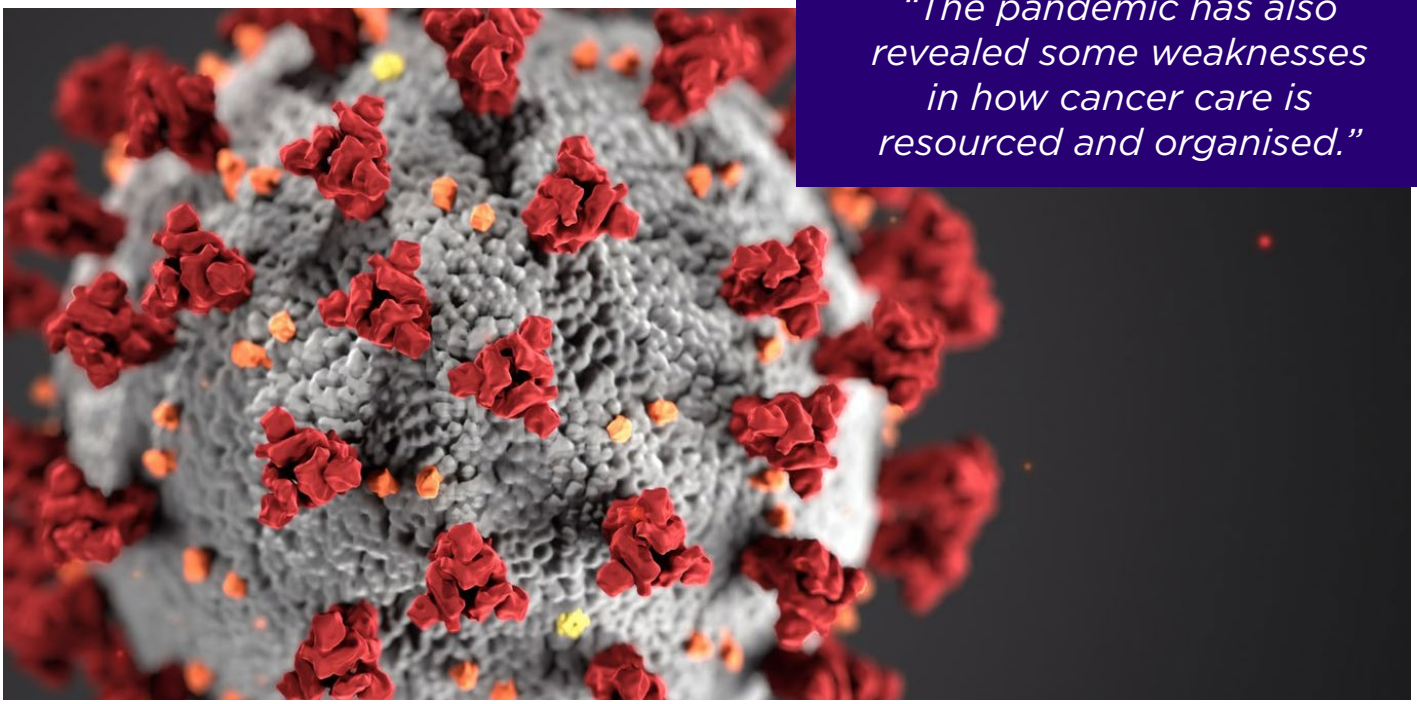
Dr Toni Choueiri of Harvard Medical School, Boston, Massachusetts, USA, and author of the study, summarised the findings: "The results with combination therapy were statistically significant and clinically meaningful. The risk of progression or death was cut by almost 50%, death was cut by 40%, and the response rate doubled. This will become an important treatment option to choose from."

Adverse events were reported in the combination arm, with >50% of patients in this group requiring a dose reduction. However, only 3% had to stop taking the combination therapy because of toxicity, compared to 9% in the sunitinib arm.

Dr Dominik Berthold, Lausanne University Hospital, Lausanne, Switzerland, expressed his belief that the combination treatment must now be considered as a new first-line option. Although, he did caution that longer-term data is needed for CheckMate 9ER: "The 18 months of follow-up is still quite short. The question is whether the responses to treatment are durable or if patients progress at some point."

Next, Dr Berthold suggests that it would be useful to know whether the combination treatment would be effective in non-clear cell carcinoma, as these patients were excluded from the trial.

"The risk of progression or death was cut by almost 50%, death was cut by 40%, and the response rate doubled. This will become an important treatment option to choose from."



"The pandemic has also revealed some weaknesses in how cancer care is resourced and organised."

COVID-19 Pandemic Halts Cancer Care and Damages Oncologists' Wellbeing

DELAYS and cancellations of cancer treatment have been implemented worldwide in order to protect vulnerable patients from exposure to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). However, it has led to a backlog of care and research at a time when oncologists are facing burnout. This is according to studies discussed in a press release at the ESMO Virtual Congress 2020 dated 14th September 2020.

Early on this year, before the pandemic, the European Cancer Information System (ECIS) estimated that the number of new cancer cases in Europe would reach 2.7 million this year, alongside 1.3 million deaths. Dr Stefan Zimmermann, ESMO Press Officer, stated that coronavirus disease (COVID-19) may not be the only factor that has put a strain on the oncology specialty: "The pandemic has also revealed some weaknesses in how cancer care is resourced and organised."

A study conducted by researchers at the Centre Hospitalier Universitaire Sart Tilman, Liège, Belgium, looked at oncology centres in 18 countries to assess the extent to which COVID-19 has challenged the management and delivery of cancer care. Study author Dr Guy Jerusalem expressed his worries about the impact of the pandemic: "There is a risk that the diagnosis of new cancer cases will be delayed and that more patients will be diagnosed at a later stage of their disease."

Results of the study showed that surgery was the treatment most likely to have been cancelled (in 44.1% of centres), followed by chemotherapy (25.7%) and radiotherapy (13.7%).

Another study, conducted by the ESMO Resilience Task Force, used online surveys to assess the impact of the pandemic on 1,520 oncology professionals from 101 countries. More than one-third said they had experienced feelings of burnout, one-quarter were at risk of distress, and two-thirds said they were unable to perform their roles as well as they could prior to the pandemic.

The ESMO Resilience Task Force will now look into developing more specific interventions to further help and support oncology professionals during and beyond the pandemic, as well as doing all they can to avoid delays to any treatment that may impact patient survival.

Gastric and Oesophageal Cancers Benefit from Immunotherapy

THREE studies, the results of which were presented on 21st September 2020 at the ESMO Virtual Congress 2020, have provided evidence that immunotherapy is beneficial for patients with gastric and oesophageal cancers. The studies analysed different patient populations and different immune checkpoint inhibitors, which are currently not approved for early therapy in Western countries, showing that immunotherapy has potential as first-line therapy in these patient populations who currently have poor survival.

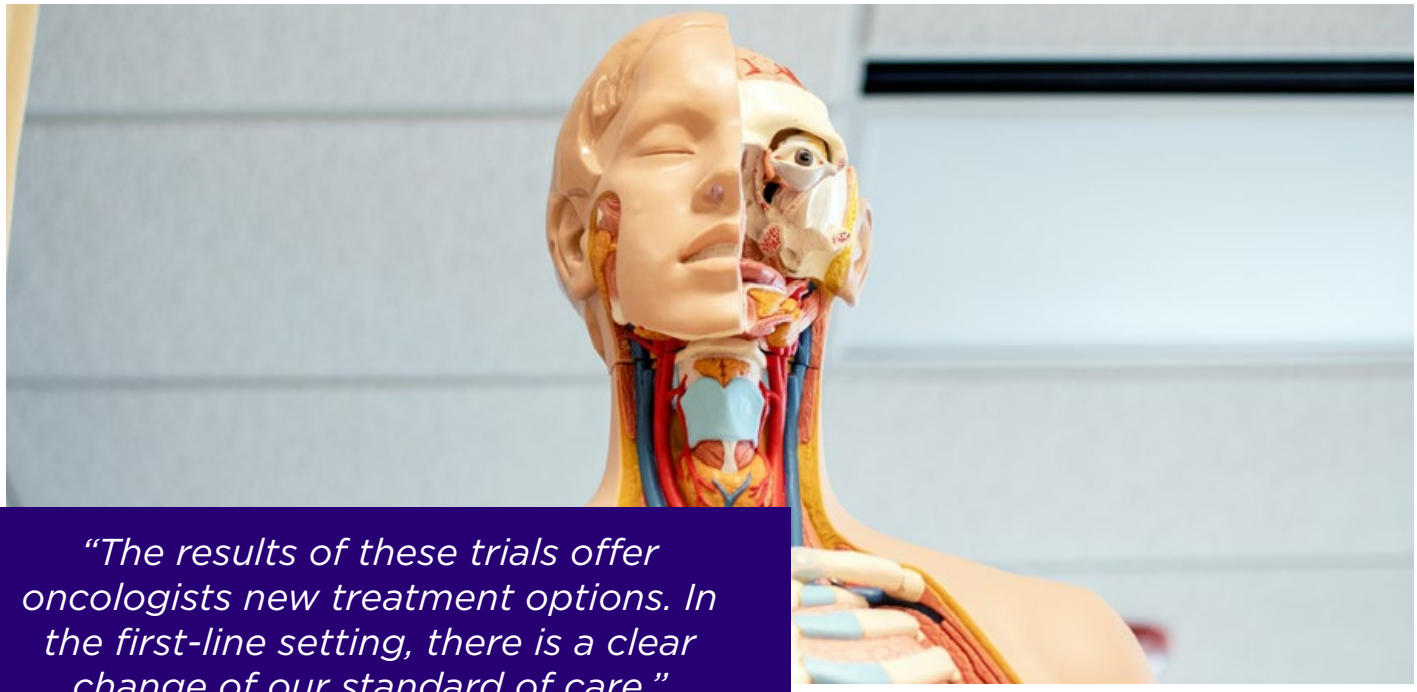
Firstly, the CheckMate 649 trial compared nivolumab plus chemotherapy to chemotherapy alone as first-line treatment in patients with non-HER-2-positive advanced gastric cancer, gastro-oesophageal junction cancer, or oesophageal cancer (all had adenocarcinoma histology). Overall survival and progression-free survival were significantly improved in patients with PD-L1 combined positive score (CPS) >5 and >1 tumours in the nivolumab plus chemotherapy group.

Prof Salah-Eddin Al-Batran, ESMO 2020 Upper Gastrointestinal Tract Chair, commented on the data: "The results are clinically very relevant. The open question is the effect in patients who have a PD-L1 CPS <5."

The second trial, ATTRACTION 4, was similar to CheckMate 649 except that it was exclusively performed in patients of Asian ethnicity and the primary endpoints were designed for all-comers, rather than a specific CPS value. Again, the first-line treatment with nivolumab plus chemotherapy improved the progression-free survival, though not overall survival. Prof Al-Batran provided a possible explanation for this: "Overall survival was not improved, possibly because all-comers were treated or because patients in Asia receive more subsequent therapies than Western populations."

Finally, the KEYNOTE 590 trial evaluated first-line chemotherapy with or without pembrolizumab in patients with squamous cell carcinoma of the oesophagus, adenocarcinoma of the oesophagus, or Siewert Type 1 gastro-oesophageal junction adenocarcinoma. Results showed improvements in both progression-free survival and overall survival for patients with squamous cell carcinoma of the oesophagus with PD-L1 CPS >10 tumours, all squamous cell carcinomas, all patients with CPS >10, and the study population as a whole.

Prof Al-Batran concluded: "The results of these trials offer oncologists new treatment options. In the first-line setting, there is a clear change of our standard of care."



"The results of these trials offer oncologists new treatment options. In the first-line setting, there is a clear change of our standard of care."

Routine Radiotherapy Does Not Improve Survival in NSCLC

RADIOTHERAPY treatment following surgical resection and (neo)adjuvant chemotherapy may not be required in non-small cell lung cancer (NSCLC). The authors of the French study, which included 501 patients, highlighted their findings in a press release from ESMO 2020 dated 19th September 2020.

Post-operative radiotherapy (PORT) for patients with mediastinal involvement of their NSCLC has been an area of clinical debate since a 1998 meta-analysis doubted the benefit of the practice. Improved patient selection practices and improvements in both (neo)adjuvant chemotherapy and radiotherapy have been thought to have improved the impact of radiotherapy in these patients since this 1998 study. However, the results of a French randomised controlled trial suggest otherwise.

"We can safely say there is no net benefit from such treatment but there is also potential harm"

An intention-to-treat analysis of 501 patients was conducted; 252 patients received PORT over 5 weeks and 249 received no PORT (control arm). There was no statistically significant difference in disease-free survival: 47.1% in the PORT arm and 43.8% in the control arm (hazard ratio: 0.85; 95% confidence interval [CI]: 0.67–1.07; p=0.16). There was also no significant difference in overall survival at 3 years: 66.5% of the PORT arm (95% CI: 59–73) compared to 68.5% of the control arm (95% CI: 61–75).

Study author Dr Cécile Le Pechoux, Institut Gustave Roussy, Paris, France, highlighted the need for further analysis to determine whether there are subsets of patients that may benefit from radiotherapy: "PORT cannot be recommended for all patients with Stage II and III NSCLC with mediastinal nodal involvement. Possibly, however, for some patients it might be useful because it does decrease the rate of mediastinal relapse by 50%. This must be put into balance with the risk of over-added cardiopulmonary toxicity."

Prof Rafal Dziadziuszko, Medical University of Gdansk, Poland, commented on the clinical insights of these findings: "This will change the practice of many institutions that adopted standard use of radiotherapy in these patients. We can safely say there is no net benefit from such treatment but there is also potential harm, which we see from this study, so any potential benefits in some patients are offset by the predominantly higher risk of cardiopulmonary toxicities."

Asymmetry in Healthcare Spending on Cancer in European Countries Revealed

DISPARITIES in healthcare spending and unequal access to clinical trials across European countries has led to limitations to cancer medicine in the continent. This is according to the results of a new study presented as part of a press release at ESMO 2020 on 18th September 2020.

A clinical trial analysis has shown that patients with cancer living in Western Europe may have greater access to new treatments because countries in this part of the continent run more trials than countries in Eastern and Central Europe. The study indicated large differences in access to new treatments and therapies in development for these different population groups. Dr Teresa Amaral, study co-author from University Hospital Tübingen, Tübingen, Germany, reinforced the results of the investigation: "Our study gives us proof of what we previously suspected, that there is a huge asymmetry in the number of clinical trials for cancer treatments in different countries."

The clinicaltrials.gov database was used to search for trials in adults with tumours between 2009 and 2019 in 34 countries. The search revealed that Albania had the fewest active interventional clinical trials and Belgium had the most. Patients with cancer who had more access to clinical trials are likely to benefit from this because they can access novel therapies during earlier phases and may not have to wait for licensing and reimbursement. "Also, all trial participants benefit from the regular follow-up and monitoring involved in taking part in a clinical study," said Dr Amaral.

Also reported at ESMO 2020 were the results of a health economics analysis that showed that 'wealthier' European countries spent 10 times as much as poorer countries per inhabitant on cancer medicines in 2018, comparable to the trend seen for clinical trials. Cancer-specific health spending was shown to be highest in Austria, Germany, and Switzerland, and lowest in the Czech Republic, Latvia, and Poland.

Researchers speculated that the asymmetry between countries was primarily to do with the countries' economic strength rather than the burden of the disease. The differences in spending can be attributed to two main factors: "One is shortage of money and the other is drugs not being approved for use by some healthcare systems," according to Dr Nils Wilking, from the Karolinska Instituet, Stockholm, Sweden. The authors of the clinical trial analysis are currently exploring the reasons for different healthcare spending in European countries to provide prospective solutions to this disparity.

"There is a huge asymmetry in the number of clinical trials for cancer treatments in different countries."

Breast Cancer Recurrence Risk Reduced by Abemaciclib Adjunct Therapy

RECURRENCE of cancer is a significant concern for patients with high-risk hormone receptor positive (HR+) breast cancer. According to results from a study presented at ESMO 2020 and in a press release dated 20th September, the risk of cancer recurrence can be reduced by 25% by adding abemaciclib to hormonal therapy in patients with high-risk early HR+ human epidermal growth factor receptor 2 negative (HER2-) breast cancer.

Developments in pharmacotherapy for HR+ breast cancer have markedly improved over the last years, with many therapies now being curative for patients. However, a significant proportion (20%) of these patients have high-risk disease and thus will develop a recurrence within the first 10 years of treatment. Given the transformative introduction of CDK4/6 inhibitors, such as abemaciclib, into the treatment landscape for metastatic breast cancer, researchers set out to determine if the addition of abemaciclib to hormone treatment could reduce the risk of cancer recurrence in patients with high-risk early breast cancer.

Patients included in the randomised, open-label Phase III study (N=5,637) had HR+ HER2- early breast cancer and were at high risk for relapse, as determined by the presence of clinical and pathological risk factors. Following the completion of their primary treatment, participants were randomised to receive either abemaciclib (150 mg twice daily for 2 years) plus endocrine therapy or endocrine therapy alone. Results showed that recurrence of cancer during this 2-year period occurred in 11.3% of patients on hormone therapy alone and in 7.8% of those with add-on abemaciclib, meaning a 25.3% reduction in risk of recurrence. Adverse effects of abemaciclib caused the discontinuation of treatment in 463 (16.6%) of patients, which mainly comprised diarrhoea. Prof Giuseppe Curigliano, University of Milan, Italy, and Chair of the ESMO Guidelines Committee, commented that: "Adherence to treatment will be an important issue to be considered in the real-life population of patients when this treatment is approved and used in clinical practice."

Commenting on the clinical impact of the results, lead author of the study Prof Stephen Johnston, Royal Marsden Hospital NHS Foundation Trust, London, UK, said: "This is a very important trial and the findings will change practice. Once approved for high risk HR+ HER2- early breast cancer, the new standard of care for these patients will be to add 2 years of abemaciclib to endocrine therapy."

COVID-19: Impact on Cancer Patients and Oncology Professionals

Layla Southcombe
Editorial Assistant

Citation: EMJ Oncol. 2020;8[1]:22-25.

TRANSFORMATIVE is a term that appropriately describes the striking developments made in the oncology field in recent years. Yet again the agile field has needed to evolve in the face of new challenges, but the challenge this time was to ensure that patients are cared for during the ongoing coronavirus disease (COVID-19) pandemic. Over two 'SARS-CoV-2 and cancer' proffered paper sessions at the European Society of Medical Oncology (ESMO) Virtual Congress 2020, oncology experts came together to discuss how the COVID-19 pandemic has affected the delivery of cancer care, the well-being of cancer patients and healthcare professionals, and the risk factors for mortality in this uniquely susceptible group.

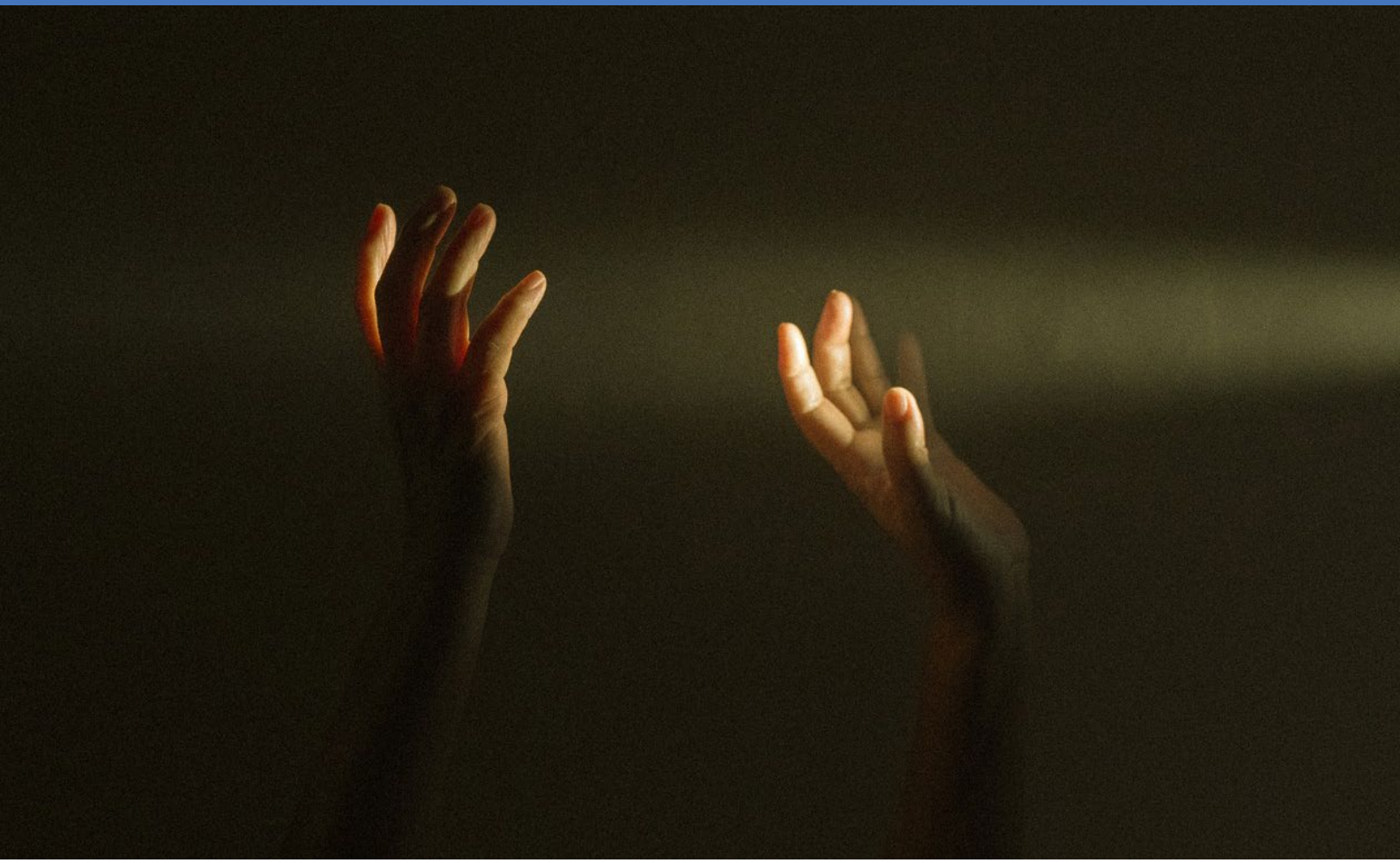
TREATMENT MODIFICATIONS

Lockdown restrictions and the general concerted effort to reduce face-to-face interactions to mitigate the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, have resulted in major changes to how the care for cancer patients is delivered. The initiation of changes, such as new management plans and telehealth services, has facilitated the continuation of treatment, but what impact has this had on the cancer patients and the caregivers involved?

Prof Florence Joly, Centre François Baclesse, Caen, France, presented data from COVIPACT, an ongoing longitudinal study investigating the impact of the pandemic on the management of cancer and the psycho-emotional well-being of patients and care providers in an outpatient setting.[1] Approximately 25% of the patients in the study experienced modifications to their cancer treatments, irrespective of metastatic/localised status, with most seen in patients with lung or head and neck cancers. The types of modifications comprised adapted monitoring through phone and video consultation, postponement or halting of treatment, and alteration to the rhythm of treatment. When breaking the patients down into the type of treatment they were receiving, the researchers found that the biggest disruption in treatment was seen in patients on immunotherapy, of whom 49% experienced modifications: 18% of patients had interruptions, 38% postponed, and 38% modified treatment rhythm. The least modifications to treatment were seen in patients on chemotherapy (18%), most of which were due to changes in consultation.

Racial Disparities

Studies have shown that individuals belonging to ethnic minority groups have been disproportionately affected by the pandemic,



particularly with regard to morbidity and mortality, when compared to the general population. Dr Deborah Doroshow, Icahn School of Medicine at Mount Sinai, New York City, New York, USA, presented data from CCOS, a study that analysed the disparities in cancer during the COVID-19 pandemic.[2] From March 2020, 40.6% of the patients in the study experienced a decrease in all visits, 51.6% experienced a decrease in in-person visits, and 32.3% experienced an increase in telehealth visits. Notably, when adjusted for cancer centre, cancer status/type, and receipt of systemic therapy, patients of Black and Hispanic heritage were less likely to have increased telehealth visits when compared to those who were White. When asked about the differences in telehealth seen between ethnicities, Dr Doroshow noted that barriers such as those relating to language and access to technology could play a significant role. "If we want to adopt telehealth, which can be a really transformative technology to keep patients safe, we really need to think about what the barriers are to universal adoption of telehealth and target those barriers to make sure that all patients can benefit," she advised. Furthermore, there was a disproportionately high COVID-19 incidence among non-White cancer patients, and those of Hispanic background were more likely to have treatment delays than patients who were White. Overall, patients of minority ethnicities experienced a disproportionate burden of cancer disruptions, with Dr Doroshow concluding that interventions to narrow these disparities are warranted.

"If we want to adopt telehealth, which can be a really transformative technology to keep patients safe, we really need to think about what the barriers are to universal adoption of telehealth and target those barriers to make sure that all patients can benefit"

"As mortality rate increases, COVID-19 job performance decreases and the well-being index scores increased, which suggest higher distress and poorer well-being."

PATIENT AND HEALTHCARE PROFESSIONAL WELL-BEING

Living through a pandemic has universally been challenging and adding a serious disease like cancer into the situation makes it harder, potentially impacting quality of life. In the COVIPACT study, the stress, sleep quality, and cognition of patients receiving outpatient cancer care in a French hospital were measured through a survey during the French lockdown period from 8th April to 29th May (n=621). More than one-half of the patients reported stress related to the event, which was more often reported in patients who had modifications to their treatment.

Stress, scale of professional exhaustion, and feeling of personal efficiency of the healthcare professionals in the outpatient departments were also assessed through a survey during this time period (n=73). High levels of perceived stress were reported; however, high levels of professional accomplishment and personal efficacy were also reported. When comparing the two groups, there was a higher level of perceived stress among caregivers than among patients.

Dr Susana Banerjee, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK, also presented data on the impact of COVID-19 on oncology professionals, from a survey by the ESMO resilience task force.[3] Answers were received from 1,520 professionals across 101 countries and were compared to the COVID-19 mortality rate of the individuals' country at that time. Summarising the results, Prof Banerjee said: "As mortality rate increases, COVID-19 job performance decreases and the well-being index scores increased, which suggest higher distress and poorer well-being." Burnout was not associated with the country's mortality rate. More than 25% of survey respondents had a well-being index that suggested risk of distress, with analysis of the demographics showing that they were more likely to be female or under the age of 40 years. When repeated 3 months later, the survey results showed that the proportion of individuals at risk of distress increased from 25% to 33% and self-reported burnout increased from 38% to 49%; however, job performance had also increased, from 34% to 51%. Having access to counselling and psychological support, workshops/courses on well-being, and burnout and coping strategies were noted as being helpful resources to have going forward, but 86% felt that having flexible hours, including working from home, would be extremely to moderately helpful in improving well-being.

MORTALITY RISK FACTORS

Dr Trisha Wise-Draper, University of Cincinnati, Cincinnati, Ohio, USA, opened her session by explaining that patients with cancer who contract COVID-19 experience higher rates of hospitalisation (40%), severe respiratory illness (20%), and mortality (9–30%) when compared to the general population, highlighting the need to identify the risk factors associated with these complications. The study Dr Wise-Draper presented analysed data from the COVID-19 & Cancer Consortium (CCC19) registry and included 3,654 patient cases (28% being treated with curative intent and 44% for non-curative). The types of treatment given to cancer patients prior to their COVID-19 diagnosis were analysed, along with when they were given (<2 weeks, 2–4 weeks, 1–3 months, and 3–12 months prior to COVID-19 diagnosis).[4] The most common treatment combinations given prior to COVID-19 diagnosis were cytotoxic chemotherapy and targeted therapy.

The highest mortality rates were seen in individuals with active cancer versus those in remission (22% versus 6%, respectively), with the highest in those with progressive cancer (34%). Interestingly, high rates of COVID-19 complications were seen in people with cancer, including hospitalisation, supplemental oxygen requirement, intensive care unit admission, mechanical ventilation, and death, whether or not they had been receiving cancer treatment or were in remission and had not been receiving treatment.

When investigating the treatment type and 30-day mortality, those on chemotherapy and immunotherapy combination had the highest mortality rate, regardless of time of administration before COVID-19 diagnosis. Those who had received targeted therapy 1–3 and 3–12 months before COVID-19 diagnosis also had a high risk of mortality. Those who received anti-CD20 at 1–3 months prior to COVID-19 diagnosis showed a striking mortality rate of 47%, which Dr Wise-Draper speculated to be a possible result of the B-cell depletion normally seen at this time period post anti-CD20 administration. Overall, 30-day mortality was highest in those who received cancer treatment 1–3 months prior to COVID-19 diagnosis (28% all-cause mortality).

SUMMARY

Knowing the factors that put cancer patients at risk of severe COVID-19 will equip physicians to make educated decisions on treatment plans, thus mitigating increased risk of morbidity and mortality. The results from the studies into racial disparities in receipt of treatment and the well-being of cancer patients and healthcare professionals have highlighted unmet needs that, when met, can aid the improvement of the delivery of care to patients with cancer during the COVID-19 pandemic and post-COVID-19 era.

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Next-Generation Sequencing Standard of Care for Molecular Profiling

An update from the European Society for Medical Oncology (ESMO) Virtual Congress 2020

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Meeting Summary

Today, the need for robust and reproducible, but also timely, molecular testing to accurately identify treatment-eligible patients is largely acknowledged within the oncology community. This year's European Society for Medical Oncology (ESMO) annual congress, in its virtual debut, gathered healthcare professionals spanning a range of disciplines and stakeholder groups together to learn from over 200 invited speakers and approximately 2,000 e-abstracts. In the coronavirus disease (COVID-19) era, attention has been focussed on the importance of appropriate molecular testing as part of an integrated cancer care workflow aiming to effectively stratify patients and enable optimal treatment selection. Additionally, emphasis was placed on the unique challenges posed by the COVID-19 pandemic to cancer care. Throughout the event, it became clear that the medical community did not begin 2020 with full appreciation of how much a crisis such as COVID-19 would have on the capacity to rapidly reveal the fragility of the cancer testing ecosystem, highlighting the urgent need to integrate the siloed stakeholders who are so dependent upon it. A major question addressed by numerous speakers, with preliminary sets of data, was: "How does COVID-19 impact the prognosis of patients with cancer?"

With the usual workshops and satellite events, though only a few new product launches compared to previous years, the ESMO Virtual Congress 2020 was characterised by many presentations focussed on molecular biomarker testing. Overall, the ESMO 2020 meeting highlighted that there are vast gaps in current molecular diagnostics, with extremely marked geographical differences and a broken clinical diagnostic testing ecosystem that currently impedes patient access to precision therapy and better outcomes. While planning for new therapies associated with specific biomarkers is growing steadily, with approximately 100 new oncology drugs or combinations expected to be launched within 5 years, no widespread diagnostic solutions are currently available and the specialty will not be able to satisfy the mounting need for molecular testing in the near future unless a radical upheaval of the current situation occurs.

How Does COVID-19 Impact the Prognosis of Patients with Cancer?

Given that COVID-19 has posed unique challenges in cancer care, a number of speakers addressed, with evidence, the impact of COVID-19 on the prognosis of patients with cancer. It should be noted that the use of immunosuppressive agents, for example, was a real and understandable concern during the initial surge of COVID-19, given the potentially life-threatening consequences of inadequate immunity. Oncology professionals globally faced tough decisions on whether to stop treatment, change treatment regimens, modify doses, and in some cases, reverse previously planned treatment decisions. Patient-oriented aspects of oncology were forced to change because of COVID-19: bad news had to be relayed via video calls instead of in person and heart-breaking situations occurred whereby patients were not allowed visits from loved ones during a hospital stay, even at the end of their lives. Results from Europe's largest prospective dataset of patients with cancer and COVID-19 revealed an adverse impact of COVID-19 on prognosis, with a hazard ratio of 1.62 for mortality in patients with cancer versus without cancer.[1] In hospitalised patients with cancer and COVID-19, the mortality rate was higher in those with a history of cancer and on active treatment for cancer, at 44.3% and 42.3%, respectively, compared with 29.5% in patients without cancer. It is therefore mandatory to reduce the risk of COVID-19 exposure in patients with cancer.

COVID-19 Has Increased Pressure on Turnaround Times, from Sample Collection to Final Results

It is clear that the COVID-19 pandemic created a paradigm shift in all modern healthcare, with regulations, protocols, and mindsets having to be reworked in just a matter of months to keep pace with the virus.[2] As already highlighted during the 2019 annual ESMO meeting, it is imperative that exhaustive biomarker testing results are available within days for clinicians, and not weeks. The pandemic has further highlighted the need to timely generate and deliver molecular profiling results, with many institutions now facing increased pressure from COVID-19.[2,3] On one hand, institutions are urged to ensure safety during sample collection and adequate infrastructure sanitisation, inevitably inducing a delay to surgical procedures; on the other hand, they are required to promptly deliver results leading to important therapy-related decisions.[2-4] In this new scenario, it is clear that the sample testing send-out model is highly challenged. Building in-house sequencing facilities is going to be critical to ensure timely results, but also to generate the necessary independence that might prove pivotal during times when shipping biological specimens could add more challenges than benefits. Despite substantial efforts from major oncology stakeholders to prevent or reduce this behaviour, rushed decisions are common in routine practice. For example, contemplating the initiation of an immune-oncology drug regimen based on a fast immunohistochemistry test (i.e., programmed death-ligand 1 positivity >1%) before the mutational status of genes such as *EGFR* are eventually investigated. Such phenomena have been further exasperated by COVID-19, when pressure on physicians to initiate treatments is even higher, leading to several unappropriated decisions. Whether national healthcare systems will be willing, or in the position, to increase structural funding to support infrastructure expansion dedicated to molecular testing, including laboratories and specialised staff, remains to be seen. However, new technological, groundbreaking solutions are available on the market today, enabling molecular profiling at a speed compatible to immunohistochemistry, easing the burden of expediting results.

Tumour Tissue Sample Requirements and Test Success Rate Have Never Been More Critical

In addition to many discussions on the value of molecular testing, fewer but deeper debates have focussed on the importance of minimal tissue sample requirements to initiate the test (e.g., working with cytological specimens).[5] Drastically reducing the molecular test failure rates has turned out to be a basic requirement for any assay to be broadly introduced into routine

clinical practice during the pandemic, when avoiding a rebiopsy is an undisputable must. Preventing re-exposure to invasive procedures for patients with cancer, such as a rebiopsy, which is usually associated with medical risks and financial costs, has become a priority. The community is now more sensitive to this topic and careful checks for test requirements occur more than ever before. Assays that require minimal input and that have demonstrated a high success rate will be greatly beneficial.[6]

New Emerging Biomarkers Are Still on Hold: No News Is Bad News

Much awaited and more conclusive data regarding tumour mutational burden (TMB) were expected at ESMO this year. Unfortunately, several presented datasets indicated that tissue-TMB needs to be carefully re-evaluated as a biomarker for combination therapies, whereas the relationship for monotherapy has been confirmed in previous studies.[7] Among the unresolved critical points, the definition of a universal TMB cut-off value (TMB ≥175 mutations per exome) continues to appear unrealistic given that accumulating evidence suggests TMB to be highly tumour-type dependent. It now seems timely to look beyond TMB, identifying further predictors for checkpoint inhibitor response, including, for example, immune infiltration scores and T-cell receptor clonality.

New Opportunities for Early Stage Cancers: A Call on Molecular Testing at Diagnosis

Also at ESMO 2020, AstraZeneca took to the stage with their data from the ADAURA study.[8] The updated results from this trial, featuring Tagrisso® (AstraZeneca, Cambridge, UK) in the postsurgery or adjuvant setting, were promising and will continue to resonate enormously in the community. Extremely mature data presented at ESMO 2020 confirmed that Tagrisso generated an 83% reduction in the risk of postsurgery recurrence of non-small cell lung cancer (NSCLC). The study recruited participants with Stages IB, II, and IIIA NSCLC, who accounted for around 30% of the population presenting with this disease. Tumours at this stage can be removed with surgery but the cancer tends to recur for most patients; adjuvant cisplatin-based chemotherapy is the current standard of care but is a treatment that carries substantial toxicities. Tagrisso unequivocally demonstrated its successful treatment potential via the ADAURA study. Disease-free survival at 2 years was 89% with Tagrisso, compared to 53% in the control arm. Overall, these results pinpoint the future importance of determining the tumour mutational status at diagnosis, even in the early stages of NSCLC, as part of a board molecular profiling, in order to select the most appropriate treatment option for patients with lung cancer, as well as in the adjuvant setting.

New Treatment Options Highlights: More Targets Need Better Testing

Outside the NSCLC field, excitement for overall survival (OS) data presented for olaparib continues in males with metastatic castration-resistant prostate cancer and *BRCA1*, *BRCA2*, or *ATM* mutations.[7,9] The PROfound trial[9] was a prospective, multicentre, randomised, open-label, Phase III study evaluating the efficacy and safety of olaparib versus control (physician's choice of enzalutamide or abiraterone). The trial enrolled 387 patients with metastatic castration-resistant prostate cancer who had progressed on a hormonal agent and had a tumour mutation in one of 15 genes that play a role in the homologous recombination repair pathway; the trial has now reached substantial data maturity. OS was significantly longer with olaparib than control treatment in Cohort A (19.1 versus 14.7 months; hazard ratio: 0.69; 95% confidence interval: 0.50–0.97; p=0.0175), with a trend towards improvement in the overall population (17.3 versus 14.0 months; hazard ratio: 0.79; 95% confidence interval: 0.61–1.03; nominal p=0.0515). These results occurred despite approximately two-thirds of the patients in the control arm crossing over to olaparib following radiographic disease progression. The long-term safety of olaparib was as expected from previous studies

of its use. This substantial winning for olaparib, however, poses a real question regarding the readiness for *BRCA1, BRCA2*, and other *BRCA*-related testing. Overall, the very positive presented data might reach the bedside with substantial delay if the testing gap is not rapidly fulfilled.

Data on gene fusion were then presented, demonstrating the efficacy of pralsetinib (BLU-667) in patients with *RET* mutation-positive medullary thyroid cancer (MTC), with or without prior treatment, as presented in the ongoing Phase II extension of the registrational ARROW trial.[10] Notably, with the U.S. Food and Drug Administration (FDA) approval of selpercatinib (Retevmo; Eli Lilly and Company, Indianapolis, Indiana, USA) for the treatment of advanced and metastatic *RET* fusion-positive NSCLC, *RET* fusion-positive thyroid cancer, and *RET*-mutated MTC, physicians and patients are now offered with more options for *RET*-fusion management. More data is expected with the Phase III trials LIBRETTO-531,[11] conducted in treatment-naïve patients with advanced or mutated MTC, and LIBRETTO-431,[12] in treatment-naïve patients with metastatic NSCLC, each comparing selpercatinib as first-line therapy versus standard of care. Expected completion of these Phase III studies is in 2025–2026.

Regarding the open fight against resistance mechanisms, Janssen presented results from the Phase I CHRYSALIS trial,[13] which tested the combination of amivantamab (JNJ-6372), a bispecific antibody targeting *EGFR* and *MET*, with lazertinib, a third generation EGFR-tyrosine kinase inhibitor, in advanced NSCLC with *EGFR* exon 19 deletion or L858R mutation. In the presentations, given by key opinion leaders, Janssen showcased promising data; the CHRYSALIS study generated a compelling 36% response rate among 45 patients who were tyrosine-kinase inhibitor-refractory, at a median follow-up of 4 months.[14] Amivantamab and lazertinib have been designed to block numerous resistance mechanisms to EGFR inhibition, and ultimately provide hope that their combination can improve response rates. If successful, this new paradigm will push the need to address all clinically relevant *EGFR* alterations further, not simply the most common locations in exon 19 and 20, advocating for comprehensive molecular profiling.

Health Economics and Real-World Evidence: Better Stratification Means Better Outcome

With increasing numbers of next-generation sequencing (NGS) tests being performed clinically, and as means to screen for company-sponsored studies, there is a growing ability to source existing data in healthcare systems and claims databases. Translating NGS results into hard outcomes and quality of life measures in a real-world setting is becoming more relevant to clinical decision-making and provides evidentiary value for payors, ultimately affecting patient access. Real-world evidence has influenced guidelines for patient care and can be used to support regulatory approval. For example, a study from the British Columbia Cancer Center (BCCC)[15] on the treatment evolution of advanced NSCLC has determined the change in OS in advanced NSCLC with new treatment options that underwent molecular profiling for treatment decisions. Data were analysed from the BCCC from 2009, 2011, 2015, and 2017. While patient demographics have changed somewhat over time, the proportion of patients treated with systemic treatment remained consistent from 2009–2017. Notably, the impact of targeted therapy and immune checkpoint inhibitor on OS in each respective year significantly improved overall OS. Relative to the best supportive care, chemotherapy alone, any-line immunotherapy, and any-line targeted therapy demonstrated clear benefit in univariate and multivariate analyses ($p<0.001$). Notably, the benefit of immunotherapy on OS was comparable to the use of targeted therapy. These data clearly demonstrate the need for upfront NGS testing, which has the benefit of quantitative outcomes. These types of collaborative analyses should provide substantial pressure on national healthcare system stakeholders to increase access to NGS screening.

Whole Genome Sequencing In The Clinics: Not Ready for Prime Time

This year, the ESMO Translational Research session was divided into two parts. The first focussed on immunotherapy-related research

with presentations on intrinsic mechanisms of sensitisation to checkpoint inhibition and immune effector score in immunotherapy-treated patients with NSCLC. The second focussed on whole genome analysis of tumours and included presentations on validation of whole genome sequencing (WGS) in routine clinical practice and the evolution of metastatic tumours under therapeutic pressure. Both sections included talks from principal investigators affiliated with the Netherlands Cancer Institute, Amsterdam, the Netherlands.[16,17] The authors provided insights into the implementation of clinical-grade WGS (cWGS) in routine practice. In the WGS Implementation in standard cancer Diagnostics for Every cancer patient (WIDE) study,[18] cWGS was performed on a prospective cohort of 1,200 patients (with Stage IV solid tumours), and feasibility and clinical validity data (primary endpoints) of the first 600 patients were presented. Notably, cWGS was successfully performed in only 69% (414/602) of patients, with a technical success rate of 96% (414/433). Ineligibility for cWGS was mostly caused by an insufficient number of tumour cells (<20%) in the received biopsy (86% [145/169]). Median turnaround time for cWGS was 14 days, which the authors claim will decrease incrementally by continuous improvements to the clinical procedure and cWGS pipeline. Overall, cWGS identified a clinically actionable (routine practice and experimental) biomarker in 74% of all patients tested. Based on the first WIDE study data, the authors concluded that cWGS can be clinically feasible in routine molecular diagnostics in a comprehensive cancer centre and has added value by providing additional treatment options for most patients. Of note, successfully delivering results for only 69% of enrolled patients is far from being clinically acceptable and speaks for the need to recalibrate the realistic expectation of cWGS uptake for routine testing. The cost implications were not discussed by the authors, constituting a large barrier for widespread application of cWGS. While these proof-of-principle studies are pivotal for advancing cWGS and getting it closer to the clinic, cWGS is not yet ready for prime time.

Conclusion

To make precision medicine a reality, the widespread application of genome analysis as a feasible diagnostic solution, and not only as a privileged option for a few national healthcare systems, is a must, but the field is falling behind. Healthcare policymakers, medical institutions, manufacturers, clinicians, biomedical researchers, and patients' associations will have to push for NGS adoption through global initiatives, while also being able to deploy them at a local level. At ESMO 2020, a number of talks and abstracts referred to the real-world testing landscape and highlighted the impressive developments and progress within NSCLC testing. However, the effects of those testing developments on patient management are not as impressive from the clinical outcome perspective. The real-world NSCLC testing landscape tells a very different story underneath the surface; one that is suboptimal and unable to deliver treatments designed to improve the lives of enough patients at the right time. For instance, a clear example are peroxisome proliferator-activated receptor inhibitors, where the lack of drug prelaunch preparation on the biomarker diagnostic front is leading to low adoption rates and patient leakage.[19] Overall, the emerging need for the inclusion of new biomarkers with sufficient prelaunch runway, to enable appropriate preparation for laboratories, is paramount. Diagnostic laboratories and providers need time to achieve the standards required to offer the right test and interpretation at the right time for the launch of new treatments. Unprecedented technological solutions are now available to mitigate these issues, enabling fast and robust NGS testing, but will require a change of attitude towards molecular diagnostics to truly consider it as an integral part of the cancer-care workflow, deserving appropriate investment.

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Oncogenic Drivers in Advanced NSCLC: Navigating an Evolving Landscape to Optimise Patient Outcomes

This symposium took place from 14th to 29th September 2020, as part of the European Society for Medical Oncology (ESMO) Virtual Congress

Chairperson: Fiona Blackhall[1,2]

Speakers: Fabrice Barlesi,[3] Maximilian Hochmair,[4] Rosario García Campelo[5]

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2. The University of Manchester, Manchester, UK
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4. Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna, Austria
5. University Hospital A Coruña, A Coruña, Spain

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Meeting Summary

Despite significant advancements in recent years, lung cancer remains the leading cause of cancer-related deaths globally. The promise of precision medicine in non-small cell lung cancer (NSCLC) is starting to become a reality owing to the introduction of numerous tyrosine kinase inhibitors targeting specific oncogenic alterations. Therefore, there is an even greater need for accurate, rapid, and accessible testing to allow for large-scale molecular profiling of patients with NSCLC. The evolution of the treatment landscape for patients with NSCLC harbouring an anaplastic lymphoma kinase (*ALK*) gene rearrangement provides an excellent example of the impact of targeted therapy. Four different ALK inhibitors are now recommended by clinical practice guidelines for the first-line treatment of *ALK*-positive metastatic NSCLC: crizotinib, ceritinib, alectinib, and brigatinib. However, despite demonstrating significant improvements in progression-free survival (PFS), disease progression and relapse in patients with advanced NSCLC is inevitable. In addition, the occurrence of brain metastases is common in patients with advanced *ALK*-positive NSCLC, and penetration of the blood–brain barrier by ALK inhibitors is important to achieve the best possible patient outcomes. Selecting the right therapy and sequencing treatments appropriately is essential to ensure each patient receives the optimal treatment for them.

The objective of this satellite symposium held at the European Society for Medical Oncology (ESMO) Virtual Congress was to provide an educational forum to discuss key concepts associated with testing and first-line treatment strategies in NSCLC, with a specific focus on *ALK*-positive disease, in order to emphasise the importance of providing truly personalised patient care.

Introduction

Professor Fiona Blackhall

The oncology community has been experiencing an unprecedented moment in lung cancer diagnosis and treatment; however, despite significant advances, lung cancer remains the leading cause of cancer mortality worldwide.[1] NSCLC, accounting for approximately 85% of lung cancer cases,[2] provides a pivotal example of how appropriate disease segmentation and treatment personalisation can markedly impact patient outcomes. NSCLC can be classified as squamous cell carcinoma (30%) or nonsquamous carcinoma (70%).[2] Substantial progress in the understanding of the disease in recent years has led to further subclassification of nonsquamous NSCLC into various molecular subtypes according to specific oncogenic driver mutations or gene translocations (Figure 1).[3,4] As a result, there is a growing list of targeted therapies that can be used to treat specific subsets of patients, including those with mutations in the epidermal growth factor receptor (*EGFR*) gene, or translocations in the *ALK* or c-ros oncogene 1 (*ROS1*) genes.

Mutations in *EGFR* are present in approximately 15–30% of patients with NSCLC,[2,4] and classical activating mutations, such as *EGFR* exon 19 deletions and point mutations in exon 21 (L858R), are associated with responsiveness to targeted tyrosine kinase inhibitor (TKI) treatment.[5] In addition, many of the less commonly observed alterations, such as *EGFR* exon 19 insertions and point mutations in exon 21 (L861Q), exon 18 (G719X), and exon 20 (S768I), are also responsive to TKI therapy.[5] However, exon 20 insertions are associated with poorer TKI responses.[6] Future research aims to further characterise these additional alterations, and three treatments are currently under investigation for patients with *EGFR* exon 20 insertions (mobocertinib, amivantamab, and poziotinib).

ALK rearrangements are identified in 3–5% of patients with NSCLC and are usually mutually exclusive with *EGFR* mutations or *ROS1* rearrangements.[3,4,7] Echinoderm microtubule-associated protein like-4 (*EML4*) is a common fusion partner of *ALK* and there are multiple *EML4–ALK* variants.[8] Variant status is associated with clinical outcome and may have implications for specific treatment strategies.[9] Patients with *ALK*-positive NSCLC are more likely to have adenocarcinoma histology and to be never smokers.[10]

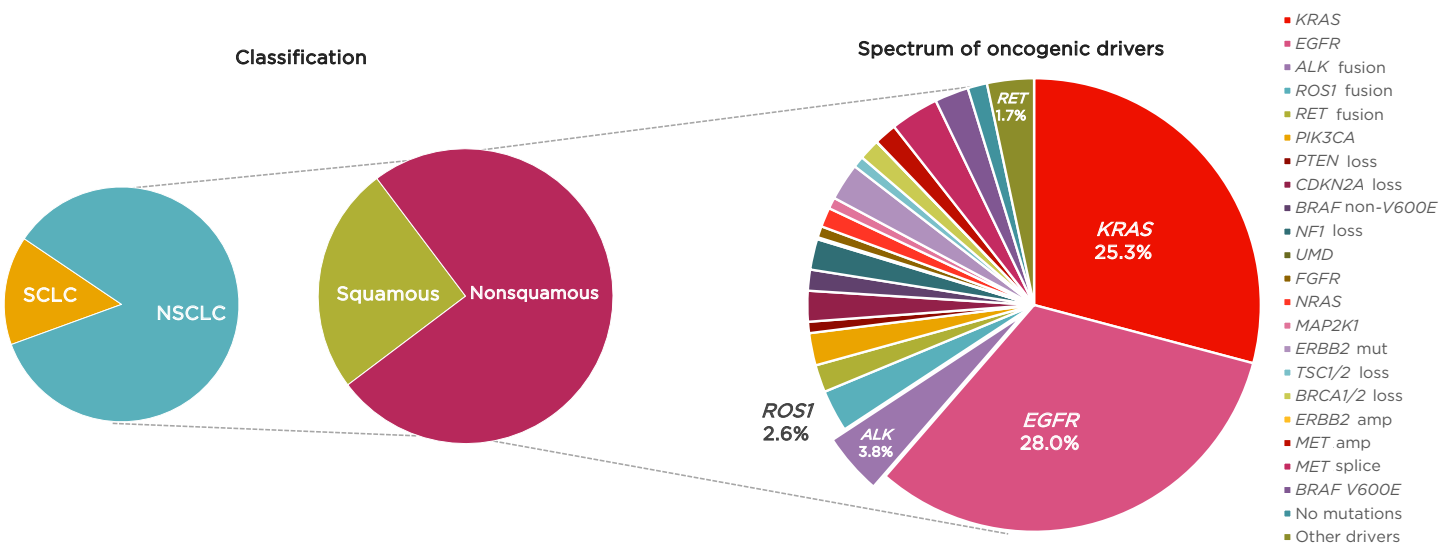


Figure 1: Subclassification of non-small cell lung cancer.

amp: amplification; mut: mutation; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

Adapted from Jordan et al.[4]

Over the last decade, several ALK inhibitors have been developed for the first-line treatment of *ALK*-positive NSCLC, including the first-generation inhibitor crizotinib and the second-generation inhibitors ceritinib, alectinib, and brigatinib. Lorlatinib was the first third-generation inhibitor to be approved for *ALK*-positive NSCLC, and several inhibitors are also in development, including ensartinib and entrectinib.

With the availability of potent targeted treatments, it is increasingly important to ensure upfront molecular testing is performed to identify oncogenic drivers. However, there is some evidence to suggest that, despite improvements, real-world *ALK* testing rates remain suboptimal.[11] More work is also needed to ensure specificity and tolerability of first-line treatments to suit individual patient needs. Disease progression in NSCLC is inevitable and clinicians must consider the optimal treatment sequencing strategy to achieve the best outcomes for patients. In addition, the central nervous system (CNS) is a known sanctuary site for NSCLC and brain metastases occur frequently in advanced *ALK*-positive disease.[12] Improved penetration of second-generation ALK inhibitors into the CNS may improve outcomes for these patients.[13]

Oncogenic Driver Testing Strategies: Identifying the Right Patients for the Right Treatment

Professor Fabrice Barlesi

Advancements in high-throughput technologies over the past decade have led to a rapid reduction in the costs associated with genome sequencing,[14] allowing these techniques to become more globally accessible. As an increasing number of targetable molecular alterations in NSCLC are identified, it is more important than ever to ensure that patients with advanced NSCLC are accurately genotyped.

The results of the 1-year nationwide French Cooperative Thoracic Intergroup (IFCT) study conducted in 2012 clearly demonstrated that the identification of actionable targets through molecular profiling provided a clinical benefit.[15] The presence of a genetic alteration was associated with improved overall survival (16.5 months; 95% confidence interval [CI]: 15.0–18.3) compared with the absence of a genetic alteration (11.8 months; 95% CI: 10.1–13.5) (Figure 2).[15] In addition, the results of the MOSCATO 01 trial[16] in patients with advanced disease refractory to standard treatment showed that matching patients to targeted therapy using high-throughput genomic analyses was associated with improved PFS.[16]

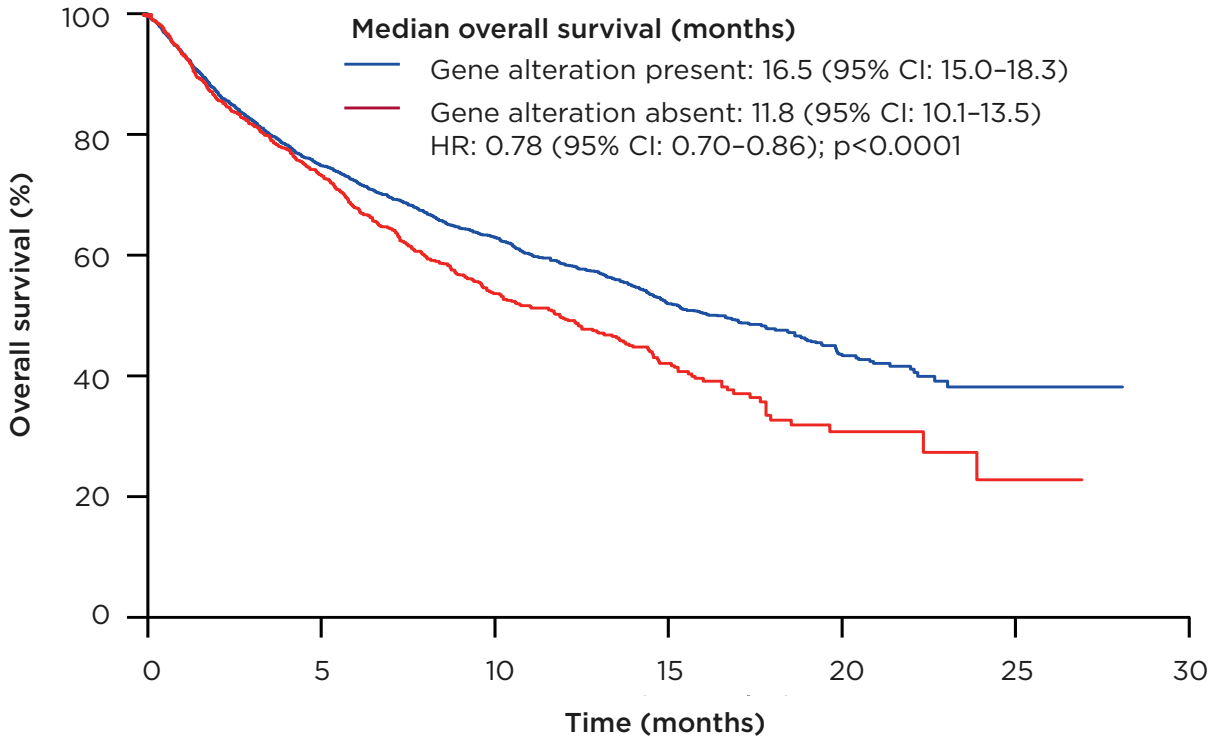


Figure 2: Median overall survival of patients who underwent molecular analysis for genomic alterations.
CI: confidence interval; HR: hazard ratio.
Adapted from Barlesi et al.[15]

Guidelines for metastatic NSCLC, including the American Society of Clinical Oncology (ASCO)/ International Association for the Study of Lung Cancer (IASLC) molecular testing guidelines and the ESMO clinical practice guidelines, clearly highlight the need for testing molecular alterations associated with targeted therapies approved by the U.S. Food and Drug Administration (FDA). These include *ALK*, *EGFR*, *ROS1,* and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF)*.[17,18] The recent National Comprehensive Cancer Network (NCCN) guidelines also recommend testing for mesenchymal epithelial transition factor (*MET*) exon 14 skipping and rearranged during transfection (*RET*) alterations.[19]

There are a wide range of possible testing solutions to identify molecular alterations. Immunohistochemistry and fluorescence *in situ* hybridisation are both approved and widely utilised methods for testing *ALK* and *ROS1* rearrangements. The advent of high-throughput next-generation sequencing (NGS), which allows simultaneous assessment of multiple genes, has the potential to revolutionise the field. The French National Cancer Institute (INCa) has supported the implementation of a national network of 28 hospital molecular genetics platforms. Data from this network show that >18,000 patients were screened using an NGS panel in 2017.[20] Commercially available genomic profiling solutions are also available, including the tissue-based FoundationOne® CDx (Foundation Medicine, Cambridge, Massachusetts, USA), which can detect >300 gene mutations as well as selected gene rearrangements, including *EGFR* and *ALK*.[21] The French Plan for Genomic Medicine 2025 (Inserm, Paris, France), launched in 2016, includes two high-throughput sequencing platforms aiming to offer centralised and efficient whole-exome sequencing data to clinicians. This may provide important data for those patients in whom alterations cannot be identified using commercial solutions.

Choosing the best testing technique can be a complex process with multiple determinants. Turnaround time is an important factor in

patients with advanced disease. The results from immunohistochemistry can be available within 48 hours, whereas NGS may take up to 1–2 weeks,[22,23] although timing may be region-dependent. The cost of the test also plays an important role. Commercially available solutions may be more expensive; however, the number of alterations that need to be tested is a key consideration. Several studies have demonstrated that upfront NGS is a more cost-effective method when testing for multiple molecular alterations compared with sequential testing strategies.[24,25] Several randomised studies are currently ongoing, including the SAFIR02 and PROFILER 02 studies, to investigate the added value of a large molecular profiling panel compared with a more limited panel. It is important to consider the availability of therapeutic solutions to target drivers and to keep in mind that the presence of a target does not necessarily lead to targeted treatment. In the MOSCATO 01 study, only 19% of patients went on to receive a targeted therapy.[16] The approval and reimbursement status of treatments is also a key factor, although certain investigational products may be available through expanded access programmes or clinical trials.

The site of tissue acquisition is also significant. Testing for genomic alterations in cell-free DNA (cfDNA) from blood samples presents a more practical option for patients than tissue sampling and may enable clinicians to offer more effective personalised treatments. Commercial liquid biopsy tests are available, including FoundationOne Liquid (Foundation Medicine) and Guardant360® (Guardant Health, Redwood City, California, USA), which can analyse >70 genomic alterations in blood samples.[22,26] Noninferiority of comprehensive cfDNA testing compared with tissue genotyping in patients with advanced NSCLC has been demonstrated, with cfDNA showing >98% concordance.[27] In addition, liquid biopsy had a faster turnaround time of 9 days compared with 15 days for tissue genotyping.[27] BFAST[28] was the first prospective study to demonstrate the clinical utility of blood-based NGS testing to identify patients who were *ALK*-positive and select targeted therapy.[28] This raises the potential for NGS from liquid biopsy samples as the future for testing in patients with NSCLC.

Treatment Selection in *ALK*-Positive Metastatic NSCLC: Optimising Outcomes

Doctor Maximilian Hochmair

Historically, the treatment of lung cancer was simple, owing to limited treatment options; however, the survival rate for patients was low. An increasing number of targeted treatment options are now available or under investigation, including for patients with molecular alterations in *EGFR*, *ROS1*, *BRAF*, *NTRK*, *MET*, *HER2*, and *RET*. This has led to a paradigm shift away from chemotherapy as the primary first-line treatment option for patients with NSCLC. As the number of options available for treating patients with *ALK*-positive NSCLC increases, treatment selection, strategy, and sequencing to optimise patient outcomes are of primary importance.

Personalisation of treatment in patients with *ALK*-positive NSCLC is vital. *ALK* rearrangements are associated with a lower response to immune checkpoint inhibitors. A retrospective analysis of 58 patients demonstrated an objective response rate (ORR) of 3.6% in patients with *EGFR*-mutated or *ALK*-positive NSCLC treated with programmed cell death protein 1 or programmed death-ligand 1 inhibitors, compared with an ORR of 23.3% for patients with *EGFR* wild-type or *ALK*-negative NSCLC (p=0.053).[29] Therefore, it is important to wait for oncogenic testing results before starting first-line treatment. Four different ALK inhibitors are now recommended by the ESMO and NCCN clinical practice guidelines for first-line treatment of *ALK*-positive metastatic NSCLC: crizotinib, ceritinib, alectinib, and brigatinib.[18,19]

Crizotinib was the first ALK inhibitor approved for the treatment of *ALK*-positive NSCLC, and the PROFILE 1014 trial[30] was the first Phase III study to demonstrate the efficacy of an ALK inhibitor compared with chemotherapy in the first-line setting. Median PFS for crizotinib, assessed by the Independent Review Committee (IRC), was 10.9 months (95% CI: 8.3–13.9) compared with 7.0 months (95% CI: 6.8–8.2) for chemotherapy. Crizotinib-associated adverse events (AE) included vision disorders, diarrhoea, nausea, and oedema.[30]

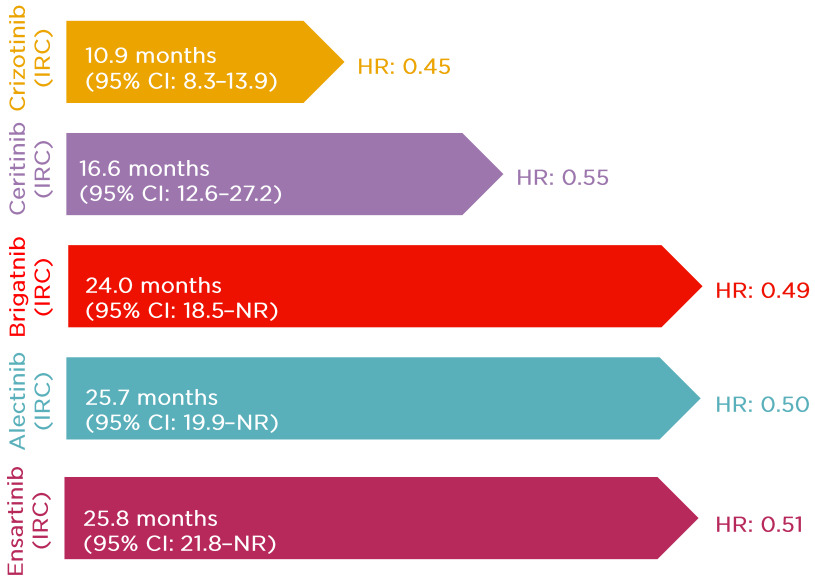
Subsequently, several second-generation ALK inhibitors have been developed. The ASCEND-4 Phase III trial[31] comparing ceritinib with chemotherapy demonstrated a median IRC-assessed PFS of 16.6 months (95% CI: 12.6–27.2) for ceritinib and 8.1 months (95% CI: 5.8–11.1) for chemotherapy. Ceritinib was associated with gastrointestinal side effects, including nausea and diarrhoea.[31] The ALEX[32,33] and ALTA-1L[34] trials provided a head-to-head comparison of the first-generation crizotinib with the second-generation inhibitors alectinib and brigatinib, respectively. The ALEX trial showed a median IRC-assessed PFS of 25.7 months (95% CI: 19.9–not reached [NR]) for alectinib compared with 10.4 months (95% CI: 7.7–14.6) for crizotinib[32] (investigator-assessed PFS with alectinib was 34.8 months [95% CI: 17.7–NR] and with crizotinib was 10.9 months [95% CI: 9.1–12.9])[33] in patients with no prior treatment for advanced disease.[32] Relevant alectinib-related AE included liver enzyme elevation and myalgia.[33] In ALTA-1L, the median IRC-assessed PFS for brigatinib was 24.0 months (95% CI: 18.5–NR) compared with 11.0 months (95% CI: 9.2–12.9) for crizotinib (investigator-assessed PFS with brigatinib was 29.4 months [95% CI: 21.2–NR] and with crizotinib was 9.2 months [95% CI: 7.4–12.9]) in patients with no prior ALK inhibitor treatment and, at most, one prior systemic therapy.[34] Brigatinib-associated AE included increased creatine kinase levels, cough, and hypertension. Exploratory analyses from the ALTA-1L trial also evaluated the impact of *EML4–ALK* fusion variant status on the clinical efficacy of brigatinib compared with crizotinib. These analyses found that patients with *EML4–ALK* variant 3 had worse PFS regardless of treatment. Brigatinib was associated with superior PFS to crizotinib regardless of *ALK* fusion variant status.[9] Data from the eXalt3 randomised Phase III[35] trial of ensartinib were recently presented at the IASLC World Conference on Lung Cancer (WCLC), demonstrating a median IRC-assessed PFS of 25.8 months (95% CI: 21.8–NR) for ensartinib compared with 12.7 months (95% CI: 9.2–6.6) for crizotinib. Low-grade rash and transaminitis were the most frequent ensartinib-related AE.[35]

Unfortunately, relapse and disease progression in patients with advanced NSCLC on targeted therapy is unavoidable owing to the development of *ALK* resistance mutations or bypass signaling.[36] Rebiopsy of tissue following ALK inhibitor failure is an option, although guidelines do not currently recommend this as mandatory for treatment decisions.[18,37] The frequency and range of *ALK* resistance mutations differs depending on the specific ALK inhibitor.[36] The third-generation ALK inhibitor lorlatinib has been shown to have strong efficacy in patients who have received prior treatment with a second-generation ALK inhibitor,[38] and the presence of *ALK* resistance mutations has been shown to be associated with sensitivity to lorlatinib in patient-derived cell lines.[36] In contrast, cell lines without *ALK* resistance mutations were resistant to lorlatinib. This may allow clinicians to personalise treatment sequencing strategies on the basis of a specific patient's *ALK* resistance mutation status.[36] Following this symposium, results of the Phase III CROWN trial,[39] comparing lorlatinib with crizotinib in first-line treatment, were presented at ESMO 2020. These data showed a 72% improvement in IRC-assessed PFS in patients treated with lorlatinib compared with crizotinib (hazard ratio [HR]: 0.28), with a median follow-up for PFS of 18.3 months (95% CI: 16.4–20.1) for lorlatinib and 14.8 months (95% CI: 12.8–18.4) for crizotinib. The majority of lorlatinib-related AE were laboratory abnormalities.[39]

Reaching the Sanctuary Site: Options for Patients with *ALK*-Positive NSCLC with Brain Metastases

Doctor Rosario García Campelo

The introduction of the first-generation ALK inhibitor crizotinib changed the treatment paradigm in *ALK*-positive NSCLC. The ALEX, ALTA-1L, and eXalt3 trials have all shown improved median PFS and duration of response for second-generation ALK inhibitors compared with first-generation treatment (Figure 3).[30-35,40-43] However, the site of disease metastases continues to be an important factor when making treatment decisions for these patients.



	Most frequent serious adverse events reported
Crizotinib	Dyspnoea, pulmonary embolism
Ceritinib	Pneumonia, pleural effusion, vomiting, nausea, dyspnoea, hyperglycaemia, increased aspartate aminotransferase, lung infection, pericardial effusion
Brigatinib	Pneumonia, interstitial lung disease/pneumonitis, pyrexia, dyspnoea, pulmonary embolism, asthenia
Alectinib	Pneumonia, renal impairment (reported in ≥2% patients)

Figure 3: Efficacy and safety of anaplastic lymphoma kinase inhibitors in the first-line setting.[30-35,40-43]

Unadjusted, indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.

CI: confidence interval; HR: hazard ratio; IRC: Independent Review Committee; NR: not reached.

The occurrence of CNS metastases is common in patients with advanced NSCLC, and approximately 30% of patients with *ALK*-positive Stage IV NSCLC have brain metastases at baseline.[44] In addition, patients with *ALK*-positive NSCLC are at higher risk of developing brain metastases during the course of disease.[45] The cumulative incidence of brain metastases was shown to be significantly higher for *ALK*-positive NSCLC compared with *ROS1*-positive cancers (p=0.0039).[46] Brain metastases also have a negative impact on patient quality of life, with patients with NSCLC and brain metastases reporting a significantly lower general health status questionnaire (EQ-5D) score (0.52; p≤0.05) than patients with metastases at other sites, including the liver (0.71) and adrenal glands (0.83).[47] Management of *ALK*-positive NSCLC in patients with CNS metastases is also associated with higher costs. A recent study showed an increase in annual costs of approximately €15,000 compared with the management of patients without CNS metastases.[48] Whole brain radiotherapy (WBRT) is often used to treat patients with NSCLC and symptomatic brain metastases. However, several randomised clinical trials have suggested that WBRT may be associated with cognitive decline.[49-51] Incorporating ALK inhibitors into first-line treatment may allow WBRT to be postponed, deferring potential long-term neurocognitive impairment to later in the disease course.

The concentration of crizotinib is lower in cerebrospinal fluid than in plasma. In a case example from a patient with *ALK*-positive NSCLC with intracranial progression, the cerebrospinal fluid-to-plasma crizotinib ratio was 0.0026, signifying poor blood–brain barrier penetration. This allows the brain to act as a 'sanctuary site' for tumour growth.[13,52] Novel second-generation ALK inhibitors have the potential for improved CNS efficacy. Results from the ALEX study demonstrated an ORR of 81% (95% CI: 58–95) for alectinib compared with 50% (95% CI: 28–72) for crizotinib in patients with measurable CNS lesions at baseline.[32] The median investigator-assessed PFS in patients with CNS metastases at baseline was 25.4 months for alectinib compared with 7.4 months for crizotinib, and the HR for PFS with any brain metastases was 0.37.[53] In the ALTA-1L trial the confirmed intracranial ORR was 78% (95% CI: 52–94) for brigatinib compared with 26% (95% CI: 10–48) for crizotinib. The median IRC-assessed PFS in patients with any brain metastases at baseline was 24.0 months

(95% CI: 18.4–NR) for brigatinib compared with 5.6 months (95% CI: 3.8–9.4) for crizotinib. The HR for PFS with any brain metastases was 0.25.[34] There are currently limited data from the eXalt3 study on the impact of ensartinib on brain metastases; however, initial results indicated an IRC-assessed confirmed intracranial ORR of 64% for patients treated with ensartinib compared with 21% for patients treated with crizotinib.[35] Recent data presented from the CROWN study showed an IRC-assessed intracranial ORR of 82% (95% CI: 57–96) for lorlatinib compared with 23% (95% CI: 5–54) for crizotinib in patients with measurable brain metastases at baseline.[39] These data indicated that there was a clear benefit of using second- or third-generation ALK inhibitors in patients with brain metastases.

Patients with NSCLC are often highly symptomatic[54] and are exposed to targeted therapy-associated toxicities over long periods of time.[55] Patient-reported outcome measures provide a more direct method of reporting outcomes that are relevant to the patient, including symptom and treatment burden and health-related quality of life (HRQoL).[56] Several clinical trials have reported data on patient HRQoL. During the ALEX trial, no significant difference in the European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire (QLQ-C30) score or the lung cancer supplement to the QLQ-C30 (QLQ-LC13) score was reported for patients treated with alectinib compared with those treated with crizotinib.[57] Conversely, the ALTA-1L trial demonstrated a significant improvement in HRQoL for patients treated with brigatinib compared with crizotinib. The median time-to-worsening HRQoL was 26.7 months for patients treated with brigatinib compared with 8.3 months for those treated with crizotinib, and brigatinib significantly prolonged the duration of improvement in HRQoL ($p<0.001$) compared with crizotinib. In addition, brigatinib demonstrated a numerical improvement in all functional domains, with substantial improvement in cognitive functioning scores (estimated difference: 4.9 [95% CI: 1.7–8.1]).[34,58] Targeted precision-based treatment for patients with advanced NSCLC has come a long way over the last decade. However, there are still a number of challenges that need to be overcome to continue improving patient outcomes and to enable the delivery of truly personalised care.

Conclusions

Upfront testing for molecular alterations is essential to ensure personalised treatment for patients with NSCLC, and NGS, which provides a cost-effective solution for analysing a large number of genes in a single panel, should become the widely adopted standard. Various effective ALK inhibitors are recommended for the first-line treatment of *ALK*-positive metastatic NSCLC, including crizotinib, ceritinib, alectinib, and brigatinib. However, multiple mechanisms ultimately drive resistance to ALK inhibitors, leading to disease progression. Some treatments may be able to overcome specific resistance mutations; however, rebiopsy at progression may be required to help guide treatment decisions in evolving disease. CNS metastases are frequent in patients with *ALK*-positive NSCLC and are associated with a negative prognosis and poorer HRQoL. Poor penetration of the blood–brain barrier by crizotinib may allow the CNS to act as a sanctuary site for tumour growth. Second-generation ALK inhibitors are a potent first-line treatment option for patients with *ALK*-positive NSCLC with brain metastases. Despite numerous advances in available therapeutics, optimal treatment sequencing remains an unmet need in patients with *ALK*-positive NSCLC, and the availability of third-generation ALK inhibitors may impact this.

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Abstract Reviews

Sharing insights from abstracts presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020, global oncologists and cancer researchers have provided these summaries of their fascinating studies.

Breast Cancer in Young Females: Real-World Data to Fill the Gap

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Keywords: Breast cancer (BC), real-world data, young females.

Citation: EMJ Oncol. 2020;8[1]:43-45. Abstract Review No. AR1.

BACKGROUND

Breast cancer (BC) is the most common cause of cancer-related deaths in females under 45 years. It has been reported as a more aggressive disease, requires more aggressive treatment, has a poorer survival rate, and leads to more serious psychosocial consequences. Evidence about the epidemiology, biologic behaviours, and treatment strategies are needed to help clinicians understand this disease. The young female population is under-represented in clinical studies and therefore, real-world data could be useful in broadening knowledge and aiding management of patients.

METHODS

The authors conducted a retrospective study, selecting patients aged ≤45 years with BC diagnosis in the Breast Cancer Unit of Puerta de Hierro Hospital, Majadahonda, Spain between 2014 and 2019. Epidemiological, clinical, and pathological information was collected. The aim was to understand the characteristics of the breast cancer in young females (BCYF) patient population and to assess the quality of care of the diagnostics and treatments.

RESULTS

A total of 348 patients with diagnosis of BC were selected; median age was 41 years (range: 38–44 years) with the majority (61%) aged 41–44 years.

Clinical and epidemiological characteristics of the patient cohort are described below: 79.9% of the patients had a previous pregnancy and almost half (49.0%) breastfed. Of the patients studied, 52% had never smoked, with this percentage being higher in the <35 years subgroup (68.8%). Regarding oral contraceptive intake, 44.3% of patients had used them at some point in their life, which increased to 54.6% in the <35 years subgroup. Median BMI was 22.8. In relation to family history, 32.0% had a history of breast cancer and 4.6% had a history of ovarian cancer. A *BRCA 1/2* mutation was carried by 7.4% of the patients; this percentage reached 21.1% in the <35 years subgroup.

Table 1: Clinical and pathological characteristics of breast cancer in the young females' cohort.

	≤35 years	36–40 years	≥41 years	All
n (%)	33 (9%)	103 (30%)	212 (61%)	348
Pregnancy	57.6%	75.8%	85.2%	79.9%
Breast feeding	37.5%	43.4%	52.9%	49.0%
Never smoker	68.8%	55.0%	48.1%	52.0%
Oral contraceptives	54.6%	35.9%	46.2%	44.3%
BMI	21.5	22.7	23.6	22.8
FA breast cancer	36.4%	28.2%	32.6%	32.0%
FA ovary cancer	12.1%	3.9%	3.8%	4.6%
BRCA1/2+	12.1%	8.7%	6.1%	7.4%
Histology				
Ductal	93.9%	86.4%	82.1%	84.5%
Lobular	3.1%	3.9%	10.9%	8.3%
Other	3.0%	9.7%	7%	7.2%
Stage				
I	33.3%	36.4%	40.1%	38.1%
II	46.7%	37.5%	37.4%	38.4%
III	16.7%	22.7%	16.6%	18.6%
IV	3.3%	3.4%	5.9%	4.9%
Axillary staging +	43.3%	46.2%	42.5%	43.8%
Subtypes				
TN	12.9%	7.2%	13.1%	11.2%
HR+ HER2-	61.3%	75.3%	68.1%	69.5%
HR+ HER2+	22.6%	11.3%	14.6%	14.3%
HR- HER2+	3.2%	6.2%	4.2%	5.0%

FA: fibroadenoma; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; TN: triple negative.

Analysis of the histological characteristics revealed results as follows: the most common histological type was ductal (84.5%) followed by lobular (8.3%), with no significant differences between age subgroups. The hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) subtype was the most prevalent (69.5%), followed by HR+/HER2+ (14.3%); 11.2% were triple-negative and only 5% were HER2+/HR-. Most of the patients presented at Stage I or II (38.1% and 38.4%, respectively); 18.6% presented at Stage III and 4.9% were metastatic at diagnosis (data consistent with literature). In relation to axillary staging, 43.8% were positive at diagnosis and this was similar between the three subgroups.

CONCLUSIONS

In our BCYF cohort, no association was found between age groups and clinical or pathological characteristics, which differs from other previously published studies reporting a poorer prognosis in young females.

The cohort distribution, per stages and subtypes, was similar to the global population described in the medical literature. This suggests the need for a detailed BCYF analysis to find evidence for the specific management of this population, and to prevent age-related disparities in BC care.

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Trends in Breast Cancer Mortality Between 2001 and 2017: An Observational Study in Europe and the UK

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Keywords: Breast cancer, Europe, trends, World Health Organization (WHO) Mortality Database.

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BACKGROUND

The global incidence of breast cancer was 1.96 million cases in 2017, making it the third highest incident cancer.[1] In Europe, breast cancer is the second most common cancer, accounting for

11.6% of cancer cases in males and females.[2] Mammography screening programmes reduce the rate of advanced breast cancer,[3] with some estimating a mortality reduction of 26% in Europe.[4] Male breast cancer is rare: the 1993 incidence in Europe was 1 in 100,000.[5] In the USA, male breast cancer has been rising from 0.96 cases per 100,000 males in 1975 to 1.32 per 100,000 in 2017.[6] Because of the availability of enhanced treatment options, as well as improved detection, breast cancer mortality is falling in most European countries.[7,8] Here, the authors present trends in breast cancer mortality in both males and females across Europe.

MATERIALS AND METHODS

The World Health Organization (WHO) Mortality Database was utilised to extract breast cancer mortality data, based on the International Classification of Diseases 10th revision (ICD 10), from 2001 to 2017. Twenty-four member states of the European Union (EU) and the UK were selected as a defined group for analysis. Crude mortality rates were dichotomised by sex and reported by year. The age-standardised death rates (ASDR) per 100,000 population using the World Standard Population were computed. Breast cancer mortality trends were described using Joinpoint regression analysis. In brief, Joinpoint analysis assesses the overall trends in mortality, initially with no Joinpoints, and tests for significant changes in the model with the sequential addition of Joinpoints where there are significant changes in the slope of the line. As the data source was a publically available database with no patient identifiable information, institutional review board approval was not necessary for the study.

RESULTS

Of the 25 countries analysed, five countries had data until 2017, 12 until 2016, six until 2015, and one until 2014. It was observed that mortality in females was down-trending in all countries except Croatia, France, and Poland. Among all the nations studied, most recently (2016) Croatia had the highest ASDR (19.29/100,000), whereas the lowest mortality was in Spain (12.8/100,000) (Supplementary Figure 1). Estonia had the highest estimated annual percentage change (EAPC) in female breast mortality (-9.3%). Denmark had the highest change in ASDR (+28.0% in 2000 versus +16.7% in 2015). It was observed that breast cancer mortality in males decreased in 18 countries. Among all the nations studied, Bulgaria had the highest male breast cancer mortality (0.54/100,000) in the year 2015, whereas Denmark had the greatest EAPC (-27.5%) for the years 2012–2015.

CONCLUSION

Across the 17-year study period, a decrease in breast cancer mortality in females in the majority of the countries was observed. There was substantial variation between the European nations. Breast cancer mortality in males continues to increase in a number of European countries.

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Identifying the Best Ki67 Cut-Off for Determining Luminal Breast Cancer Subtypes Using Immunohistochemical Analysis and PAM50 Genomic Classification

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Disclosure: The others have declared no conflicts of interest.

Keywords: Breast cancer (BC), immunohistochemistry (IHC), luminal, PAM50.

Citation: EMJ Oncol. 2020;8[1]:47-48. Abstract Review No. AR3.

BACKGROUND AND AIMS

Gene expression profiling has a significant impact on understanding the biology of breast cancer (BC). Over the past 15 years, four main intrinsic molecular subtypes of BC have been identified.[1-3] At the 13th Saint Gallen International Breast Cancer Consensus, a surrogate classification of BC molecular subtypes by immunohistochemistry (IHC) was established.[4] The most controversial point was the difference between the luminal A and luminal B subtypes according to the Ki67 values.[5] Commonly, 14% is the Ki67 cut-off that has been established for differentiating BC subtypes; however, in later studies this value has been questioned and a cut-off of 20% has been proposed.[6] This study aimed to analyse the correlation between the surrogate BC subtypes using IHC and PAM50 gene expression assay,[7-10] considering Ki67 as an independent factor to identify the best Ki67 cut-off.

MATERIALS AND METHODS

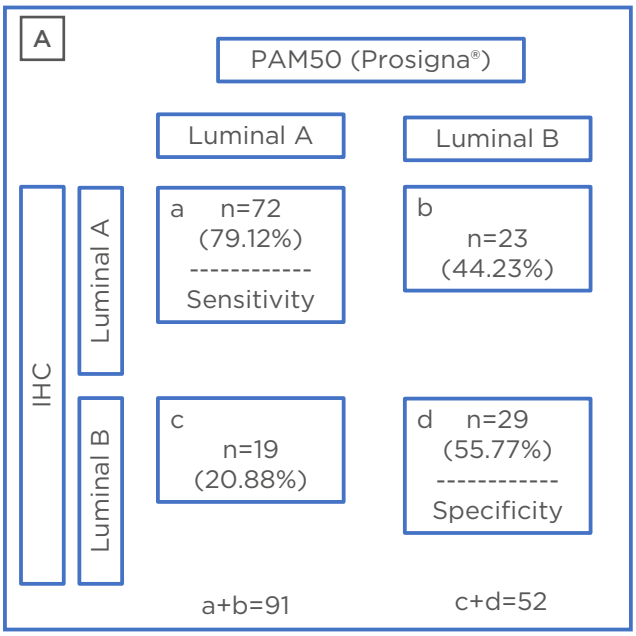
Included in the study were females diagnosed between 2015 and 2020 with early stage luminal BC whose samples underwent genomic testing using PAM50/Prosigna® (NanoString Technologies, Seattle, Washington, USA). A total of 143 samples were analysed at a single institution. The IHC subtypes were classified using two independent Ki67 cut-offs, 14% and 20%, and these were compared to the subtypes identified by PAM50.

RESULTS

Using the Ki67 cut-off >14% (Figure 1A), a correlation of 70.6% with a sensitivity of 79.1% and a specificity of 55.8% was observed, as well as a positive predictive value of 75.8% and a negative predictive value of 60.4%. By modifying the Ki67 cut-off to be >20% (Figure 1B), the percentage of well-classified tumours as determined by IHC was 76.2%, improving the agreement by 6.2%. The sensitivity was 93.4%, but the specificity was 46.1%. The positive predictive value was 75.2% and the negative predictive value was 80.0%, which suggests that IHC has a high probability of diagnosing luminal A and luminal B.

CONCLUSIONS

Based on the results from this study, the authors demonstrated that modifying the Ki67 cut-off to >20% provides a better surrogate classification by IHC and a higher sensitivity for classifying the luminal subtypes than ≥14%. The authors propose that the Ki67 cut-off should be globally modified to >20% as an independent factor; however, due to the low specificity, other factors, such as progesterone receptor expression, should be considered.



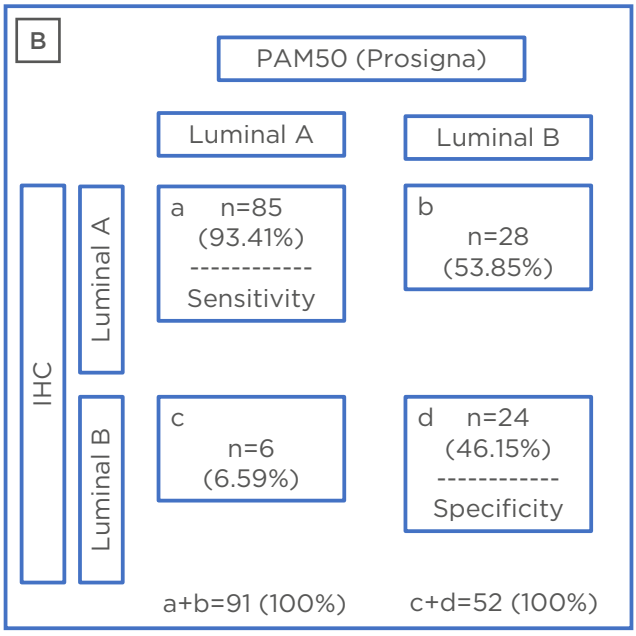


Figure 1: Concordance between immunohistochemistry and PAM50 using two different cut-off values.

A) Concordance between IHC (Ki67 cut-off 14%) and PAM50. **B**) Concordance between IHC (Ki67 cut-off 20%) and PAM50.

IHC: immunohistochemistry.

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Prognostic Value of Compartmental Spatial Analysis of Tumour-Infiltrating Lymphocytes in Triple-Negative Breast Cancer

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Keywords: Biomarkers, central tumour (CT), invasive margin (IM), triple-negative breast cancer, tumour-infiltrating lymphocytes (TIL).

Citation: EMJ Oncol. 2020;8[1]:49-50. Abstract Review No. AR4.

INTRODUCTION

Analyses on tumour-infiltrating lymphocytes (TIL) to date have mainly evaluated stromal TIL and possibly intratumoural TIL. The authors of this study were not able to find any analyses in which TIL were evaluated spatially, by stromal or intratumoural categories, separately by compartments of central tumour and invasive margin, nor any with prognostic values for the evaluation of this arising biomarker.

METHODS

The authors retrospectively analysed consecutive samples of 152 patients with early triple-negative breast cancer (TNBC) treated at an institution in Croatia from 2009–2012. TIL were assessed morphologically by haematoxylin and eosin stain using standard formalin-fixed paraffin-embedded samples according to the International TILs Working Group recommendation for the evaluation of TIL. Stromal TIL (sTIL) and intratumoural TIL (iTIL) were assessed spatially in compartments of central tumour (CT) and invasive margin (IM).[1,2]

RESULTS

Spatial analysis revealed that the most prevalent TIL were sTIL at IM, with median intensity of 30%, and as many as 85.5% of patients with intensity ≥10%. The rarest TIL and with lowest intensity were iTIL in CT, with a median intensity of 1.0% and only 23.0% of patients with ≥10% intensity. One-quarter of patients had TIL >50% in any of the evaluated compartments. There was a statistically significant correlation between sTIL and iTIL in the presence of TIL in all four evaluated compartments; the correlation was stronger among sTIL and iTIL in CT and sTIL and iTIL at IM, than between the two separate spatial compartments. In a bivariable analysis, all TIL indicators were statistically significantly associated with longer disease-free and overall survival. Patients with TIL ≥10% in all four evaluated compartments (sTIL and iTIL, in CT and IM) were shown to have statistically significantly less risk of disease recurrence or death, compared to those with TIL <10%. After adjustment for potential confounders using Cox proportional hazard regression, significant predictors of overall survival were sTIL (p=0.007), iTIL if present in ≥10% (p=0.022), IM TIL (p=0.002), sTIL at IM (p=0.001), and iTIL at IM if present in ≥10% (p=0.036).

DISCUSSION AND CONCLUSION

Compartmental morphological analysis of TIL reveals frequent intermediate to high density of TIL content on IM and their overall statistically significant prognostic impact. This draws attention to this neglected tumoural

compartment and directs the question towards the different biology, cell composition, and role of each tumour morphological compartment, a phenomenon that should definitely be further explored.

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Table 1: Multivariable analysis of correlation of tumour-infiltrating lymphocytes and tumour-infiltrating lymphocytes ≥10% by compartments (stromal tumour-infiltrating lymphocytes and intratumoural tumour-infiltrating lymphocytes, in central tumour and at invasive margin) to 5-year overall survival (n=152).

	OR	(95% CI)	p
sTIL CT	**1.03**	**(1.00–1.07)**	**0.065**
sTIL CT ≥10%			
No	1	-	-
Yes	2.74	(0.98–7.68)	0.055
iTIL CT	**1.03**	**(0.97–1.08)**	**0.366**
iTIL CT ≥10%			
No	1	-	-
Yes	14.05	(1.54–128.33)	0.019
sTIL IM	**1.04**	**(1.01–1.07)**	**0.015**
sTIL IM ≥10%			
No	1	-	-
Yes	1.35	(0.33–5.46)	0.677
iTIL IM	**1.05**	**(0.99–1.11)**	**0.103**
iTIL IM ≥10%			
No	1	-	-
Yes	3.76	(1.09–13.03)	0.036

Adjusted for age, comorbidities*, menopausal status, histology, tumour size, nodal involvement, stage, grade, Ki-67, surgery, and chemotherapy†.

*Data missing for six (3.9%) patients, supplied as if no comorbidities.

†Data missing for four (2.6%) patients, supplied as if no adjuvant chemotherapy.

CI: confidence interval; CT: central tumour; IM: invasive margin; iTIL: intratumoural tumour-infiltrating lymphocytes; OR: odds ratio for 5 years overall survival; p: statistical significance by multivariable binary logistic regression; sTIL: stromal tumour-infiltrating lymphocytes.

Long-term Survival Following Photodynamic Therapy for Glioma Depending on MGMT

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Keywords: Glioma, malignant, MGMT, neuro-oncology, photodynamic therapy (PDT), survival.

Citation: EMJ Oncol. 2020;8[1]:51-52. Abstract Review No. AR5.

BACKGROUND AND AIMS

The gross total resection of a glial tumour is the aim of complex treatment and gives greater efficiency of the subsequent treatment stages, defining patients' longevity. The impossibility of radical surgical treatment, short period of recurrency, and average longevity dictates the search for new treatment methods. Intraoperative photodynamic therapy (PDT) may lead to an increase in totality of tumour resection.[1-4]

The aim of the study was to increase the survival rate and duration of the relapse-free period in patients with malignant brain gliomas by using PDT as part of complex treatment.[5-7]

MATERIALS AND METHODS

The study included patients with glial brain tumours of supratentorial localisation with a high degree of malignancy (Grade IV glioblastoma) undergoing treatment at the Russian Neurosurgical Research Institute. The study group included 50 patients and there were 50 patients in the control group. Patients in the study group were injected intravenously 1.5 hours before the operation with a photosensitiser of the chlorine e6 group (2nd generation). After resection of the tumours, a PDT session was performed using a Latus-2.5 laser (Lotus Laser Systems, Basildon, UK) as a radiation source. The average dose was 180 J/cm^2. In the postoperative period, patients in both groups received adjuvant therapy (chemotherapy and radiation therapy).[8,9] Long-term results (inter-recurrence period and overall survival) were evaluated depending on the results of immunohistochemical studies (the presence of IDH mutation and MGMT).

RESULTS

The median survival for patients with Grade IV gliomas (MGMT+) using PDT was 23.3±4.1 months; in the control group (without PDT) the median survival was 16.5±3.3 months (p=0.0002). The median survival for patients with Grade IV gliomas (MGMT-) using PDT was 18.2±3.5 months; in the control group (without PDT) this was 11.2±2.4 months (p=0.0001). The median duration of the inter-relapse period for patients with Grade IV gliomas (MGMT+) was 13.5±2.3 months in the study group and 9.1±1.4 months in the control group (p=0.0003). The median duration of the inter-relapse period for patients with Grade IV gliomas (MGMT-) was 10.1±2.2 months in the study group and 7.0±1.1 months in the control group (p=0.0001).

CONCLUSION

PDT increased the median of the inter-relapse period and life expectancy in patients with malignant gliomas. In patients expressing MGMT, the magnitude of the inter-relapse period and life expectancy was significantly higher in the group receiving PDT.

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Long-Term Follow-Up of Patients With Nodular Lymphocyte Predominant Hodgkin Lymphoma: A Report From the Spanish Lymphoma Oncology Group

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Hodgkin lymphoma (HL), long-term follow-up, lymphocyte predominant.

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BACKGROUND

Nodular lymphocytic predominance Hodgkin lymphoma (NLPHL) is a very uncommon subtype of Hodgkin lymphoma (HL), representing approximately 5% of all HL cases, with an incidence of 0.3/100,000 cases per year and with unique characteristics that distinguish it from classic HL.[1] The tumour cell that defines it, which the presence of is a requirement for diagnosis, is a malignant cell that was reclassified by the World Health Organization (WHO) 2008 as predominantly lymphocytic cell, and is also known by the more descriptive term of 'popcorn' cells.[2]

Table 1: Baseline characteristics and survival rates.

	n (%)	Log-rank
Gender		-
Male	65 (76.5)	
Female	20 (23.5)	
Age at diagnosis (years)		-
Mean	37	
Median (25–75%)	35 (23–48)	
Range	8–88	
Subtype		-
Ganglionar	61(71.8)	
Extraganglionar	4 (4.7)	
Missing	20 (23.5)	
Stage at diagnosis		-
I	39 (46.4)	
II	34 (40.5)	
III	7 (8.3)	
IV	4 (4.8)	
ECOG		-
0	67 (80.7)	
1	14 (16.9)	
2	2 (2.3)	
Primary treatment		-
No treatment	4 (3.5)	
Chemotherapy only	15 (44.7)	
Radiotherapy only	43 (21.0)	
Chemotherapy and radiotherapy	23 (27.1)	
Follow-up time (years)		-
Mean	16	
Median (25–75%)	14.5 (5.5–27.2)	
Range	0–44	
10-year overall survival	92.9%	0.142
Males	90.8%	
Females	100.0%	
10-year specific survival (lymphoma survival)	98.8%	0.560
Males	98.5%	
Females	100.0%	
20-year overall survival	81.2%	0.208
Males	78.5%	
Females	90.0%	
20-year specific survival (lymphoma survival)	96.5%	0.298
Males	95.4%	
Females	100.0%	

Given its low frequency, it becomes difficult to perform randomised studies, with the accumulated experience of academic groups being the main source of relevant information for the management of these patients.[3]

METHODS

In the study, 85 patients recruited by the Spanish Lymphoma Study Group (GOTEL) from 12 different hospitals and diagnosed between January 1970 and December 2015 were retrospectively analysed in order to describe their clinical and sociodemographic characteristics, survival rates, and causes of death.

RESULTS

The mean age of the study group was 37 years (range: 18–88), with 76.5% being male. Baseline characteristics are summarised in Table 1. Patients received different modalities of first-line treatment; the mean time to relapse was 3 years and 47% presented relapses beyond 5 years (higher probability in Stage IV; p<0.001). A total of 31% of tumour relapses were found, 77% of which were in 3/4 (75%) patients who did not receive any type of treatment, 7/15 (47%) that received only chemotherapy treatment, 12/43 (27%) who received radiotherapy, and 6/23 (26%) who received both chemotherapy and radiotherapy (26%).

The median follow-up was 16 years, with a 10-year overall survive of 92.9% and 81.2% at 20 years (Table 1). The overall lymphoma-specific survival was 98.8% at 10 years and 96.5% at 20 years, without significant differences between sex. It was evaluated whether survival differed depending on the time of treatment, before or after 1990; nonsignificant differences were found.

Of the 22 patients who had died by the time of analysis, only three died because of the primary lymphoma. There were five patients who developed a second tumour: two breast cancer (at 19 and 26 years from initial diagnosis), two head and neck cancer (at 7 and 5 years), one leukaemia (10 years from diagnosis). There were no patients who developed transformation to another more aggressive lymphoma.

CONCLUSIONS

The low prevalence of NLPHL makes the development of prospective randomised studies very difficult. The authors' series is one of the longest follow-ups of NLPHL published, including extensive clinical information and specific causes of death. This work confirms the excellent prognosis of NLPHL, with high cause-specific survival rates and a very infrequent rate of NLPHL transformation. Given the high cure rates, treatment should be selected considering toxicity and side effects and could be adapted with early-stage radiation therapy when possible.

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Evolution of Adjuvant Therapy in Radically Resected Carcinoma Gallbladder Over a Decade: A Real-World Experience from a Regional Cancer Centre

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Keywords: Adjuvant therapy, chemoradiation, chemotherapy (CT), gallbladder cancer (GBC).

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INTRODUCTION

Because of the rarity and high mortality of gallbladder cancer (GBC), the best adjuvant modality of radically resected GBC is not well established. Before the publication of the BILCAP study (adjuvant capecitabine versus observation in biliary tumours), the authors were practicing chemoradiation as adjuvant therapy. Over the past few years, the authors have offered chemotherapy (CT) as an adjuvant for moderate risk patients. Hence, the authors audited their records over a decade (2007–2017) to evaluate the change in outcomes with the introduction of CT (cisplatin-gemcitabine combination).

MATERIALS AND METHODS

In the period 2007–2012, only concurrent chemoradiation therapy (CTRT; n=40) was practised. Since 2013, low-risk patients were kept on observation (R0, T2, T3, N0), moderate-risk patients (R0, T2, T3 and N0, N1) received CT, and high-risk patients (R1, N2, T3, T4, lymphovascular invasion, perineural invasion) received CTRT. The lack of concrete guidelines for adjuvant therapy according to risk stratification and treatment offered according to physician discretion resulted in an overlap of treatment modalities (CT versus CTRT). Univariate and multivariate analysis was performed to ascertain the effect of different treatment modalities on prognostic factors and outcomes (overall survival [OS]) using SPSS (v.20).

RESULTS

The median age of patients (N=142) was 50 years (interquartile range: 42–58 years). At a median follow-up of 50 months, the median OS of all patients was 34 months. Between 2007–2012 and 2013–2017 period, the gain in median OS was 6 months (42 to 48 months; p= not significant) and the median disease-free survival improved by 3 months (30 to 33 months; p= not significant). The median OS was not reached versus 46 months versus 32 months with CT, CTRT, and observation, respectively (p=0.24). On univariate analysis, the median OS of patients <50 years was 48 months versus 42 months for >51 (p=0.29), females had better OS (50 months versus 26 months; p=0.07), those with comorbidities had worse outcomes (26 months versus 48 months; p=0.29). T2 patients had the best OS (72 months versus 40 months [T3] versus 16 months [T4]; p=0.13), node negative had better OS than node positive (72 months versus 40 months; p=0.08). The effect of various adjuvant therapy modalities on OS based on the prognostic factors is given in Table 1. The superior efficacy of CT was irrespective of the nodal status. The higher efficacy of CT was evident in T2 disease but not T3 disease. CTRT showed marked benefit in younger patients, females, and those with T3 disease. On multivariate analysis, the hazard ratio (HR) of various prognostic factors influencing OS were resection status (HR: 2.49; p=0.00), male sex (HR: 1.3; p=0.25), T status (HR: 2.1; p=0.15), and nodal status (HR: 1.3; p=0.2)

Locoregional recurrence rate was 37% with observation, 13% with CT, and 18% with CTRT, while respective distant metastases rate were 18%, 27%, and 20%.

Table 1: The effect of various adjuvant therapy modalities on overall survival.

	Observation (n=23)	CT (n=39)	CTRT (n=80)
Overall median OS	32 months	NR	46
<50 years of age (n=73) >50 years of age (n=64)	30 months 26 months	48 months NR	108 months (p=0.44) 34 months
Male (n=35) Female (n=107)	6 months 32 months	NR (n=9) 50 months (n=30)	27 (p=0.07) 72 months
T2 (n=79) T3 (n=58) T4 (n=5)	25 months 50 months -	NR 39 months 20 months	34 (p=0.13) 46 months 16 months
Node negative (n=65) Node positive (n=77)	32 months 18 months	NR 48 months	51 (p=0.08) 34 months
R0 (n=107) R1 (n=35)	32 months -	NR -	NR (p=0.00) 23 months

CT: chemotherapy; CTRT: chemoradiation therapy; NR: not reached.

CONCLUSION

The outcomes of postoperative GBC have improved in terms of OS and DFS over the years. All GBC patients should receive adjuvant therapy after radical surgery. Young age, female sex, early T stage, and node negative status are good prognostic factors for OS. CT should be the standard of care as adjuvant therapy for low-risk patients. CTRT should be used in patients with high-risk features, such as R1 resection status, lymphovascular invasion, and perineural invasion. These findings need to be validated in a larger database.

Safety of Fertility Treatments in Breast Cancer Survivors

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Keywords: Breast cancer (BC) survivors, disease-free survival, *in vitro* fertilisation (IVF).

Citation: EMJ Oncol. 2020;8[1]:56-58. Abstract Review No. AR8.

BACKGROUND AND AIMS

Quality of life for cancer survivors has become a priority in cancer care and research. Almost 50% of the young patients who have survived breast cancer (BC) have expressed their desire to become pregnant.[1] Several studies have demonstrated the safety of pregnancy in BC survivors[2] and the safety of ovarian stimulation for oocytes cryopreservation in order to preserve fertility, as advised by oncological guidelines.[3,4] However, many patients face infertility after neoadjuvant BC therapy and would require fertility treatments (FT) in order to achieve a pregnancy. Nevertheless, the safety of FT after BC remission is still unclear, as there is poor evidence on the prognostic impact of increased oestrogen exposure induced by FT not followed by anticancer treatments,[5,6] even in endocrine-sensitive disease. Yet infertility remains common following systemic treatment. To date, only two small studies have evaluated the safety of assisted reproductive technology, leading to discordant attitudes. Therefore, the safety of FT in BC survivors urgently requires further investigation.

MATERIALS AND METHODS

The authors conducted a retrospective, multicentre study including BC survivors <40 years old at BC diagnosis who underwent FT between January 2006 and December 2016. They were compared to a nonexposed (NE) group of BC survivors who did not perform FT, matched (2:1) for *BRCA* status, BC stage, anticancer treatment, length of disease-free period (not inferior to the time between BC diagnosis and first FT in the FT group), and age at diagnosis when feasible. Patients with Stage IV cancer at diagnosis, BC during pregnancy, pre-existing neoplasia, or ovarian failure at BC diagnosis were excluded. FT included controlled ovarian stimulation, clomiphene citrate ovulation induction, and hormone replacement therapy for embryo transfer.

RESULTS

Nine fertility centres and two oncologic centres in Belgium participated in the study. A total of 39 eligible patients were matched with 73 NE patients, as appropriate matching 2:1 was not feasible for five patients carrying *BRCA* mutations. No statistical difference was found between the two groups for *BRCA* mutation

status, BC stage, oestrogen and progesterone receptors, HER2 status, use of chemotherapy, or adjuvant endocrine therapy. However, differences were observed for age at diagnosis (mean 31.8 [3.9] versus 34.3 [3.6] years in the FT and NE groups, respectively; p<0.001) and nulliparity at diagnosis (89.7% versus 46.6% in the FT and NE groups, respectively; p<0.001). Median follow-up time from BC diagnosis was 9 (4–22) and 12 (6–19) years in the FT and NE groups, respectively (p=0.004). FT were performed at a mean age of 37.1 (4.6) years. During FT, the median oestrogen peak level was 696.5 pg/mL (139.7–4,130.0). In the FT group, 59% conceived after BC versus 26% in the NE group (p=0.001). To evaluate the impact of FT exposure on oncological outcomes, the time of the first FT exposure was used as a starting point and the follow-up time was adjusted accordingly for matched patients in the NE group. BC relapsed in 7.7% in FT versus 20.5% in NE groups (hazard ratio: 0.46; 95% confidence interval: 0.13–1.60; p=0.23); median relapse time was 1.3 years (range: 0.3–2.7) after FT versus 4.5 years (range: 0.4–11.1) in the NE group following FT adjusted time (p=0.14).

CONCLUSION

This is the largest reported cohort of BC survivors having undergone FT following the completion of oncological treatments. This study provides reassuring evidence based on long median follow-up, showing that FT are safe in BC survivors who had an early stage disease, a good prognosis, and an unfulfilled desire for pregnancy.

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PEAR Study: UK Experience of the Management of Pregnancy-Associated brEast cAnceR: A National Retrospective Review of Practice

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Keywords: Collaborative, pregnancy-associated breast cancer (PABC).

Citation: EMJ Oncol. 2020;8[1]:58-60. Abstract Review No. AR9.

BACKGROUND

Breast cancer is the leading cause of death in females aged 35–54 years and 15% of breast cancers first present in females of reproductive age.[1,2] A trend of delaying childbearing to later ages, with falling birth rates in the <30 year olds and the average maternal age being >30 years,[3] is likely to cause increasing rates of pregnancy-associated breast cancers (PABC).[4,5] A national collaborative approach was used to evaluate the management of PABC in the UK; herein, the authors report the largest UK patient series of PABC.

METHODS

PABC cases (January 2010 to January 2020) were identified and demographic, tumour characteristic, oncology treatment, and obstetric data were collected retrospectively. Hospitals were recruited via collaborative research and trainee networks. Descriptive statistics were used to describe the treatment received, which were then compared between sites in and outside of London, UK.

RESULTS

Data for 57 patients from eight National Health Service (NHS) Trusts were included. The median age at diagnosis was 34 years, ranging from 24 to 43 years. Gestation of pregnancy at diagnosis ranged from 2 to 38 weeks. The majority of patients were diagnosed with early, localised breast cancer (97%), and 3% had metastatic disease. 58% of patients had oestrogen receptor positive (ER+) breast cancer, 34% were human epidermal growth factor receptor 2 (HER2) positive, and 32% were triple negative. Tumours were of histology Grade 2 in 25% and Grade 3 in 68%.

Surgery was performed in 95% of cases, with 40% receiving breast conserving surgery. All 57 patients received chemotherapy; the intention of treatment, pregnancy gestation, and choice of therapy is shown in Figure 1. Granulocyte colony stimulating factor (GCSF) support was prescribed in 39% to prevent neutropenia. Toxicity was reported in 70% of regimens, though only 1% reported a Grade 3 toxicity.

All ER+ patients received oestrogen receptor targeting therapy. All patients with HER2+ breast cancer received targeted therapy with trastuzumab (58%) or trastuzumab plus pertuzumab (42%) postpartum. No patients received radiotherapy whilst pregnant and 38 (67%) received it postpartum. Radiotherapy was delivered to the whole breast (27%), partial breast (2%), chest wall (34%), supraclavicular fossa (25%), axilla (3%), internal mammary chain (7%), and spine (2%).

In this UK data series, 18 (32%) underwent a preterm delivery (<36 weeks gestation). Although complete obstetric data was missing in 37% of cases, reported delivery modalities were spontaneous vaginal delivery, assisted vaginal delivery, and caesarean section in 28%, 7%, and 33%, respectively.

In terms of regional variations, patients treated outside of London were more likely to receive radiotherapy (80% versus 65%), more likely to deliver at term (48% versus 19%), and less likely to have a caesarean (24% versus 40%). More patients received anthracycline/cyclophosphamide/taxane regimens in London (64% versus 32%), whilst the triplet regimen, with the addition of fluorouracil chemotherapy, was more commonly used outside London (13% versus 48%). Neoadjuvant chemotherapy was less frequently given in London (28% versus 56%).

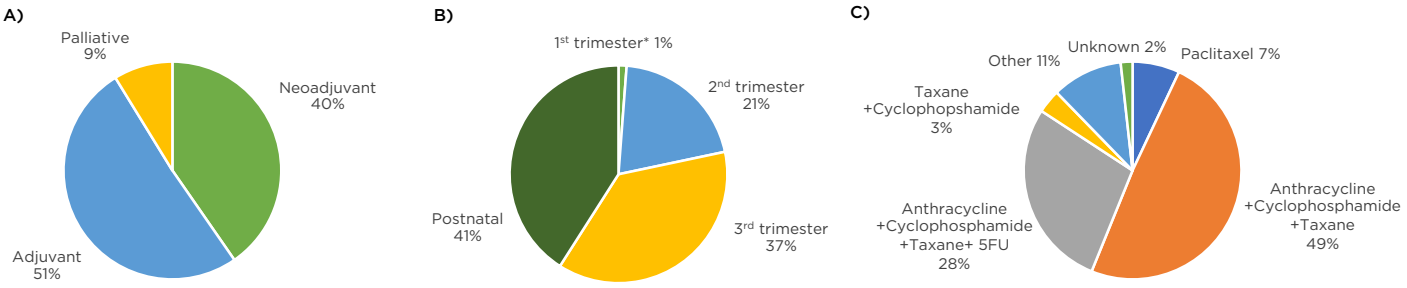

Figure 1: Chemotherapy treatment of PABC of A) intention of treatment; B) gestation of pregnancy at the start of treatment; and C) chemotherapy regimens prescribed.

*Patient scheduled for termination of pregnancy.

CONCLUSION

Historically, uncertainties regarding the safety of treatment modalities of PABC may have led to worse outcomes in this group of younger females with breast cancer. However, consistent with more recent data, further clarity has been provided by this study on the safety of a complete, albeit adjusted, treatment pathway in this heterogeneous disease process. Although some geographical variations in the management of PABC were observed, the authors advise exercising caution in its interpretation, as these may have been impacted by year of diagnosis, stage of disease, and gestation at presentation. Further prospective work is planned to explore national variation in PABC management and patient outcomes.

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Chemotherapy Options in Recurrent Glioblastoma

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Glioblastoma, glioblastoma multiforme, procarbazine/lomustine/vincristine (PCV), temozolomide (TMZ).

Citation: EMJ Oncol. 2020;8[1]:60-62. Abstract Review No. AR10.

BACKGROUND AND AIMS

Most patients with glioblastoma will develop a recurrence despite initial aggressive therapy with maximum surgical resection and postoperative chemoradiation.[1]

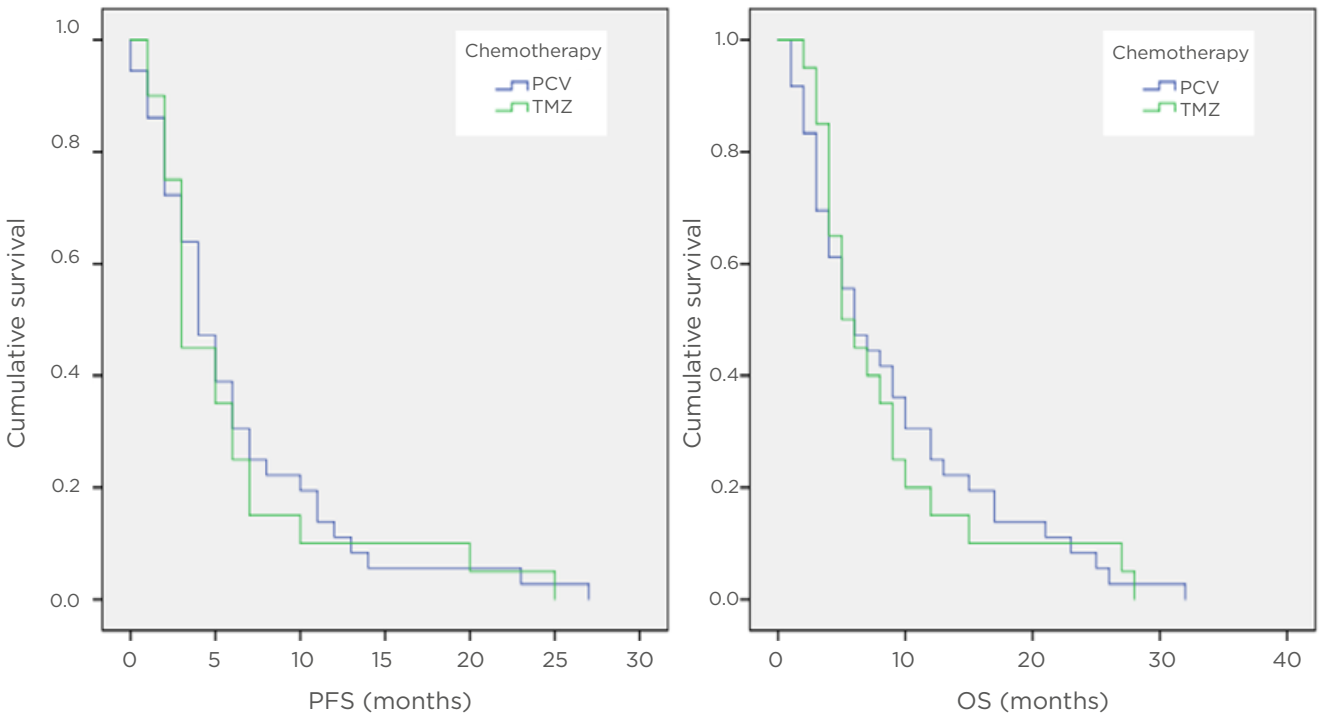

Figure 1: Survival curves for progression-free and overall survival, comparing temozolomide and procarbazine/lomustine/vincristine.

OS: overall survival; PCV: procarbazine/lomustine/vincristine; PFS: progression-free survival; TMZ: temozolomide.

A re-excision is often not feasible, but palliative chemotherapy can be considered depending on fitness, performance status, and other patient factors. In the absence of Level 1 evidence, different chemotherapy regimens have been used in this setting. The aim of this study was to evaluate an approach that included rechallenge temozolomide (TMZ) for patients with disease-free survival greater than 6 months after initial therapy, and procarbazine/lomustine/vincristine (PCV) for those exhibiting shorter responses to initial treatment.

MATERIALS AND METHODS

The authors retrospectively collected and analysed the data of patients with glioblastoma treated with systemic therapy for recurrent disease during 2009–2019. After the initial diagnosis, they all had a surgical resection and received treatment on the Stupp protocol.[2] The Response Assessment in Neuro-Oncology (RANO) criteria[3] were used to assess response to palliative chemotherapy after recurrence. Patient demographics and disease/treatment characteristics were described and survival outcomes were estimated using the Kaplan–Meier method. Haematological toxicities were recorded and chemotherapy-related admission rates were used as surrogate for other toxicities.

RESULTS

Fifty-six patients were identified, of whom 20 received rechallenge TMZ and 36 received PCV. Measured from the start of palliative chemotherapy, the median progression-free survival was 3 months for TMZ and 4 months for PCV, while median overall survival was 5.5 months for TMZ and 6 months for PCV (Figure 1).

Both regimens were reasonably well tolerated. Grade 3–4 haematological toxicity was 10% and Grade 1–2 was 25% with TMZ. Corresponding figures for PCV were 13.9% and 30%. Only one patient was admitted into hospital for pneumonia (who had received PCV).

CONCLUSION

Rechallenging patients with recurrent glioblastoma with TMZ after a durable initial response to surgery and chemoradiotherapy, and offering PCV to those with a worse response to primary therapy, is a reasonable, pragmatic approach adopted by many UK cancer centres. Of interest, patients treated with rechallenge TMZ had similar progression-free and overall survival as their PCV counterparts, despite belonging in a theoretically better prognosis group (in view of a better response to primary treatment). This toxicity data suggests this treatment protocol is safe.

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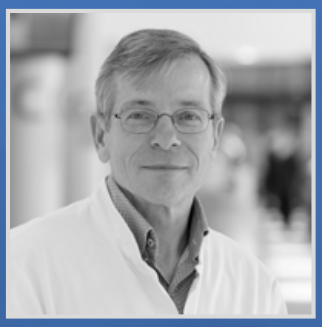
Congress Interview



Professor John B.A.G. Haanen

Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands; Leiden University Medical Centre, Leiden, The Netherlands; Scientific Chair of the European Society for Medical Oncology (ESMO) Virtual Congress 2020

Q1 You have an impressive scientific background, completing a scientific PhD in immunohaematology in addition to your clinical training as a medical oncologist. How does your detailed scientific training improve your clinical work as a doctor?

Thank you! The work that I am doing as a PhD in basic immunology has been extremely valuable. It allows me to think and discuss at both basic and clinical research levels. It has been an enrichment of my work as a clinician and scientist that I would advise for anyone who wants to follow an academic career.

Q2 Immunotherapy has really exploded in oncology, haematology, and now into other clinical disciplines, and you have been involved in this area of therapeutics for many years. What were your observations of the growth of these therapies, and how do you think they will further develop over the coming years?

I have been working in the field of cancer immunotherapy for more than two decades. I have always been convinced that eventually this would work, but it was a struggle for many years. We did not understand how to mobilise the endogenous immune system to fight cancer. This has completely changed in the past 20 years, but the way we give immunotherapy now is absolutely beyond any of our expectations. It has sparked so many more lines of research and increased our knowledge of the immune system exponentially; indeed, not only in cancer but also in infectious disease, autoimmunity, and organ transplantation.

As a clinician, it is amazing to see patients responding, cancers disappearing, sometimes for a very long time, perhaps forever.

Q3 Your work includes involvement in the translation of novel immunotherapy strategies into clinical practice. What challenges must be considered in bringing a novel therapy into the wider clinical domain?

Bringing new therapies to the clinic requires team efforts: bringing together basic researchers, pharmacists, clinicians, and many more people. One needs to have, or build, this team, which requires time and money. For most novel therapies, special Good Manufacturing Practice laboratories are needed for setting up a robust, reproducible, and validated manufacturing process. One must liaise with the regulatory authorities to be able to perform an innovative trial. So, there are many hurdles to cross.

Q4

What are your ambitions for the Amsterdam Biotherapeutics Unit (AmBTU), which you cofounded, and what motivated you to set up the centre?

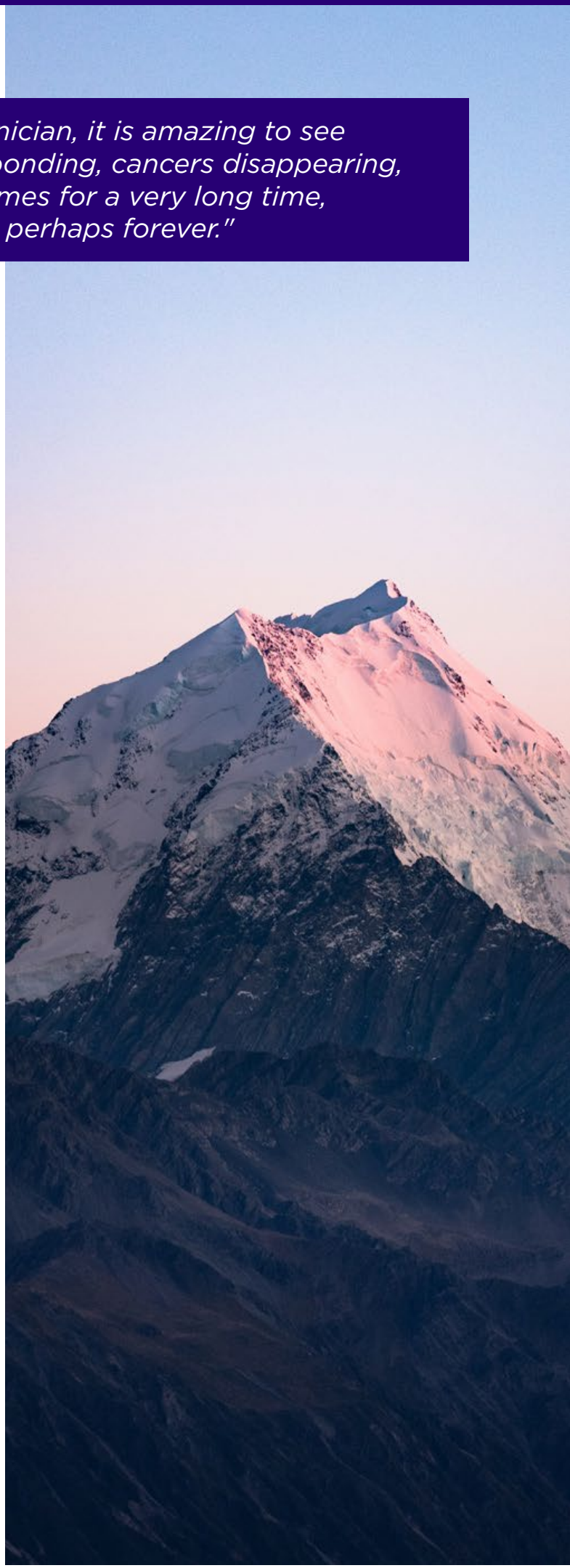
"As a clinician, it is amazing to see patients responding, cancers disappearing, sometimes for a very long time, perhaps forever."

We started the AmBTU almost 15 years ago to be flexible, develop experience (from the research and manufacturing perspectives), and to produce innovative immunotherapies. Currently, the AmBTU is focussing on development of cellular therapies, especially highly individualised cellular therapies, which are hard for the pharmaceutical industry to produce. I am convinced that one of the next waves in immunotherapies lies in the development of these living drugs. We want to be at the forefront!

Q5

The European Society for Medical Oncology (ESMO) Virtual Congress 2020 was the first digital congress for the society. What adaptations and strategies were needed to bring the event to life?

Of course, we were not the first to adapt our face-to-face meeting to a completely virtual meeting but being later in the year gave us the opportunity to learn from other organisations. One realises how densely packed a live event is. It would be impossible to do this virtually. So, the first change was to divide the meeting into two parts: the scientific meeting and the educational meeting. Both are at the core of the ESMO strategy. The second change was that the most interactive sessions were cancelled as it was considered too challenging. Having said that, we did incorporate a lot of live 'question and answer' sessions during the scientific weekend, which worked brilliantly. Other changes were to have all posters online from the start, the same for the mini oral presentations, and the setup of the satellite symposia with pharmaceutical companies was done digitally. We learned a lot in a very short time. The ESMO staff are absolutely amazing, having worked around the clock to make the ESMO Virtual Congress 2020 a success.



Q6 The focus for ESMO 2020 was 'bringing innovation to cancer patients'. What innovative technologies and therapies can patients expect to be available to them soon?

I am sure you saw that we had three presidential symposia packed with practice-changing data. Again, immunotherapy, especially now in kidney and upper gastrointestinal cancer, was right at the forefront, as well as novel drugs like lorlatinib in anaplastic lymphoma kinase-translocated non-small cell lung cancers, the use of maintenance osimertinib in epidermal growth factor receptor-mutated non-small cell lung cancers, prevention of brain metastases, and bringing personalised therapies to *PTEN*-mutated prostate cancer.

For other novelties in biomarker research, such as circulating free DNA and gene signatures, it is perhaps not prime time for clinical use yet, although highly promising data were presented.

Q7 You spoke at ESMO about coronavirus disease (COVID-19) and cancer research. Could you tell our readers the key take-home messages of this talk?

This year is about COVID-19. Our lives have changed because of COVID-19, both personal and work lives. Patients are affected, societies are affected, and healthcare workers like oncologists have been affected. We have shown that despite the impact that COVID-19 had and still has on our work, including in cancer research, we are highly resilient, flexible, and creative in bringing new research and insight into how cancer treatments impact COVID-19 and how COVID-19 impacts cancer patients, their treatment, and their doctors. Unfortunately, the price is high: [there have been] far less cancer diagnoses, less treatment, and more burn-out in oncologists; but, some good things came out of this, including telemedicine, no impact of targeted and immunotherapies on the outcome of COVID-19, and more working from home for oncologists.

Q8 Since your appointment as ESMO Scientific Chair, what has been your proudest achievement?

Definitely to have been able to turn a successful live meeting into a successful virtual meeting together with ESMO president, Prof Solange Peters, and the ESMO staff.

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1. Braftovi Summary of Product Characteristics. Pierre Fabre Médicament, 2020.
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Interview

Dr Vinay Prasad

Haemato-oncologist and Associate Professor of Medicine at the University of California, San Francisco, California, USA

Q1 You have an impressive background in science communication within the medical field, not only working with patients as a haematologist and oncologist, and with medical students and residency trainees as an associate professor and mentor, but educating the wider community of doctors and researchers through your podcast, YouTube channel, twitter discussions, books, and academic publications. How would you describe your work and what do you consider your primary focus?

That's a generous summary. I will draw a distinction. There is the work I do, and the way I disseminate that work. The work I do is studying cancer health policy and low-value medical care. I'm interested in the cost, usage, approval, and evidence supporting cancer drugs. The primary output of that work is peer-reviewed academic articles that readers can find at my website.[1] Having done this work, I am interested in using all the modern methods of dissemination. That's why I write books, tweet, make a podcast, and am a novice YouTuber. It's a sad truth of our business that many academics write articles that end up having very low readership or metrics. That's why I try to take advantage of all the tools of 2020 to get the findings and ideas to other people to run with. That's what science boils down to: sharing and discussing your ideas and findings with others.

Q2 You characterise your field of work as 'meta-research': interrogating the methods, analyses, intentions, and evidence that underpin cancer drug development and the ways that research is translated into practice. What drew you to this broader curiosity and scepticism, beyond bedside practice?

I went to medical school to be a doctor, and later decided to be a cancer doctor. In a perfect world, that is all I would do. I would go to my clinic and see patients, go home and ride my bicycle, read books, and watch Netflix. I would be able to trust the clinical trials to give me useful information, and trust the experts who write the guidelines.

As I went through my training, I realised slowly and with growing horror that we did not live in that world. We live in a world where the evidence for new products can be poor. The cost is often excessive. On several occasions, experts have recommended the use of products for which they are paid by the makers; this could be problematic as it may result in a large scientific and moral discrepancy in the system.

Having realised my predicament, I started trying to brainstorm ways to do research that would re-orient the compass of care back to doctors and patients. After a while, I had done enough projects that I became known for this work. I picked up the tool of meta-research from academics before me because it is the perfect way to illustrate the problems in the cancer drug ecosystem. Eventually, these projects kept me busy, and that's where I am today. Now half my time is service and clinic, but half my time is research. I still dream of living in a world where all my time can be clinical.

Q3 Do you think that clinicians should generally have more active engagement with drug development and research, and how can we build towards this?

I think clinicians should understand drug development, as it can be misused to deceive them. My book *Malignant* tries to explain it as simply as I can. I think clinicians should encourage patients to participate in good clinical trials (a fraction of all trials) and accrue patients on these studies. Beyond that, I don't think the average clinician has any further obligation for research and development. Those are separate pursuits for those inclined.

Q4 You have a particular interest in medical reversal, where new clinical trial results contradict existing practice and previous trials, in both your >250 academic publications and in a book you co-authored: *Ending Medical Reversal: Improving Outcomes, Saving Lives*. How can clinicians have confidence in research processes to improve evidence-based medicine, and what steps can they take to help limit medical reversal in the future?

A medical reversal is when we do something, often for decades, that provides no benefit to our patients. It runs up costs, and harms, and has no countervailing gains. The key prerequisite is the hasty adoption of costly, bioplausible technology without good trials. Cancer therapy is an area where bioplausability is a particular concern. But too often, we don't run the correct studies and settle for plausibility. The best thing we can do to curb medical reversal is to demand better evidence for products when they debut. In cancer medicine, we have gone the opposite way, and embrace more and more $200,000 /year therapies based on less and less data.

Q5 You have highlighted fundamental process, economic, and ethical issues with both medical research and drug development in your research, writing, and your podcast *Plenary Session*. Do these issues affect your management and care for your own patients, and how do you then determine the best treatment to offer your patients?

The job of a good oncologist is not to determine the best treatment for a patient, it is to arm a patient with knowledge to empower their decision. What would happen if we do X, and what happens if we do Y. What are the potential benefits, and known harms. What do we know for sure, and what is uncertain. My goal as an oncologist is to guide a patient to choices that are right for them. That means sometimes people choose things differently than other people, and differently than what I choose for myself. That's OK. Not all of us have the same appetite for risk and uncertainty as others. I find that the more I study and practise medicine, the less certain I become.

Q6 Your recent book, *Malignant: How Bad Policy and Bad Evidence Harm People with Cancer*, is "a book about cancer drug policy, medical evidence, and governmental regulation" that highlights issues with the strategies and incentives in current drug development, and champions approaches towards "serious and sustained progress against cancer." What are you hoping that doctors and researchers will take away from your book?

I hope they learn precisely why the current system is problematic. It generates costly $200,000 /year medications that are not good enough for our patients. Why is the system the way that it is? And what can fix it? Finally, while we try to fix it, what can individual doctors and patients do tomorrow to improve cancer care? Those are the goals of the book.

"The job of a good oncologist is not to determine the best treatment for a patient, it is to arm a patient with knowledge to empower their decision"

Q7 You have highlighted issues in research and development, but still advocate for the positives of evidence-based practice. What is the value of research and evidence-based medicine in patient care and how can clinicians and researchers amplify useful strategies and benefits?

Randomised controlled trials are an aeroplane. They're a really useful tool, a technological marvel. Simultaneously, the current research system is a failing airline: it is a miserable experience. But blaming randomised trials for the current system is like blaming the aeroplane for the failing airline. It's not the aeroplane's fault.

We have a choice: to make a research system that empowers patients or one that enriches shareholders. We have chosen, over and over, the latter, but I think we can focus on the former. This means rethinking our studies: better controls, better post-protocol therapy, better endpoints. I have a lot of specifics in the book, but I want to be careful. Just because an airline has packed too many seats on an aeroplane does not mean there is something wrong with flying. We can spread the seats out and make it a more pleasurable experience, which ironically, it once was.

Q8 You have been recognised as a fantastic teacher, receiving several awards from medical students, residents, and trainees for teaching and mentoring (including: 2017 Craig Okada Teaching Award for Best Teacher of the Fellowship Program, 2018 Faculty Mentorship Award from Internal Medicine Residency Program, 2019 J. David Bristow Award, and 2020 Excellence in Research/Scholarship Mentoring Award). How do you approach teaching and training, so that it is so valued by your students?

I can only tell you my philosophy about working with students, residents, fellows, and trainees; you will have to ask them what they value. I don't consider myself superior to any trainees. Many are more talented than me in many things, and I learn from them. I ask them questions about what they are passionate about, and benefit from what they share. Whenever I tell them any facts I believe I know, I make sure that I really know what I am talking about. I don't repeat things people told me without understanding the root of the fact. In doing that research, I find that many things I have been told are wrong. So, when I tell a trainee something, I have high confidence that it is accurate, or at least I can trace why I am saying that. I try to explain what I am thinking about in clinical situations, explain why I approach situations as I do, and I am prepared for them to push back. I try to foster an environment where trainees are comfortable asking follow-up questions and challenging my assumptions and reasoning. I try to remember all the experiences I had when I was at their stage, and retain the good parts and omit the bad ones. For every question, I only answer them as honestly as possible.

Q9 What is next for your career personally, and your hopes for the future of oncological research and practice? How do you hope the field, and your career, will look differently over the next 20 years?

In 20 years, I hope that most oncologists recognise the core problems of our profession and commit to solutions. Although I provide very detailed and specific solutions in *Malignant*, I hope future doctors and patients commit to testing proposals. I would be the last person to recommend we adopt a practice just because it makes sense. If someone else has better ideas than me, I encourage them to put those forward, and I will embrace whatever works.

It's a common interview question in medicine to ask 'where do you see yourself in 5 years?' During my training, I provided unsatisfying answers many times, and all of my predictions have been off the mark. After five years on faculty, I can answer confidently: I no longer care. Don't get me wrong, I still have career goals, but they are external. I hope we fix the policy issues that trouble me at a national level, but I no longer have personal goals. I have no aspirations for leadership positions. No desire to work for a governmental agency. Promotions and tenure won't change my life, nor do they guarantee any freedom or protection in 2020. I am happy to go where life takes me. I think more people would be happier if they give up personal ambitions, which are mostly brass rings.

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Precision Medicine in Lung Cancer

EDITOR'S PICK

In their review of precision medicine in oncology, Joshi et al. comprehensively detail evolving strategies in diagnosis, the importance of subtype classification, and novel therapeutic approaches that harness the immune system and target oncogenic driver mutations; this review should be considered essential reading for anyone with an interest in oncology.

Dr Caroline Michie

Edinburgh Cancer Centre and the University of Edinburgh, Edinburgh, UK

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Abstract

Lung cancer has a devastating global impact, with diagnosis of more than 2 million new cases annually, and poor long-term survival. Recently, the landscape of lung cancer diagnosis, staging, and treatment has changed profoundly, with further developments on the horizon.

It has become of increasing importance to comprehensively characterise lung tumour tissue. Minimally invasive diagnostic modalities, including standard bronchoscopy and radial probe endobronchial ultrasound (EBUS), enable adequate tissue sampling for tumour subtyping. Sophisticated electromagnetic navigation software and novel biopsy procedures have allowed for sampling of even very peripheral tumours, in the hands of experienced bronchoscopists. Linear EBUS is now widely used for simultaneous diagnosis and cancer staging, reducing time to treatment initiation and effectively replacing invasive mediastinoscopy. Liquid biopsy is an emerging noninvasive technology with potential for diagnosis, prediction of tumour response, and detection of resistance-related gene mutations.

Significant advancements in our understanding of the immunologic and oncogenic processes involved with lung cancer biology have helped revolutionise management. Whilst chemotherapy remains a

therapeutic cornerstone for many, evolving evidence supports a personalised approach, particularly in advanced disease. Specific inhibitors targeting driver mutations and key immunological pathways confer survival benefits in metastatic lung cancer, with emerging data in early stage disease.

In this review, lung cancer histological subtypes are discussed, with a focus on non-small cell lung cancer, along with current and evolving approaches to diagnosis and staging. Therapeutic options in the era of precision medicine will also be considered within the context of targetable oncogenic driver mutations and the growing field of immuno-oncology.

INTRODUCTION

Lung cancer has a devastating global impact. Claiming over 2 million lives in 2018, it is the world's leading cause of cancer-related morbidity and mortality.[1] Five-year survival rates are estimated to be less than 20%. Until recently, treatment options have been limited to surgery for early stage disease, and systemic chemotherapy for unresectable, locally-advanced, and metastatic disease. Recent advances in our understanding of molecular pathobiology of lung cancer have paved the way towards a personalised approach to treatment. The discovery of specific targetable mutations and understanding of the pivotal role of immunosurveillance in suppressing malignant growth have allowed for the development of innovative therapeutic strategies. This review will broadly cover updates in the personalised management of lung cancer, particularly the non-small cell subtype, including the importance of accurate histological characterisation through to novel treatment options guided by targetable oncogenic driver mutations, the immunological influences on tumour growth, and the emerging technologies for precise molecular profiling of individual cancers.

THE IMPORTANCE OF DISTINGUISHING HISTOLOGICAL SUBTYPE IN LUNG CANCER

Lung cancer can be subdivided into two major histological subtypes: non-small cell lung cancer (NSCLC), accounting for approximately 85% of cases, and small cell lung cancer, in the remaining 15%.[2] NSCLC can be further subclassified into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Tumour subtype can be determined by morphological features on cytology and histopathology, as well as immunohistochemical staining. For example, TTF1, napsin A, and cytokeratin 7 positivity favour a diagnosis of adenocarcinoma, whilst positivity for p40, p63, and cytokeratins 5 and 6 are suggestive of squamous cell carcinoma.[3]

Treatment, staging, and outcomes can be markedly different between small-cell and non-small cell lung tumours, with small cell cancers generally behaving more aggressively and conferring poorer prognosis. Historically, distinguishing the non-small cell tumours by subtype had minimal impact on management until the discovery that histology influenced therapeutic outcomes was made. Specifically, treatment of adenocarcinoma with bevacizumab, a humanised monoclonal antibody targeting VEGF, improved both progression free and overall survival in adenocarcinoma but increased the risk of catastrophic pulmonary haemorrhage in patients with squamous cell carcinomas.[4] More recently, the discovery of specific oncogene mutations in certain tumour subtypes has further emphasised the importance of detailed tumour characterisation. Specific driver mutations have been identified in many lung adenocarcinomas (less frequently, however, in squamous cell carcinomas), and have been associated with cell proliferation, tumour growth, and survival. These mutations are usually mutually exclusive of each other and result in the transformation of noncancerous cells towards malignant cell lines, resistant to the usual regulatory processes. Targeting the protein products of these mutations with specific inhibitors can have a major effect on susceptible tumours, allowing for a precision medicine approach to treatment.

ESTABLISHING A DIAGNOSIS

In order to inform appropriate management, sufficient quantities of tissue must be obtained to identify the precise histological diagnosis (Table 1).[5]

Table 1: Diagnostic and staging methods in lung cancer.

Method	Sensitivity (%)	
	Central lesions	Peripheral lesions
Initial diagnosis		
Sputum cytology	71	49
Bronchoscopy	88	78
Washings	47	43
Brushings	56	54
Biopsy	74	57
Radiologically guided percutaneous biopsy	-	90
Radial probe EBUS	-	73
Cryobiopsy	95	74
EMN	-	68
Linear EBUS TBNA	82	-
Mediastinal staging	**Sensitivity (%)**	
Bronchoscopic TBNA	78	
Linear EBUS TBNA	89	
EUS	89	
EUS + EBUS	91	
Video-assisted surgical mediastinoscopy	89	

Adapted from McLean et al.[5]

EBUS: endobronchial ultrasound; EMN: electromagnetic navigation; EUS: endoscopic ultrasound; TBNA: transbronchial needle biopsy.

Lung tumours can be biopsied percutaneously using radiologic guidance with CT or endobronchial ultrasound (EBUS), with either direct bronchoscopic sampling of the primary tumour or indirect sampling of involved thoracic lymph nodes.

Due to the rising prevalence of peripheral lung lesions, percutaneous fine-needle and core biopsies with CT guidance have become increasingly utilised, with a pooled sensitivity of up to 90%.[6] Biopsies of lesions under 1.5 cm are less likely to be diagnostic, with a sensitivity of approximately 70%.[7] More centrally located tumours and concomitant emphysema are associated with a higher risk of pneumothorax, with one study reporting rates of up to 27%.[8] Fibreoptic bronchoscopy performed under conscious sedation facilitates a number of different diagnostic approaches depending on the tumour location. The diagnostic rate for central tumours with use of bronchoscopic forceps is reportedly 65–82%, increasing up to 88% if combined with bronchial brushings and washings for cytology assessment.[6,9] However, for peripheral lesions that cannot be directly viewed, the sensitivity of diagnostic bronchoscopy has been shown to be as low as 14%, particularly if the lesion is less than 2 cm in size.[10] Another bronchoscopic approach for targeting peripheral lesions is with radial probe EBUS, which utilises an ultrasound, enabling 360-degree imaging of surrounding structures. Peripheral lesions can be localised and targeted for transbronchial needle aspiration (TBNA) biopsy. In a recent meta-analysis, pooled diagnostic sensitivity was 73%, with a pneumothorax rate of only 1%.[11] Although diagnostic yield of radial-EBUS is lower than transthoracic percutaneous biopsy, the advantage of this approach is a significantly reduced pneumothorax risk.[7] Importantly, whilst it may confirm the presence of a target lesion, radial-EBUS does not itself provide a

means of navigating to the lesion of interest. Combining radial-EBUS with highly specialised electromagnetic navigation (EMN) technology allows real-time navigation to the target lesion when mapped against a contemporary CT image. In a small randomised controlled trial, Eberhardt et al.[12] showed that combining EMN with radial-EBUS significantly improved diagnostic yield to 88%, compared to either radial EBUS (69%) or EMN-standard bronchoscopy (59%) alone, independent of lesion size and lobar distribution.

STAGING THE MEDIASTINUM

Staging of NSCLC (I–IV) is important for determining treatment and prognosis, and requires evaluation of tumour size, lymph node involvement, and presence of metastatic disease, following the International Association for the Study of Lung Cancer (IASLC) TNM staging guidelines.[13] Whole-body PET is a sensitive imaging tool for staging NSCLC, particularly when integrated with CT. PET-CT provides accurate assessment of mediastinal disease, helping to guide treatment decisions in patients with NSCLC. Linear or convex probe EBUS with TBNA is the standard diagnostic procedure for patients with radiological PET-avid nodal disease or central primary tumours adjacent to airways.[14] It is a minimally invasive procedure with few complications (<1%), even in the elderly population.[15] The convex-probe EBUS-TBNA is advantageous over other methods, allowing simultaneous diagnosis and staging, hence reducing time to treatment. In a randomised control trial comparing EBUS with conventional diagnosis and staging, those undergoing EBUS had reduction in median time to treatment decision by >50% (14 versus 29 days, hazard ratio [HR]:1.98, p<0.0001).[16]

False negative rates of PET-CT can be as high as 25%, and so EBUS-TBNA is also recommended in those who have hilar lymphadenopathy and central tumours, irrespective of mediastinal node PET-avidity.[17] Endoscopic ultrasound with TBNA may be a reasonable alternative for lymph node stations that cannot be accessed bronchoscopically.

TREATMENT IN THE ERA OF PRECISION MEDICINE: TARGETING DRIVER MUTATIONS

For decades, cytotoxic chemotherapy has been the cornerstone of management for all but early-stage NSCLC (Table 2).[18] The recognition of specific somatic 'driver' mutations in NSCLC has transformed both the treatment and outcomes for patients with advanced-stage lung cancer. These mutations occur in oncogenes and tumour suppressor genes, resulting in unregulated cell proliferation and tumour survival. The frequencies of identifiable mutations in lung adenocarcinomas are shown in Figure 1A.[19] Targeting these mutated proteins with specific inhibitors has led to a paradigm shift in cancer therapeutics. Agents targeting mutations in *EGFR*, *ALK*, *ROS1*, and *BRAF* proto-oncogenes have been approved in NSCLC. Specific therapies for the other driver mutations are under development.

EGFR Mutations

EGFR mutations were first described in 2004.[20] They occur in 10–35% of lung adenocarcinomas, with higher frequency in east Asian populations and in younger females with no previous smoking history.[21] The net result of these mutations is constitutive activation of EGFR with stimulation of proliferative signalling pathways (Figure 1B).[22] There are now three generations of tyrosine kinase inhibitors (TKI) that target the mutated EGFR. These include first generation erlotinib and gefitinib, second generation afatinib and dacomitinib, and third generation osimertinib. Their efficacy has been established in 13 Phase III randomised controlled trials, clearly highlighting the role of EGFR-TKI as first line treatment in EGFR-mutated Stage IIIB and Stage IV NSCLC.[23] The role of EGFR-TKI in the adjuvant setting in Stage II and Stage IIIA disease, however, is less certain. The ADJUVANT/CTONG1104 trial randomised 222 patients with completely resected, *EGFR*-positive Stage II-IIIA (with N1-N2 nodal involvement) to receive either gefitinib or vinorelbine plus cisplatin. There was a significant improvement in median disease-free survival in the gefitinib arm in comparison to the standard platinum-based chemotherapy arm, (28.7 versus 18.0 months, HR:0.60, p=0.0054).[24]

Table 2: Treatment options for Non-Small Cell Lung Cancer.

Stage	Treatment options	Comments
Stage IA and IB	First line: Surgery Alternatives: SABR or RFA or Adjuvant CTx	• Surgical resection is first-line treatment for Stage I and II NSCLC. • For those unfit for surgery, curative SABR is the treatment of choice. SABR is particularly advantageous for peripheral lesions in patients with COPD and the elderly, due to reduced toxicity. • For tumours >5cm and/or central tumours, high-dose RT may be an option. • RFA may be considered in those with contraindications for surgery and SABR. • Adjuvant CTx may be offered to those with resected stage IB disease and primary tumour >4cm.
Stage IIA and IIB	Surgery + adjuvant chemotherapy	• Adjuvant CTx is offered to patients with Stage II and III NSCLC after surgical resection.
Stage IIIA	Induction CTx + surgery OR Induction CTx + RTx + surgery OR Concurrent chemoradiotherapy	• There are many approaches to the management of IIIA (N2) disease as outlined. Preoperative staging must be carried out to stage the mediastinum, and rule out extrathoracic metastasis prior to treatment. • For unresectable IIIA (N2) disease, concurrent chemoradiotherapy is the modality of choice.
Stage IIIB	Concurrent chemoradiation +/- durvalumab	• If considered unsuitable for concurrent chemoradiotherapy, induction CTx and high-dose RTx can be given. • Although not a standard of care in all centres, durvalumab following concurrent chemoradiotherapy has demonstrated a significant improvement in progression-free survival. • Other Immune checkpoint inhibitors currently under evaluation.
Stage IV	Immunotherapy OR Targeted therapy OR Chemotherapy OR Best supportive care, as appropriate.	• NSCLC with driver mutations: targeted treatment for EGFR, ALK, ROS-1, BRAF tumour mutations. • NSCLC without driver mutations: chemotherapy should be considered in EGFR- and ALK-negative disease, if immunotherapy is contraindicated. • NSCLC with TPS≥50% for PD-L1, EGFR- and ALK-negative disease: single agent pembrolizumab +/- CTx. • NSCLC with TPS<50% for PD-L1, EGFR- and ALK-negative disease: pembrolizumab + CTx. • Maintenance chemotherapy may be appropriate after first-line chemotherapy in some patients.

Adapted from Postmus et al.[18]

ALK: anaplastic lymphoma kinase; CTx: chemotherapy; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD-1PD-L1 : programmed death-1/ programmed death-ligand 1; RFA: radiofrequency ablation; RTx: radiotherapy; SABR: stereotactic ablative body radiotherapy; TPS: tumour proportion score.

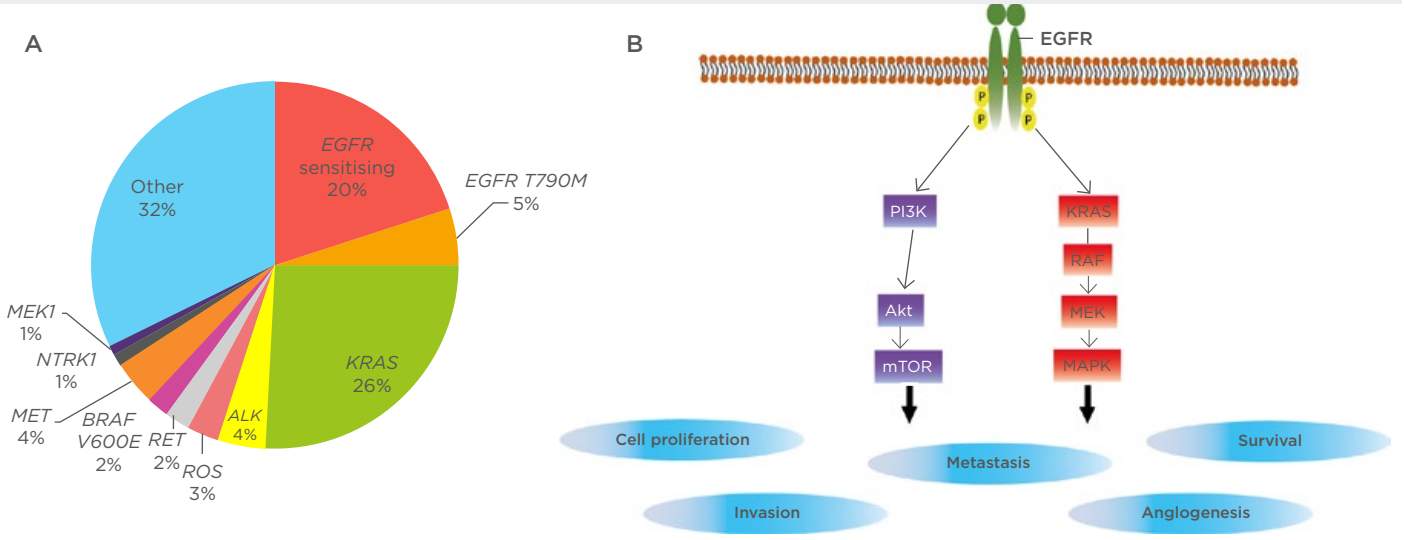

Figure 1: Driver mutations in lung adenocarcinomas.

A) Frequencies of identifiable oncogene driver mutation in non-small cell lung cancers. *Adapted from Jordan et al.*[19]

B) The molecular pathogenesis of EGFR sensitising mutations. EGFR mutations lead to ligand-independent activation of downstream signalling pathways, leading to cellular proliferation and survival.
Akt: Protein kinase B; E: glutamic acid; EGFR: epithelial growth factor receptor; M: methionine; MEK: mitogen-activated protein/extracellular signal regulated kinase; mTOR: mammalian target of rapamycin; RAF: rapidly accelerated fibrosarcoma; ROS: reactive oxygen species; T: threonine; V: valine.

Most tumours will develop resistance to these agents even where there is initial good response. The most common resistance mechanism is the *T790M* mutation.[25] Given that second generation TKI have limited ability to overcome *T790M* resistance, third generation TKI osimertinib was developed as a mutant-sensitive therapy. The AURA3 study included patients with progression on first generation TKI, showing improved overall tumour response rates and progression free survival (PFS) in those randomised to osimertinib, compared to standard platinum-based chemotherapy.[26] Further third generation EGFR-TKI are under development.

ALK/ROS1 Mutations

Less common targetable mutations include the *ALK* gene rearrangements, which result in a chimeric protein (EML4-ALK) with constitutive ligand-independent tyrosine kinase activity.[27] Crizotinib has been developed as an agent with specific activity against the chimeric EML4-ALK protein. The PROFILE 1014 study, including patients with *ALK* rearrangements, demonstrated significant improvements in median PFS and objective response rates for crizotinib versus standard first-line chemotherapy.[28] Studies have also demonstrated efficacy in the second line setting, in comparison to standard chemotherapy.[29]

Newer generation ALK-TKI, including ceritinib, alectanib, and lorlatinib, have been developed to treat tumours with acquired resistance to crizotinib.[30] The ASCEND-5 trial revealed superiority of ceritinib over single agent chemotherapy in crizotinib-resistant patients, with significant improvement in median PFS.[31] As crizotinib has limited central nervous system (CNS) penetration, a common mode of disease progression is through new brain metastases, necessitating vigilant CNS surveillance.[32] Second and third generation ALK inhibitors have improved CNS penetrance with evidence supporting superior outcomes.[33] The ALEX study compared alectinib with crizotinib as first line therapy in patients with *ALK* gene rearrangements. Alectanib was associated with longer median PFS and time to CNS progression.[34]

ROS1 gene rearrangements account for 1–2% of NSCLC and are more commonly found in young patients with minimal tobacco exposure and with adenocarcinoma histology.[35] Crizotinib and other ALK-TKI have shown activity against NSCLC harbouring *ROS1* rearrangements because of their structural homology to the ALK protein. In a

Phase II study of 127 patients with this oncogene, crizotinib led to objective response rates of 71.7% and median PFS of 15.9 months.[36] Specific ROS1 inhibitors are being tested in early-phase trials.

KRAS Mutations

The *KRAS* mutation is the most common oncogenic driver mutation, occurring in 25–34% adenocarcinomas and 3–6% squamous carcinomas, particularly in smokers of non-Asian ethnicity.[37,38] To date, treatment strategies for *KRAS*-mutant lung cancer have been disappointing. Despite increasing understanding of the molecular biology of these mutations, there are no current specific therapies. Recommended treatment is similar to that of NSCLC without identifiable driver mutations.[39]

BRAF Mutations

BRAF mutations are found in many cancer cell lines, the prototypical example being melanoma.[40] The most common *BRAF* mutation is the *V600E* mutation and is observed in 1–2% of lung adenocarcinomas, particularly in patients with a significant tobacco smoking history.[41] Following on from experience in melanoma populations, the Phase II BRF113928 trial investigated the combination of BRAF inhibitor dabrafenib and MEK inhibitor trametinib in *BRAF*-positive NSCLC. Given the rarity of this mutation, the study was small and open label in design. In 36 treatment-naïve patients with metastatic *BRAF V600E*-mutant lung cancer, combination therapy led to complete or partial response in 23 of the patients (64%).[42] These findings have led to regulatory approval of this combination in the *BRAF V6003*-mutant patient group.

IMMUNOTHERAPY IN THE ERA OF PRECISION MEDICINE

Despite recent advances in the understanding of oncogene-dependent tumour biology and the success of driver mutation targeted therapy, all Stage IV lung cancers will eventually progress. Understanding the role of immunosurveillance in controlling tumour progression has been fundamental in the development of new immune based strategies for the treatment of lung cancer.[43]

The immune destruction of tumour cells is mediated by cross-talk between the adaptive and innate immune systems, and the tumour cells.[44] Tumour cell elimination occurs when antigen-presenting cells recognise neo-antigens expressed on tumour cells and subsequently present them to T cells, priming these cells to affect an antitumour response. The ability of the tumour cell to escape immunosurveillance depends on the production of immunosuppressive cytokines; loss of major histocompatibility complex antigen expression; T cell inhibitory signals including increased expression of CTLA-4, PD-1, and its ligand PD-L1; and increased regulatory T (T_{reg}) cells in the tumour microenvironment.[45] Overexpression of PD-L1 in NSCLC, for example, inhibits primed T-cell activation and promotes immune evasion of the tumour.[46]

Immunotherapy takes advantage of these tumour features and has been a greatly successful strategy in lung cancer. The PD-1/PD-L1 pathway can be specifically targeted with a class of drugs known as immune checkpoint inhibitors. These agents have been trialled in first-line, second-line, and adjuvant settings in both early and late-stage disease, and across all NSCLC histologic subtypes. In the wake of a growing body of evidence, monoclonal anti-PD1 antibodies nivolumab and pembrolizumab, and the anti PD-L1 antibody atezolizumab, have firmly established roles in the treatment of advanced NSCLC. Landmark studies CheckMate-017 and CheckMate-057 used second-line nivolumab in patients with metastatic squamous and non-squamous NSCLC, respectively.[47,48] Both studies showed improved overall survival and response rate, and reduced toxicity compared to docetaxel.[49] Similar findings have been demonstrated for pembrolizumab and atezolizumab, and all three agents are now approved for second-line therapy in advanced NSCLC. At present, pembrolizumab is the only approved first-line single-agent treatment for advanced-stage NSCLC in tumours with a PD-L1 expression of ≥50%, with impressive improvements in overall survival when compared to standard platinum doublet therapy.[50] In patients with unresectable Stage II and III disease, PD-L1 inhibitor durvalumab has also been shown to confer survival benefit when given as adjuvant therapy.[51]

Importantly, patients harbouring an *EGFR* mutation have not benefited from immune checkpoint inhibitors in these studies, possibly because tumours with a known driver-mutation

characteristically have a reduced tumour mutational burden (TMB).[49] Indeed, TMB has emerged as a promising biomarker for predicting treatment response. In the CheckMate-227 trial, combination therapy with nivolumab and ipilumimab (an anti-CTLA-4 antibody) demonstrated efficacy in comparison to standard first line platinum doublet chemotherapy in patients with a high TMB, irrespective of PD-L1 expression.[52] Notably, increased immune-related adverse effects were observed in the combination therapy arm.

Although used in some studies for inclusion purposes, PD-L1 expression may not be the best biomarker for all check-point inhibitors. For instance, nivolumab and atezolizumab demonstrated efficacy in comparison to docetaxel in the second-line treatment setting, irrespective of PD-L1 expression.[47,48,53] Furthermore, pembrolizumab in combination with platinum doublet chemotherapy, irrespective of PD-L1 expression, showed improvement in overall 1-year survival in patients with both squamous and non-squamous histology.[54,55]

Immunotherapy in Small Cell Lung Cancer

Despite the significant advances in precise and targeted treatment for NSCLC, therapy for small cell lung cancer (SCLC) has developed more slowly. The majority of SCLC is extensive-stage at the time of diagnosis, with median overall survival 8–13 months.[56] Standard first-line therapy includes combination platinum and etoposide chemotherapy. Supporting the use of immune therapies in SCLC is their high immunogenicity, with an increased prevalence of associated paraneoplastic disorders. The IMpower133 trial has been practice changing, showing that the addition of atezolizumab to carboplatin and etoposide in previously untreated patients with metastatic SCLC led to clinically significant improvements in overall survival. Furthermore, this treatment effect occurred irrespective of the TMB.[57] Studies of nivolumab, ipilimumab, pembrolizumab, durvalumab, and other immune checkpoint inhibitors in SCLC have also been conducted, with varying benefit.

Novel Approaches to Immunotherapy

Aside from targeting the PD-1/PD-L1 pathway, the immune response can be harnessed in other ways to affect an antitumour response. Two approaches under investigation include development of tumour specific vaccines, and manipulation of T-cells *ex vivo* to specifically target tumour cells. Overall, studies in lung cancer vaccines have been disappointing compared to those in immune checkpoint inhibitor therapy, perhaps due to the immunosuppressive tumour microenvironment.[58] One strategy that has led to vaccine approval in Cuba is CIMAvax-EGF, a vaccine combining EGF with p64, which is a protein conjugate designed to enhance immunogenicity. In a Phase III randomised control trial of 405 Stage IIIB/IV NSCLC patients, CIMAvax-EGF vaccination resulted in a per-protocol median overall survival benefit, compared to best supportive care (12.43 versus 9.43 months, p=0.036).[59]

Adoptive cell therapy utilises T lymphocytes that have been isolated from the patient and genetically transformed to express a chimeric antigen receptor (CAR) targeted against a tumour derived antigen. CAR T-cells have mostly been studied in the setting of CD19 expressing haematological malignancies, with complete remission achieved in 68–100% of acute lymphocytic leukaemia patients.[60] One of the primary obstacles for CAR T-cell therapy in solid organ cancers is identifying tumour antigens that are not also expressed by healthy tissue. It is possible that the antitumour activity of CAR-T cells may be optimised with the addition of immune checkpoint inhibitors, with clinical trials currently underway.[61] A novel approach utilises CRISPR gene editing technology to destroy the PD-1 receptor, removing the inhibitory signal and thereby augmenting CAR-T cell cytotoxic tumour activity.[62]

FUTURE DIRECTIONS FOR PRECISION MEDICINE IN LUNG CANCER: BIOMARKERS AND TECHNOLOGY

The Role of Liquid Biopsies

Liquid biopsy is an emerging technology at the forefront of precision medicine in lung cancer, with potential for screening, diagnosis, and prediction of treatment response. It is a noninvasive method that can detect exosomes, circulating cell-free tumour DNA (cfDNA), cell-free tumour RNA (cfRNA), and circulating tumour cells (CTC).[63] Liquid biopsies show great promise for cancer

screening, however due to the rarity of CTC and tumour DNA products, extremely sensitive methods are required for their detection. Blood-based assays for detecting cfDNA, a chromatin DNA fragment, include PCR, droplet digital PCR, beads, emulsions, amplification and magnetics (BEAMing), and next-generation sequencing. A study using the sensitive method Cancer Personalized Profiling by deep Sequencing (CAPP-Seq) showed that cfDNA was detectable in 100% of Stage II–IV NSCLC patients, and in 50% of patients with Stage I disease.[64] Interestingly in this study, cfDNA levels correlated with tumour volume. Due to a short half-life in circulation and potential for contamination with wild-type DNA, tumour-specific DNA can be difficult to isolate. Evolving technologies provide hope for future clinical application of cfDNA for diagnostic purposes.

CTC originating from tumour tissue can be detected with multiple techniques of varying sensitivities and specificities. A recent study demonstrated the presence of CTC in patients without evidence of clinically detectable lung cancer.[65] The study included patients at risk for lung cancer, specifically those with chronic obstructive pulmonary disease. At baseline, 3% of the cohort had detectable CTC at baseline. Subsequent annual surveillance CT scans revealed the development of lung nodules 1–4 years after CTC detection. Early stage lung cancers were confirmed with resection. This study supports the fact that CTC migrate into the blood stream at an early stage of cancer development, potentially serving as a screening tool in high risk populations.[65] As CTC can be morphologically heterogeneous, refinement of highly sensitive techniques for isolation has been challenging. Lack of standardisation of these methods has also limited their implementation into clinical practice to date.

Liquid biopsy specimens taken before, during, and after treatment can also elucidate tumour genomic changes over the course of the disease. In particular, this technology is clinically useful for the detection of drug resistance-related gene mutations.[66] The use of cfDNA genotyping for detection of *T790M* mutations conferring resistance to EGFR-TKI treatment is now U.S. Food and Drug Administration (FDA)-approved.[67]

Lipidomics

In addition to liquid biopsies, the emerging science of lipidomics may also play a role in the early detection of cancer. Lipidomics, a branch of metabolomics, refers to the quantification of all lipids within a biological system.[68] Lipids assist in membrane structure, storage of energy, and signal transduction in human cells, properties also utilised by cancer cells. Lipid metabolic profiles of serum from patients with early-stage NSCLC have been shown to be distinguishable from healthy controls and benign lung disease, showing promise as a biomarker for lung cancer diagnosis.[69]

Breathprinting

Analysis of exhaled volatile organic compounds can be undertaken to detect a cancer-related fingerprint, or 'breathprint', by an electronic nose. This approach to cancer diagnosis was derived from studies in trained household dogs, demonstrating the ability to distinguish exhaled breath samples of patients with lung and breast cancer from healthy controls.[70] Subsequent studies of different electronic nose platforms for the early detection of lung cancer have shown high sensitivity (73–93%) and specificity (73–100%).[71] Furthermore, there may be a unique volatile organic compound breathprint produced by tumours with *EGFR*, *ALK*, and *p53* rearrangements, helping to facilitate noninvasive diagnosis and genotyping.[72] Application of this technology is still translational and requires further validation prior to broader clinical use.

Radiomics and Deep Learning Techniques

Computational methods including radiomics and deep learning algorithms are developing technologies that can extract qualitative and quantitative data from radiological images, aiming to provide noninvasive biomarkers to aid with personalised clinical decision making. Radiomics refers to the quantification of radiological image texture, with subsequent correlation to clinical and genetic features, allowing a deeper processing of the image beyond the resolution of the human eye.[73] A study utilising radiomics in a subset of the National Lung Cancer Screening Trial (NLST) data demonstrated high accuracy for predicting malignancy in nodules found on

low dose CT.[74,75] False positive rates were also much lower than in the original study (9.0% versus 96.4%). CT radiomic features (including air-bronchograms, ground glass components, pleural retraction, and tumour size) have also been correlated with mutations in *EGFR*, *KRAS*, and *ALK* genes in NSCLC.[76-78] This combination of highly detailed radiologic and genomic data, so-called 'radiogenomics', has the potential to provide precise cancer characterisation as sophisticated technologies become increasingly available.

Deep learning algorithms are artificial neural networks that can be taught to recognise and interpret radiological patterns for diagnostic, therapeutic, and prognostic outputs. As with radiomics, deep learning has also been applied to the NLST low-dose CT data set, demonstrating superiority over human experts for predicting development of lung cancer, with AUC 0.94 and false positive rate 11%.[79] The prognostic value of this technology was shown in a cohort of patients with surgical resection of NSCLC.[80] In this study, deep learning networks outperformed traditional prognostic models such as tumour volume and TNM staging, with an AUC of 0.71.

Clinical Decision Support Systems

Clinical Decision Support Systems (CDSS) are electronic systems developed for clinicians, integrating a vast array of clinical data extracted from the electronic health record to inform management and surveillance decisions in cancer patients. Although currently limited in utility, CDSS for lung cancer patients have been shown to positively influence cancer care, and may foreseeably augment decisions made by the multidisciplinary team.[81] Future CDSS that will incorporate radiomic and genomic data with other important clinical variables to enable therapeutic decision-making will offer tremendous advantages in the field of personalised medicine.

Summary of 'Omics' Data

Omics data, including the technologies described above, can be integrated to comprehensively understand the processes involved with cancer cell biology. There is huge potential for genomic and transcriptomic information to enable complex molecular profiling of individual cancers, giving new insights into tumour survival mechanisms, progression, and metastatic potential.[82]

CONCLUSION

The diagnosis and management of lung cancer have come a long way in the last decade, with increasing focus on a personalised approach. Novel technologies, such as liquid biopsy, omics data, and artificial intelligence present exciting opportunities for minimally invasive cancer diagnosis and characterisation. It is feasible that such techniques will serve as potential screening tools for populations at risk of developing lung cancer. The discoveries of driver mutations and key immunological pathways in many lung cancers have revolutionised therapy, highlighting the importance of accurate tumour characterisation. The development of resistance to targeted treatments continues to pose significant therapeutic challenges, requiring further interrogation into the underlying molecular processes promoting tumour growth. Further work needs to be done to elucidate patients who will derive the greatest benefit from available therapies, and to uncover tumour-specific biological processes that may be exploited for therapeutic purposes.

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The Importance of Molecular Testing in the Treatment of Cholangiocarcinoma

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Abstract

Cholangiocarcinomas (CCA) are uncommon malignant tumours and are classified as intrahepatic, perihilar, or distal, depending on where they arise within the biliary epithelium. Surgery is still the only curative treatment, yet diagnosis is often made too late for this to be a viable option. For patients with locally advanced (unresectable), metastatic, or recurrent CCA, guidelines recommend palliative first-line chemotherapy with platinum compounds plus gemcitabine. However, the benefits are limited, with median overall survival being below 1 year, and there is an urgent need for novel, more effective treatment options.

Next-generation sequencing has revealed information about the genetic makeup of the CCA subtypes and CCA, especially intrahepatic, rank among tumours with the highest rate of potentially actionable gene alterations. A number of next-generation sequencing platforms are now commercially available, opening up the possibility for routine molecular testing at the time of diagnosis to allow a more personalised, targeted treatment approach. However, despite the availability of these platforms, barriers to their use remain, including issues with reimbursement in some countries.

Several clinical trials have been completed or are underway in CCA, investigating treatments directed against potentially actionable targets, such as *FGFR2*, *IDH*, *NTRK*, *BRAF*, and *HER2*. Some of these treatments are showing promising efficacy. Alongside, or before, initiating standard chemotherapy, efforts should be made to identify specific targets in all patients via molecular testing and treat eligible patients accordingly or enrol them in appropriate clinical trials.

INTRODUCTION

Cholangiocarcinomas (CCA) belong to the constellation of biliary tract cancers (BTC), along with gallbladder carcinomas and ampullary carcinomas. Among this heterogeneous group of uncommon tumours, CCA are notable for their high frequency of molecular alterations that are potentially amenable to therapeutic interventions. As such, CCA may be the ideal playground for a systematic policy of molecular testing. In this review, the authors underscore the need for early molecular testing in patients with advanced CCA as a result of the poor prognosis and limited therapeutic arsenal; the critical role of close communication between the molecular tumour board and the treating clinicians; co-operation in recommending appropriate novel tests, targeted therapies, or clinical trials based on the interpretation of individual patient's data to fulfil the unmet needs in CCA; and the need for patient education, which should facilitate personalised decision-making, particularly when considering participation in appropriate clinical trials.

EPIDEMIOLOGY AND DIAGNOSIS

CCA are tumours of the biliary epithelium. They are categorised according to anatomical location into intrahepatic, perihilar, and distal. Intrahepatic CCA (iCCA) comprise 10–20% of all CCA[1] and arise above the second-order bile ducts within the liver parenchyma. They can be further subdivided into large-duct type, resembling CCA that arise outside the liver, and smallduct type, which share pathological, aetiological, and imaging characteristics with hepatocellular carcinoma.[2] Perihilar CCA (pCCA) involve the hilar region where the left and right bile ducts exit the liver and join to form the common hepatic duct; they make up 50% of all CCA.[1] Distal CCA (dCCA), which account for 30–40% of all CCA,[1] involve the common bile duct outside the liver.

CCA is the second most common hepatic cancer after hepatocellular carcinoma.[3] In most countries it is rare, with an annual incidence of <6 cases per 100,000, but certain countries, such as Thailand and South Korea, have a particularly high incidence.[4] Epidemiological studies suggest that rates of iCCA are increasing, particularly in Western countries; conversely, the incidence of both pCCA and dCCA appears to be declining.[5] However, inconsistences in the classification of the subtypes indicate that these trends should be interpreted with caution.[5] Worldwide, the average age at presentation is 50 years, although this is closer to 70 years in Western countries.[6] CCA is slightly more common in males than females; data from the USA suggest a male:female ratio of 1.5:1.0.[6]

There are several risk factors for CCA, including biliary cysts and stones, primary sclerosing cholangitis, chronic liver diseases that lead to liver fibrosis (e.g., viral hepatitis), and congenital biliary tree abnormalities.[6-8] In parts of Asia, CCA is often associated with liver fluke infestation and hepatolithiasis,[6,7] but most cases arise in the absence of any known risk factor.[7,9]

Early diagnosis of CCA is challenging because most patients with early-stage disease are asymptomatic or have mild and/or nonspecific symptoms,[10] particularly those with iCCA, in which

jaundice is a late symptom. These patients may be identified incidentally with imaging studies or testing for liver enzyme abnormalities.

CURRENT TREATMENT OPTIONS FOR CHOLANGIOCARCINOMA

Patients with early-stage disease should undergo frontline surgical resection with curative intent; however, most patients are diagnosed too late for this to be feasible.[4] Even after curative intent surgery, the probability of relapse is high at 50–60%[11] and there is a need for effective adjuvant therapy to improve survival.[12] Based on the BILCAP study,[13] international guidelines currently recommend adjuvant chemotherapy with capecitabine for 6 months as standard after resection.[12] The ACTICCA-1 study comparing capecitabine with combination of cisplatin and gemcitabine (CISGEM) as adjuvant therapy following resection is ongoing.[14] Patients with an early diagnosis of pCCA may be put forward for neoadjuvant chemotherapy and radiotherapy followed by liver transplant,[7,15] but firm evidence of the survival benefit with such complex multimodal therapy is lacking.

Most patients with CCA have locally advanced (unresectable) or metastatic disease at presentation.[9] Patients with unresectable, metastatic, or recurrent CCA receive palliative systemic therapies; those with locally advanced disease may also receive locoregional therapies.[1] Chemotherapy is the mainstay of systemic treatment, with CISGEM being the current standard of care for first-line therapy.[1,9,16] Alternative first-line regimens include CAPOX (capecitabine plus oxaliplatin, also known as XELOX)[17] and GEMOX (gemcitabine plus oxaliplatin).[18] Overall, palliative chemotherapy has very limited efficacy in BTC: median overall survival (OS) with CISGEM is <1 year.[16] Published data suggest that 17.5–32.5% of patients who fail first-line therapy may be fit enough to receive second-line chemotherapy.[19-22] Based on the findings of the ABC-06 trial,[23] FOLFOX (folinic acid, fluorouracil, and oxaliplatin) can be considered the standard of care in this setting,[9] although with modest efficacy (median OS: 6.2 months).[23] There is currently no validated standard of care for third or further lines of therapy.

There is an urgent need for more effective treatment options for patients with unresectable, metastatic, or recurrent CCA. BTC have one of the highest frequencies of actionable molecular alterations among hard-to-treat solid tumours,[24,25] so one potential route is via molecular testing to detect these alterations and open up the possibility of targeted, personalised medicine.

MOLECULAR TESTING USING NEXT-GENERATION SEQUENCING

Next-generation sequencing (NGS) encompasses several modern DNA and RNA sequencing technologies.[26] It requires significantly less DNA or RNA than traditional Sanger sequencing, and is quicker, cheaper, and more accurate.[27] A number of NGS platforms are commercially available (Table 1), and all are designed to screen for a wide panel of genetic alterations involved in cancer, including those described in CCA. Because of the ability of certain genes (e.g., *FGFR2* and *NTRK*) to form fusions with multiple partners (described below), not all fusions are detected by DNA NGS platforms. Centres may therefore need to use additional RNA sequencing to obtain a more robust result, either through RNA NGS or other techniques. RNA NGS requires less sequencing than DNA NGS because of the intron splicing that occurs during mRNA production,[28] and RNA sequencing has shown extremely high sensitivity and specificity in detecting actionable gene fusions.[29] However, RNA is highly labile and can easily be damaged during preparation for the screen, leaving fragments that are too short to be informative.[28] Some platforms offer both DNA and RNA NGS (Table 1); for example, the Oncomine™ Focus Assay (Thermo Fisher Scientific, Waltham, Massachusetts, USA) can screen both DNA and RNA in a single workflow.

Fluorescence *in situ* hybridisation and immunohistochemistry (IHC) are commonly used techniques that may be employed when NGS is unavailable. However, they are of limited use in characterising genetic aberrations, particularly fusions. Although both can detect the fusion gene, neither can further identify the fusion gene partner.[30] Fluorescence *in situ* hybridisation can only detect a single target at a time; designing the multiple probes required to screen for every gene of interest is labour-intensive and not cost-effective.[28,30]

Table 1: Next-generation sequencing panels for genomic profiling of solid tumours.

Assay name	FoundationOne® CDx	MSK-IMPACT™	Molecular Intelligence®	Oncomine™	
				Tumour Mutation Load assay	Focus
Company/institution	Foundation Medicine, Inc., Cambridge, Massachusetts, USA	Memorial Sloan-Kettering Cancer Center, New York City, New York, USA	Caris Life Science, Irving, Texas, USA	Thermo Fisher Scientific Waltham, Massachusetts, USA	
Sequencing platform	Illumina HiSeq 4000	Illumina HiSeq 2500	Illumina MiSeq	Ion GeneStudio S5 series, Ion S5™ XL	Ion GeneStudio S5 series
DNA or RNA	DNA	DNA	DNA and RNA	DNA	DNA and RNA
Number of genes	324	468	592 for DNA;* 10 for RNA	409	52
Types of alterations	Substitutions, indels, CNV, rearrangements. Analyses microsatellite instability and tumour mutational burden.	SNV, indels, CNV, rearrangements. Analyses microsatellite instability and tumour mutational burden.	Mutations, indels, CNV, fusions, variant transcripts.	SNV, indels.	Hotspots, SNV, indels, CNV, fusions.
Add-on tests available?	IHC for PD-L1	Not stated	IHC, *in situ* hybridisation, Sanger sequencing, Pyro sequencing, fragment analysis.	Not stated	Not stated
Turnaround time	<2 weeks	<3 weeks	8–14 days	2–3 days	3 days

The table shows a representative sample of the available next-generation sequencing platforms.

*Whole exome sequencing performed for all breast, ovarian, pancreas, and prostate cancers; all other tumours undergo 592-gene next-generation sequencing.

CNV: copy number variation; IHC: immunohistochemistry; SNV: single nucleotide variant.

Guidelines on the use of molecular screening are becoming available; for example, in 2019 the European Society for Medical Oncology (ESMO) published recommendations on the use of NGS and other technologies for the detection of *NTRK* fusions.[30] For cancers in which these fusions are rare, such as CCA, ESMO recommends using an NGS platform that is known to reliably detect these fusions and to include RNA testing where possible. IHC could then be used to confirm protein expression in positive cases.[30] Where NGS is not readily available, ESMO recommends first using IHC to detect protein expression, and then to use NGS in cases where protein overexpression is detected. More recently, ESMO has recommended routine use of NGS in a number of advanced cancers, including CCA (described below).[31]

ACTIONABLE MOLECULAR TARGETS AND EMERGING TARGETED THERAPIES IN CHOLANGIOCARCINOMA

Molecular profiling using NGS has revealed the complex genetic makeup of the different CCA subtypes.[32,33] For example, *FGFR2* fusions and mutations in *IDH1*, *IDH2*, and *BRAF* genes are most frequent in iCCA, whereas *HER2* (*ERBB2*) mutations and amplifications are predominantly found in pCCA and dCCA, as well as gallbladder cancers. *KRAS* and *TP53* mutations are common in all subtypes.[9,32,33] The distribution of *NTRK* mutations between CCA subtypes has not yet been reported.

The identification of these potentially actionable targets in CCA is of great clinical significance and has driven clinical trials investigating specific agents. Here, the authors highlight Phase II/III studies of the most promising agents directed at the key actionable molecular targets: *FGFR2*, *IDH*, *NTRK*, *BRAF*, and *HER2.* Immunotherapies are also briefly discussed.

Treatments Targeting *FGFR2*

The *FGFR2* pathway is involved in cellular migration, proliferation, differentiation, and survival.[34] 50% of patients with CCA have a clinically significant genomic abnormality, such as an *FGFR2* fusion or rearrangement.[35] They are constitutively active and can occur with multiple partners.[34-37] The most common *FGFR2* fusions include *FGFR2–PPHLN1*, *FGFR2–AHCYL1*, and *FGFR–BICC1*.[36] NGS has allowed the identification of novel *FGFR2* fusions.[38,39] For example, in an analysis of 118 *FGFR2*-positive patients enrolled in the Phase II FIGHT-202 study, Hollebecque et al.[39] observed 54 unique *FGFR2* rearrangements, of which 40 (74%) were unique to a single patient.

Pemigatinib is an FGFR1-3 selective kinase inhibitor that has recently received accelerated U.S. Food and Drug Administration (FDA) approval for treatment of adult patients with previously treated, unresectable locally advanced, or metastatic CCA with *FGFR2* fusions or other rearrangements as detected by an FDA-approved NGS platform.[40] This approval was based on the results of the FIGHT-202 study (Table 2[41-58]), an international, multicentre, open-label, single-arm, multicohort, Phase II study in patients with CCA whose disease had progressed following at least one previous treatment and who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2.[41,42] In this study, patients were assigned to one of three cohorts depending on *FGF/FGFR* status: patients with *FGFR2* fusions or rearrangements, patients with other *FGF/FGFR* alterations, or patients with no *FGF/FGFR* alterations. They received oral pemigatinib at a starting dose of 13.5 mg once daily (21-day cycle; 2 weeks on, 1 week off) until disease progression, unacceptable toxicity, withdrawal of consent, or physician decision. The primary endpoint was the proportion of patients with *FGFR2* fusions or rearrangements who achieved an objective response, assessed by independent central review. A total of 146 patients were enrolled: 107 with *FGFR2* fusions or rearrangements, 20 with other *FGF/FGFR* alterations, 18 with no *FGF/FGFR* alterations, and one with an undetermined *FGF/FGFR* alteration. The median follow-up was 17.8 months (interquartile range: 11.6–21.3). There were 38 (35.5%; 95% confidence interval [CI]: 26.5–45.4) patients with *FGFR2* fusions or rearrangements who achieved an objective response (three had complete responses and 35 had partial responses). The median duration of response was 7.5 months, and median progression-free survival (PFS) was 6.9 months.[42] *FGFR–BICC1* was the most common fusion (present in 30% of patients); however, there were no meaningful differences in objective response rate (ORR), median PFS, or median OS between patients with *FGFR–BICC1* fusions and those with other *FGFR2* rearrangements.[39] Hyperphosphataemia was the most common adverse event across all three cohorts, which was reported by 88 (60%) of 146 patients.[42] Grade 3 or worse adverse events occurred in 93 (64%) patients, with the most frequent being hypophosphataemia (18 patients [12%]) and arthralgia (nine [6%]). Sixty-five (45%) patients had serious adverse events, with the most frequent being abdominal pain (seven [5%]) and pyrexia (seven [5%]). Overall, 71 (49%) patients died during the study; the most common cause of death was disease progression (61 [42%]) and no deaths were treatment related. The results of FIGHT-202 showed the therapeutic potential of pemigatinib in previously treated patients with CCA with *FGFR2* fusions or rearrangements. Pemigatinib is currently being compared with CISGEM as first-line therapy for

patients with unresectable and/or metastatic CCA in the Phase III FIGHT-302 study (Table 2).[43]

The FGFR inhibitors infigratinib and futibatinib (TAS-120) have also been shown to be effective in Phase II studies in pretreated patients with *FGFR2* alterations, with manageable toxicity (Table 2).[44,45,47,48] Corresponding Phase III studies in patients with previously untreated advanced CCA are ongoing.[46,49] Other FGFR inhibitors are also under investigation in Phase II studies (Table 2).[50-53]

Table 2: Recent or ongoing Phase II/III studies of treatments targeting the key driver mutations *FGFR2*, *IDH*, *NTRK*, and *BRAF* in cholangiocarcinoma.

Target/agent	Study acronym/ design	Comparator	Population	Results	Reference
FGFR2 Pemigatinib	FIGHT-202 Phase II, multi-cohort	None	Advanced CCA with or without *FGFR2* alterations; failed previous therapy	Interim results for pts with *FGFR2* fusions/ rearrangements (n=107): objective response rate 35.5%; PFS: 6.9 mo; DoR: 7.5 mo	NCT02924376[41] Abou-Alfa et al.,[42] 2020
	FIGHT-302 Phase III, open-label	CISGEM	Advanced CCA with *FGFR2* rearrangement; treatment-naïve	Ongoing	NCT03656536[43]
Infigratinib	Phase II	None	Advanced CCA with *FGFR2* fusions or mutations; failed previous therapy	Interim results (n=61): overall response rate 14.8%; PFS: 5.8 mo	NCT02150967[44] Javle et al.,[45] 2018
	PROOF Phase III, open-label	CISGEM	Advanced CCA with *FGFR2* fusions/ translocations; treatment-naïve	Ongoing	NCT03773302[46]
Futibatinib	FOENIX-CCA2 Phase II	None	Advanced iCCA with *FGFR2* fusions or rearrangements; failed previous therapy	Interim results (n=67): objective response rate 34.3%; DoR: 6.2 mo	NCT02052778[47] Goyal et al.,[48] 2020
	FOENIX-CCA3 Phase III, open-label	CISGEM	Advanced iCCA with *FGFR2* gene rearrangements	Yet to begin recruitment	NCT04093362[49]
Erdafitinib	Phase II	None	Asian patients with advanced NSCLC, urothelial or gastroesophageal cancer, or CCA	Ongoing	NCT02699606[50]
Debio-1347	FUZE Phase II, basket	None	Advanced solid tumours (including CCA) harbouring *FGFR1-3* fusions or rearrangements	Ongoing	NCT03834220[51]
Ponatinib	Phase II	None	Advanced solid tumours (including CCA) with *FGFR1-4*, *RET*, *KIT*, *PDGFRα*, *RET*, *ABL-1*, or *FLT3* mutations	Ongoing	NCT02272998[52]
	Phase II, single centre	None	Metastatic BTC with *FGFR2* fusions or *FGFR* pathway mutations/ amplifications; failed previous therapy	Clinical benefit (i.e., complete response, partial response, or stable disease): 45.5% of 11 pts	NCT02265341[53]

Table 2 continued.

Target/agent	Study acronym/ design	Comparator	Population	Results	Reference
IDH1/2 Ivosidenib	ClarIDHy Phase III, double-blind	Placebo	Advanced *IDH1*-mutant CCA; progressed on previous therapy; had received at least two previous therapies for advanced disease	Interim results (n=185) ivosidenib vs placebo: PFS: 2.7 mo vs 1.4 mo (HR: 0.37; 95% CI: 0.25-0.54; p<0.0001); OS: 10.8 mo vs 9.7 mo (HR: 0.69; 95% CI: 0.44–1.10; p=0.06)	NCT02989857[54] Abou-Alfa et al.,[55] 2020
NTRK Entrectinib	STARTRK-2 Phase II, basket	None	Advanced solid tumours (including CCA) harbouring a *NTRK1-3*, *ROS1*, or *ALK* rearrangement	Ongoing	NCT02568267[56]
BRAF Dabrafenib + trametinib	ROAR Phase II	None	Rare cancers (including CCA) harbouring a *BRAF V600E*-mutation	Interim results for patients with BTC (n=43): overall response rate 47%; DoR: ≥6 mo in 54% of responders; PFS: 7.2 mos; OS: 11.3 mo	NCT02034110[57] Subbiah et al.,[58] 2020

CCA: cholangiocarcinoma; CI: confidence interval; DoR: median duration of response; HR: hazard ratio; mo: months; NSCLC: non-small cell lung cancer; OS: median overall survival; PFS: median progression-free survival; pts: patients; vs: versus.

Treatments Targeting *IDH*

Mutations in *IDH1* and *IDH2* are associated with the production of the aberrant, oncogenic metabolite, 2-hydroxyglutarate.[59] *IDH1* mutations are present in approximately 13% of patients with iCCA, compared with 0.8% of patients with pCCA/dCCA.[60] ClarIDHy is an international, randomised, placebo-controlled Phase III study of the IDH1 inhibitor ivosidenib in 185 patients with advanced, pretreated CCA with *IDH1* mutations who had progressed on previous therapy, and had up to two previous treatment regimens for advanced disease and an ECOG PS score of 0 or 1 (Table 2).[54,55] The primary endpoint was PFS, assessed by an independent central review.

An interim analysis showed that treatment with ivosidenib 500 mg once daily resulted in a significant improvement in median PFS over placebo (2.7 months versus 1.4 months; hazard ratio [HR]: 0.37; 95% CI: 0.25–0.54; p<0.0001).[55] Median OS was 10.8 months with ivosidenib versus 9.7 months with placebo (HR: 0.69; 95% CI: 0.44–1.10; p=0.060). The study, however, allowed patients in the placebo group to cross over to the ivosidenib group at disease progression. Adjustment for this gave a median OS of 6.0 months for the placebo group, which was significantly shorter than for the ivosidenib group (HR: 0.46; 95% CI: 0.28–0.75; p=0.0008).[55] More mature data regarding OS are awaited. The most common Grade 3 or worse adverse event in both treatment groups was ascites, which occurred in four (7%) of 59 patients receiving placebo and nine (7%) of 121 patients receiving ivosidenib. Thirty-six (30%) patients receiving ivosidenib and 13 (22%) patients receiving placebo had serious adverse events. There were no treatment-related deaths. The results of ClarIDHy support the clinical benefit of targeting *IDH1* mutations in advanced, *IDH1*-mutant CCA.

Treatments Targeting *NTRK*

The *NTRK1*, *NTRK2*, and *NTRK3* genes encode the receptor tyrosine kinases TRKA, TRKB, and TRKC, which are pivotal in the development and function of the nervous system.[61] *NTRK* fusions are rare in CCA: recent studies suggest they are present in <1% of patients.[62,63] They are better characterised in Asian patients than in Caucasian

patients[64] and the development of specific NTRK inhibitors means that interest in this mutation is growing. Like *FGFR2*, *NTRK* can partner with a variety of other genes,[38,65] and novel fusions have been identified through NGS.[38]

The NTRK inhibitor larotrectinib is approved in Europe and the USA for patients with solid malignancies and a proven *NTRK* gene fusion without a known acquired resistance mutation.[66,67,68] In a Phase I/II study in 55 adults and children who had tumours with these fusions, the overall response rate (primary study endpoint) was 75% (95% CI: 61–85%) according to an independent review, including one of the two patients in the study with CCA.[68] At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression-free. Toxicity was mild, with most adverse events being Grade 1.

Entrectinib has received FDA breakthrough designation status for treatment of cancers harbouring *NTRK*[69] and is currently being evaluated in the Phase II STARTRK-2 basket study (Table 2).[56]

Although *NTRK* fusions are rare in CCA, and CCA are uncommon in most Western countries, the marked and durable antitumour activity of NTRK inhibitors in patients with *NTRK* fusion–positive cancer, regardless of the age of the patient or the tumour type, warrants adding these targeted agents to the therapeutic armamentarium of CCA.

Treatments Targeting *BRAF*

Mutations in *BRAF* lead to constitutive activation of the mitogen-activated tyrosine kinase pathway, resulting in increased cell proliferation and decreased apoptosis.[70] The most common *BRAF* mutation is *V600E*, which occurs in approximately 5% of patients with iCCA.[71,72] The combination of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) has shown activity in several *BRAF V600E*-mutated cancers. In a study that forms part of an ongoing, Phase II, open-label, single-arm, multicentre, Rare Oncology Agnostic Research (ROAR) basket trial in patients with *BRAF V600E*-mutated rare cancers, 43 patients with *BRAF V600E*-mutated, advanced BTC (iCCA, 39 patients), an ECOG PS of 0–2, and who had received previous systemic treatment were treated with oral dabrafenib 150 mg twice daily and oral trametinib 2 mg once daily until disease progression or intolerance of treatment.[58] The overall response rate (the primary study endpoint) was 47% (95% CI: 31–62%). The most common Grade 3 or worse adverse event was increased γ-glutamyltransferase level, which was reported by five (12%) patients. Seventeen (40%) patients had serious adverse events; these were treatment-related in nine (21%) patients. The most frequent treatment-related serious adverse event was pyrexia, which occurred in eight (19%) patients. These results support consideration of dabrafenib plus trametinib combination treatment in patients with *BRAF V600E*-mutated BTC. The study authors recommend that routine testing for *BRAF V600E* mutations should be considered in all patients with BTC.

Treatments Targeting *HER2*

Overexpression of *HER2* is a key driver of tumour development in several cancers.[73] A number of targeted treatments are already available for *HER2*-positive patients with breast cancer, non-small cell lung cancer, gastric cancer, and pancreatic cancer. These include the tyrosine kinase inhibitors lapatinib, erlotinib, and afatinib, and the anti-HER2 antibodies trastuzumab and pertuzumab. Given this, HER2 is considered a candidate for targeted therapy in CCA. Presently, evidence is lacking, but preclinical studies suggest that the antibody-cytotoxic drug conjugate trastuzumab emtansine and the dual EGFR/HER2 inhibitor NVP-AEE788 may be effective in BTC.[74,75] There are also isolated reports of *HER2*-positive CCA patients responding to treatment with targeted therapy.[76,77]

HER2 targeting may benefit patients with *HER2* amplifications rather than those with mutations.[77] *HER2* amplifications are rarely seen in iCCA, so HER2-directed treatment may benefit patients with pCCA/dCCA more than those with iCCA.[78]

Immunotherapies in Cholangiocarcinoma

Upregulation of immune checkpoint molecules has been shown in CCA,[32] making immunotherapy another area of interest for targeted treatment. The antiprogrammed death-1 antibody pembrolizumab is being investigated as single-agent therapy in pretreated patients with advanced BTC in the ongoing Phase II KEYNOTE-158[79] and Phase Ib KEYNOTE-028[80]

studies. Analysis of data from KEYNOTE-158 (n=104) revealed an overall response rate of 5.8% and a median OS of 7.4 months.[81] Pembrolizumab is also being investigated as combination therapy with CISGEM.[82]

Another antiprogrammed death-1 antibody, nivolumab, is also under investigation as a treatment for CCA. A small Phase I study in Japan showed encouraging efficacy for nivolumab both as monotherapy (median PFS: 1.4 months; median OS: 5.2 months) and in combination with CISGEM (median PFS: 4.2 months; median OS: 15.4 months).[83] In a Phase II study, 45 patients with advanced BTC who received nivolumab as monotherapy had a median PFS of 3.98 months and a median OS of 14.22 months.[84,85] Nivolumab is currently being investigated in a Phase II study as combination therapy with either CISGEM or the anticytotoxic T-lymphocyte-associated protein 4 antibody ipilimumab in advanced BTC,[86] and in combination with ipilimumab in two basket studies.[87,88] A subgroup analysis of data from 39 patients with BTC enrolled in one of these basket studies[88] has been published: the ORR was 23%, with a median PFS of 2.9 months and a median OS of 5.7 months.[89]

The combination of the antiprogrammed death ligand-1 antibody durvalumab and the anticytotoxic T-lymphocyte-associated protein 4 antibody tremelimumab has shown promising efficacy when given alongside CISGEM in treatment-naïve patients with advanced BTC:[90] an interim analysis revealed an ORR of 73.3%, a median PFS of 11.9 months, and a median OS of 20.7 months.[91] Durvalumab is also currently being evaluated in combination with CISGEM in the Phase III TOPAZ-1 trial.[92]

PROPOSED CLINICAL WORKUP FOR PATIENTS WITH UNRESECTABLE CHOLANGIOCARCINOMA

Figure 1 shows how molecular testing should fit into the clinical pathway once CCA has been diagnosed via imaging and histology.

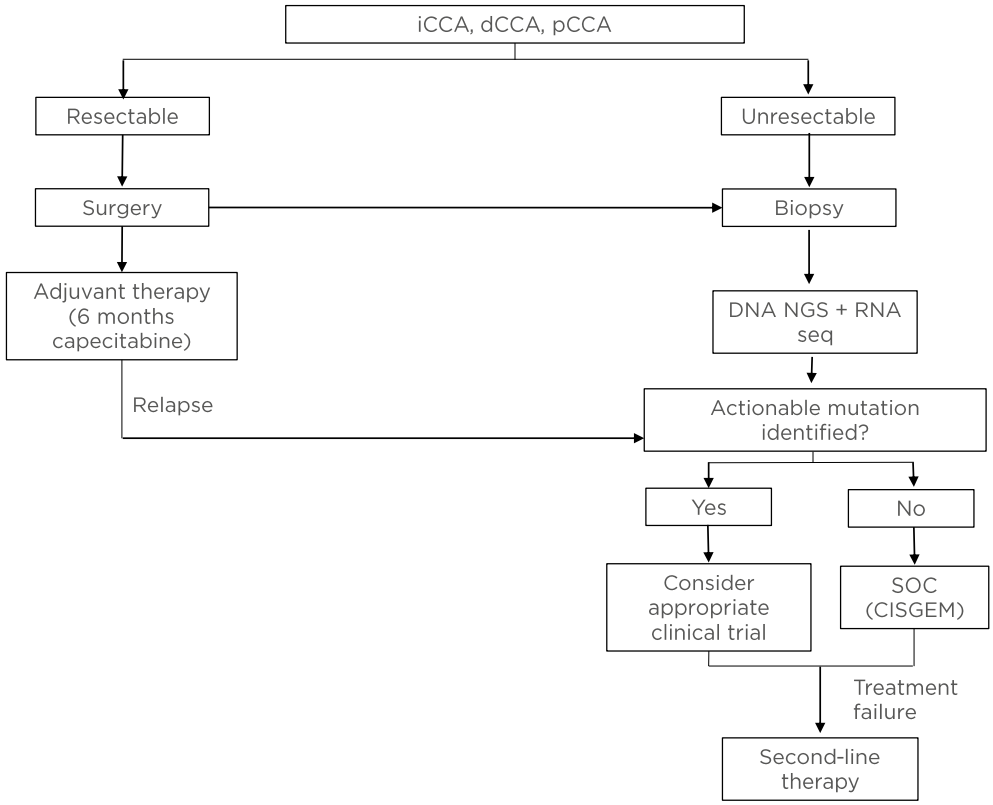

Figure 1: Proposed clinical workup for patients with unresectable or metastatic cholangiocarcinoma.

CISGEM: cisplatin plus gemcitabine; dCCA: distal cholangiocarcinoma; iCCA: intrahepatic cholangiocarcinoma; NGS: next-generation sequencing; pCCA, perihilar cholangiocarcinoma; seq: sequencing; SOC: standard of care.

The authors propose that all patients with unresectable CCA should undergo molecular testing at the time of initial diagnosis. A combination of DNA NGS and RNA sequencing (either via NGS or other techniques) should be used. In addition, patients who have already been diagnosed and are receiving CISGEM could be tested at the point of disease progression to determine whether they have a mutation that would allow enrolment into a clinical trial for those who have failed previous therapy. If a patient fails targeted therapy, NGS could be used to determine whether a resistance mutation is present.

Given the high incidence of tumour recurrence among patients who undergo surgery, molecular testing might also be carried out for these patients so that the appropriate course of treatment can be implemented in the event of relapse. However, whether molecular profiling at the time of surgery reliably reflects the molecular contexture at the point of recurrence is currently unclear.

Unfortunately, not all patients are currently able to benefit from molecular testing. In some European countries, such as France, molecular profiling is only available through institutional programmes or clinical trials. In addition, reimbursement varies across Europe. For example, in France there is no reimbursement for molecular testing, and it is not available privately. In Switzerland, NGS is reimbursed, but reimbursement for molecular targeted medications may not yet be established. This means that if a clinician wants to prescribe a particular targeted therapy, individual approval by the patient's health insurer needs to be obtained. It is important that barriers to molecular testing and subsequent targeted treatment are removed, so that all eligible patients can be considered for personalised therapy.

The data generated by NGS and other molecular profiling techniques can be complex. A molecular tumour board, with experts such as molecular oncologists, clinical geneticists, and molecular pathologists, can help clinicians interpret the data and suggest treatment options.[93,94] A multidisciplinary oncology board that includes an oncologist, hepatologist, pathologist, radiologist, radiation therapist, surgeon, nurse specialist, and primary care physician should then be involved in discussion of diagnosis and treatment. Research has shown that these boards have several benefits, including improved diagnostic decision-making, enhanced care, and knowledge transfer between teams.[94-96]

ESMO recently recommended routine use of NGS on tumour samples in CCA, advanced non-squamous, non-small cell lung cancer, prostate cancers, and ovarian cancers.[31] Other recommendations include using off-label drugs matched to genomics only when a national or regional access programme and decision procedure is in place, and that research centres develop multigene sequencing as a tool to screen patients eligible for clinical trials and to accelerate drug development. Data that could inform optimisation of the technology should be prospectively captured.

CONCLUSION

There has traditionally been a severe lack of treatment options for patients with unresectable CCA. However, there are now several promising emerging therapies that target driver mutations and may pave the way for a more personalised treatment approach. It is therefore important that patients undergo molecular screening at the time of initial diagnosis so that instead of standard of care chemotherapy, they are offered the option to enrol in an appropriate clinical trial, thereby giving them access to a more promising treatment while expanding the knowledge of the genetic makeup of CCA. Patients educated in the process of their own care and multidisciplinary oncology teams should collaborate as 'partners', so that the proposed algorithm for unresectable CCA can be practically applied for many patients in need. This may be the first step in overcoming barriers to performing molecular testing and using novel targeted therapies, prior to starting standard chemotherapy, whenever possible, in this aggressive malignancy.

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Race Against Time: Addressing the Unmet Needs of Patients with HER2-Positive Metastatic Breast Cancer

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Abstract

Over the last 20 years, there has been remarkable progress in the development of the therapies for human epidermal growth factor receptor-2 (HER2)-positive breast cancer (BC). Targeted treatment agents, such as trastuzumab, pertuzumab, lapatinib, and trastuzumab emtansine (T-DM1), are currently recommended as key components in the standard of care regimens for patients with HER2-positive BC. However, some patients still develop disease progression despite using such therapies. Since brain metastases present an urgent unmet need in many women with HER2-positive BC, clinical studies focussing on novel strategies in this field are a high priority.

This brief overview outlines some recent results from relevant clinical trials, such as HER2CLIMB, SOPHIA, and DESTINY-Breast01, in patients with HER2-positive metastatic BC, highlighting beneficial effects and safety issues of tucatinib, margetuximab, and trastuzumab deruxtecan (T-DXd), respectively. New research directions for the applications of these medications in combination with established treatment regimens are outlined. This article presents some insights into the potential transformation of clinical management and provides reasonable hope and encouragement to both the afflicted patients and their treatment teams.

INTRODUCTION

Breast cancer (BC), which is the most prevalent malignancy in women worldwide, is a heterogeneous disease, in which human epidermal growth factor receptor-2 (HER2) has a particular impact on the disease course, therapeutic response, and patient outcomes.[1] The HER2 oncogene (termed *HER2, HER2/neu,* or *ERBB2*) is located on chromosome 17[2] and its main function is to encode the transmembrane receptor tyrosine kinase.[3] *HER2* gene amplification or overexpression (present in approximately 20% of all BC) has been related to tumour cell proliferation and invasion, causing local disease progression and distant metastases.[4] In comparison to HER2-negative breast tumours, HER2-positive BC are characterised by aggressive behaviour and poor response to standard chemotherapy (CHT) regimens.[5] The expansive

tumour behaviour resulting in poor patient outcomes had to date been devastating, until the era of anti-HER2-directed therapies.[6]

In fact, targeted anti-HER2 therapies, as the key strategies for HER2-positive BC (both early and advanced/metastatic stages), have altered the management and prognostic horizons for numerous women with HER2-positive BC.[6] In particular, trastuzumab, a monoclonal IgG1 class humanised murine antibody, which binds to the extracellular domain of the HER2 transmembrane receptor; and lapatinib, a small-molecule tyrosine kinase inhibitor (TKI), which targets HER1 and HER2, have led to a therapeutic breakthrough in HER2-positive BC.[6]

Subsequently, pertuzumab has shown substantial benefits in the HER2-positive advanced and metastatic BC setting when added to trastuzumab-based therapy. It is a humanised monoclonal antibody that binds to HER2 on the extracellular domain II (a different domain than trastuzumab), preventing homo- and heterodimer formations, and blocking the heterodimers HER2/HER3.[6] Similarly, trastuzumab emtansine (T-DM1), an antibody–drug conjugate (ADC), which contains trastuzumab linked to a maytansine derivative (DM1) (a potent antimitotic agent binding to microtubules), has been added to the therapeutic armamentarium in this patient population.[6]

At present, in the first-line treatment for patients with HER2-positive metastatic BC, a dual anti-HER2 blockade (with trastuzumab and pertuzumab) plus CHT (a taxane) is recommended. T-DM1 (an ADC) is recommended for second-line treatment, and lapatinib or neratinib (a TKI) plus capecitabine or trastuzumab plus capecitabine or lapatinib for third-line or beyond.[7] Although trastuzumab, pertuzumab, lapatinib, neratinib, and T-DM1 represent effective anti-HER2 agents, some patients still develop BC progression and subsequently have very limited treatment options.[6,7] In particular, brain metastases present an urgent unmet need in many women with HER2-positive BC, and thus, clinical trials exploring novel treatment strategies in this area remain a high priority.[8]

This overview presents findings from several recent clinical studies, such as HER2CLIMB, SOPHIA, and DESTINY-Breast01, in patients with HER2-positive metastatic BC, highlighting the beneficial effects and safety issues of tucatinib, margetuximab, and trastuzumab deruxtecan (T-DXd).[9-11] In addition, new perspectives for using these medications in combination with established treatment regimens, which may renew clinical practice strategies, are briefly discussed. This article also provides some insights into the potential transformation of clinical management, giving reasonable hope and encouragement to both the afflicted patients and their treatment teams.

BRAIN METASTASES: THE GROWING CHALLENGE IN PATIENTS WITH HER2-POSITIVE BREAST CANCER

About 50% of patients with HER2-positive BC develop central nervous system (CNS) metastases during their BC course. Because this is an unmet medical need, attempts to provide systemic therapies that can penetrate the blood-brain barrier are critically important.[8] Unfortunately, the incidence of CNS metastases in patients with HER2-positive BC has increased as the targeted therapies have recently extended the patient survival.[8] At this point, conventional therapy for brain metastases includes surgery, radiation therapy, and some systemic HER2-targeted medications, such as TKI and CHT. Because surgery and radiation therapy for the treatment of CNS metastases have been associated with serious adverse effects, targeted therapies have been considered as an important option for this treatment group.[8]

Currently, there are no specific systemic treatments for patients with metastatic BC and CNS metastases, and therefore, there is an urgent need to explore novel therapies in this patient population. Unfortunately, different anti-HER2 agents (e.g., trastuzumab, pertuzumab, and T-DM1), because of their molecular structure and size, cannot cross the blood-brain barrier, and thus their role in the treatment of brain metastases has been limited.[12] In contrast, small molecules, such as TKI (e.g., lapatinib or neratinib), represent better options to reach therapeutic levels within the CNS structures.[13] For instance, lapatinib (a reversible TKI) has been studied as a targeted therapy for CNS metastases in patients with HER2-positive metastatic BC after progression on the first-line trastuzumab-based treatment.[13]

Similarly, neratinib (an irreversible pan-HER [HER1, HER2, and HER4] and EGFR TKI), which additionally blocks PI3K/AKT and MAPK signalling pathways after HER2 receptor activation, has also been investigated as a therapy for CNS metastases in this patient population.[13]

It should be highlighted that the SUMMIT basket, a Phase II, single-arm trial, has been exploring the combination of endocrine therapy (ET), a monoclonal antibody, and neratinib, in heavily pretreated patients with HER2-positive metastatic BC (whose tumours harbour *HER2* mutations).[14] Based on the preliminary results of the SUMMIT trial, neratinib will be considered for use in combination with capecitabine in patients with HER2-positive BC in the third-line, and beyond, metastatic setting, especially in the management of CNS metastases.[14] In fact, data from the SUMMIT trial, such as the objective response rate of 53% and the progression-free survival (PFS) of 10 months, has been encouraging. Although diarrhoea was the most common adverse effect reported in the SUMMIT study, it was effectively managed by using antidiarrhoeal agents.[14]

TUCATINIB: A NEW PERSPECTIVE FOR PATIENTS WITH BREAST CANCER AND BRAIN METASTASES

Tucatinib is a highly selective TKI for the kinase domain of HER2.[9] With regard to the mechanism of action, and in contrast to other TKI (which inhibit both HER2 and EGFR), tucatinib mostly spares the EGFR and blocks mainly the HER2 component.[9] Because of this selectivity, the gastrointestinal adverse effects (e.g., diarrhoea) and skin rash are reduced in patients.[9]

Table 1: A comparison between the tyrosine kinase inhibitors tucatinib, neratinib, and lapatinib.

TKI name	**Tucatinib**	**Neratinib**	**Lapatinib**
TKI type	A selective HER2 TKI	An irreversible pan-HER TKI (HER1, HER2, HER4, EGFR)	A reversible TKI
Mechanism of action	A highly selective blocker for the kinase domain of HER2, with low affinity for the EGFR	A blocker of the PI3K/AKT and MAPK signalling pathways	An intracellular blocker of HER1, HER2, and EGFR receptors A blocker of the downstream MAPK/Erk1/2 and PI3K/AKT pathways
Clinical trial, Phase, identifier, main outcomes, author	HER2CLIMB Phase III NCT02614794[15] In the tucatinib arm (tucatinib & trastuzumab/capecitabine) versus placebo arm (trastuzumab/capecitabine) 1-year PFS rates: 33% versus 12%; median PFS: 7.8 months versus 5.6 months; 2-year OS rates: 45% versus 27%; median OS: 21.9 months versus 17.4 months Murthy et al.,[9] 2019	SUMMIT basket trial Phase II NCT01953926[16] Neratinib (plus fulvestrant) is clinically active in pretreated patients with *HER2*-mutant, HR-positive metastatic BC median PFS: 5.4 months; ORR: 30%; CBR: 47% Smyth et al.,[14] 2019	NALA Phase III NCT01808573[17] In pretreated women with HER2-positive metastatic BC, in neratinib/capecitabine (N/C) versus lapatinib/capecitabine (L/C) arm: 1-year PFS rates: 28.8% versus 14.8%; 1-year OS rates: 72.5% versus 66.7%; ORR: 32.8% versus 26.7%; CBR: 44.5% versus 35.6% Saura et al.,[13]2019

Table 1 continued.

TKI name	Tucatinib	Neratinib	Lapatinib
Important clinical implications	In pretreated women with HER2-positive metastatic BC (including those with brain metastases), adding tucatinib to a combination trastuzumab/capecitabine resulted in longer PFS and OS than in the placebo arm; compared to lapatinib and neratinib, tucatinib has: • A stronger activity for CNS metastases • A better synergy with trastuzumab and CHT; • A decreased potential for EGFR-related toxicities; • A better tolerability that increases the patient's compliance;	Synergistic effects with trastuzumab in patients with HER2-positive metastatic BC (including those with brain metastases); N/C improved PFS (with a trend towards improved OS) versus L/C; N/C contributed to a delayed time to intervention for symptomatic brain metastases	Penetrates into the CNS; active against CNS metastases; In patients with HER2-positive advanced or metastatic BC acts synergistically with trastuzumab
AE	Diarrhoea, increased serum aminotransferase levels	Diarrhoea, neutropenia, dehydration	Diarrhoea, nausea, vomiting, skin rash, fatigue
Therapy for the AE	Antidiarrhoeal agents (loperamide, colestipol, or budesonide)	Antidiarrhoeal prophylaxis with loperamide	Antidiarrhoeal agents (loperamide, colestipol, or budesonide)

AE: adverse events; BC: breast cancer; CBR: clinical benefit rate; CHT: chemotherapy; CNS: central nervous system; HER2: human epidermal growth factor receptor-2; HR: hormone receptor; L/C: lapatinib/capecitabine; N/C: neratinib/capecitabine; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TKI: tyrosine kinase inhibitor.

It should be emphasised that the HER2CLIMB trial was the pioneering study that involved patients with heavily pretreated HER2-positive metastatic BC (with and without CNS metastases, including those with progressive CNS metastases) (Table 1).[9,15-17]

The HER2CLIMB study has compared tucatinib plus trastuzumab/capecitabine (the tucatinib arm) to the trastuzumab/capecitabine standard therapy (the placebo arm) among patients with HER2-positive metastatic BC (Table 1).[9] Notably, the HER2CLIMB trial allowed patients with CNS metastasis (approximately half of the participants had brain metastases at baseline) of any type to enrol.[9] For instance, the study patients could have treated/stable or untreated brain metastases, as well as previously treated but subsequently progressing CNS metastatic lesions.[9] The participants' performance status based on Eastern Cooperative Oncology Group (ECOG) was 0 or 1.[9] An analysis of survival (PFS and overall survival) is presented in Table 1.[9] It should be highlighted that the risk of BC progression or mortality in women with CNS metastases was decreased by 52% in the total HER2CLIMB trial population; 1-year PFS in the tucatinib arm was 25% versus 0% in the placebo arm, while the median PFS was 7.6 versus 5.4 months, respectively.[9] The HER2CLIMB is a pioneering trial, revealing that it is possible to positively influence the survival of women with CNS metastases related to the HER2-positive BC.

Table 2: A comparison between the monoclonal antibodies margetuximab and trastuzumab.

Name of the antibody	Margetuximab	Trastuzumab
Anti-HER2 antibody	A monoclonal IgG1 humanised antibody that binds the extracellular domain of HER2 transmembrane receptor	
Fab	Structure, affinity and specificity for HER2 binding;	
(similarities)	Impact on disruption of the cell signalisation (for proliferation and survival)	
Fc (differences)	Fc-engineered region contains five different amino-acids (compared to the wild-type IgG1); it expresses: • A higher affinity for FcyRIIIA (CD16A) • A lower affinity for FcyRIIB (CD32B)	Wild-type IgG1 immune effector domain; binds and activates immune cells
Clinical trial	SOPHIA	The Retreatment after HErceptin
Phase	Phase III	Adjuvant trial
Identifier	NCT02492711[18]	NCT00475670[19]
Design, findings	Margetuximab plus CHT versus Trastuzumab plus CHT (as third-line treatment) in patients with HER2-positive metastatic BC (after prior anti-HER2 therapies including pertuzumab)	Trastuzumab plus a taxane as first-line treatment in patients with metastatic BC (who had relapsed after adjuvant trastuzumab for HER2-positive early BC) (median PFS: 8 months; median OS: 25 months)
Author, year	Rugo et al.,[10] 2019	Láng et al.,[20] 2014
Unique features	Fc-engineered region activates immune response; Fc portion tightly binds to the Fc receptors and stimulates strong ADCC (e.g., in patients with low-affinity Fc receptors); a possibility of combination with immunotherapy or CHT; a potential treatment role in earlier stages of BC	A monoclonal antibody that binds to the HER2 and inhibits the proliferation of cells overexpressing HER2 protein
AE	Infusion reactions	Alopecia, diarrhoea, risk of cardiac toxicity (e.g., LVEF decline, CHF), haematologic deficiencies
Practical implications for the patients	Margetuximab plus CHT improves PFS (in third-line treatment) compared to Trastuzumab plus CHT; PFS benefits are more expressed in low-affinity *CD16A-158F* allele carriers (FF or FV) than in high-affinity ones (VV); In contrast, the VV carriers respond better to trastuzumab	Trastuzumab, in combination with CHT (a taxane), is an effective and well-tolerated first-line treatment for HER2-positive metastatic BC, in patients who relapsed after trastuzumab-based adjuvant therapy

AE: adverse events; ADCC: antibody-dependent cell-mediated cytotoxicity; BC: breast cancer; CHF: congestive heart failure; HER2: human epidermal growth factor receptor-2; CHT: chemotherapy; LVEF: left ventricular ejection fraction; OS: overall survival; PFS: progression-free survival.

With regard to the safety concerns, diarrhoea, increased aminotransferase levels, palmar-plantar erythrodysesthesia syndrome, nausea, vomiting, and fatigue were common adverse effects in the tucatinib-combination (trastuzumab/capecitabine) group.[9] A comparison of tucatinib with the other TKI (e.g., lapatinib and neratinib) is presented in Table 1.[9,13-17]

MARGETUXIMAB: A UNIQUE OPPORTUNITY FOR PATIENTS WITH BREAST CANCER HARBOURING GENETIC ALTERATIONS IN THE ANTIBODY FRAGMENT CRYSTALLISABLE REGION

Margetuximab is a unique anti-HER2 monoclonal antibody, which gives new hope that immunotherapy can bring some advantages to patients with HER2-positive BC.[10] Moreover, it may initiate a certain way of selecting patients, according to their type of fragment crystallisable (Fc) immune receptors (low versus high-affinity), possibly via introducing a genetic test which can facilitate a choice of therapeutic agent (e.g., margetuximab versus trastuzumab).[10] Margetuximab is considered a modified version of trastuzumab which, in addition to inhibiting HER2 signalling, stimulates the immune system to attack the HER2-positive BC cells.[10] This is mediated via antibody-dependent cellular cytotoxicity (ADCC), and occurs when the Fc region of the trastuzumab antibody binds to the Fc receptors on natural killer cells and other immune effectors.[10] Margetuximab has been engineered with the Fc portion of the antibody that allows it to bind more tightly to the Fc receptors. This ability is critically important, because many patients display a polymorphism in their Fc receptors, resulting in poor binding to the antibodies, which in turn can impair therapeutic effects (Table 2).[10,18-20] It should be emphasised that margetuximab represents an Fc-optimised anti-HER2 antibody, which has an augmented affinity for CD16a and a decreased affinity for CD32B.[10] The purpose of this affinity modification is to augment host immunity (innate and adaptive).[10] The SOPHIA trial has compared the therapeutic effects between margetuximab (in combination with CHT) and trastuzumab (in combination with CHT), and enrolled patients with HER2-positive advanced or metastatic BC who had received prior treatment with trastuzumab, pertuzumab, and T-DM1 (in the third-line setting) (Table 2).[10] The SOPHIA study population resembled that of the HER2CLIMB trial, apart from the patients with progressive CNS metastases, and including patients with stable CNS metastases.[9,10]

According to the results of the SOPHIA trial, in the group with the *CD16a F* allele (low-affinity), approximately a 4-month difference in the median OS has been reported.[10] In contrast, when evaluating the group of patients with the *CD16a V* allele (high-affinity), this trend was reversed.[10] However, it should also be noted that in the SOPHIA study, the subpopulation with high-affinity Fc receptors was very limited, and such patients had different characteristics compared to the majority of the trial population.[10] Furthermore, the patients in the margetuximab arm were usually more heavily pretreated and had more metastatic lesions (e.g., hepatic and CNS).[10] At this point in time, it appears that the women with the *CD16a F* allele have achieved greater benefits from the application of margetuximab.[10]

The main unanswered question is whether or not the use of margetuximab should be linked to the patient's genotype (e.g., should a genetic test be used to verify the presence of the *CD16a F* allele). In addition, the findings from the SOPHIA trial have provided an important clue that immunotherapy offers valuable clinical potential in the HER2-positive BC setting.[10] Moreover, since the SOPHIA trial has included a group of heavily pretreated patients, it is conceivable that if the benefits in such patients have been driven by immune mechanisms, potentially even larger benefits in previously untreated patients with HER2-positive BC may be expected. However, this would require validation in future trials.[10] Additionally, margetuximab can be used in combination with other anticancer agents. In particular, because of its ability to stimulate intense ADCC, margetuximab may work in concert with immunotherapy (e.g., immune checkpoint inhibitors) or CHT (e.g., anthracyclines).[10] Margetuximab is well-tolerated, with a toxicity profile similar to trastuzumab, with one exception relevant to more frequent infusion-related reactions (Table 2).[10]

Table 3: A comparison between the antibody drug-conjugates trastuzumab deruxtecan (T-DXd) and trastuzumab emtansine (T-DM1).

Similarities and differences of the ADC	Trastuzumab deruxtecan (T-DXd; DS-8201)	Trastuzumab emtansine (T-DM1)
Antibody class	Trastuzumab: an anti-HER2 IgG1 humanised monoclonal antibody (an identical part)	
Payload	Topoisomerase I inhibitor (exatecan derivative) high potency, membrane-permeable, short systemic half-life	Anti-tubulin (DM1) (maytansine derivative) a microtubule inhibitor
Linker	Tumour-selective, cleavable, stable bond linker-payload	Covalently linked to trastuzumab
Drug: Antibody ratio	7:8 (high)	3:5 (low)
Mechanism of action	Inhibition of topoisomerase 1; bystander killing effect in the BC tumour tissue	DM1 (a potent cytotoxic agent that inhibits microtubules) is selectively delivered to the HER2-positive BC cells
Clinical trial	DESTINY-Breast01	EMILIA
Phase	Phase II	Phase III
Identifier	NCT03248492[22]	NCT00829166[23]
Main outcomes	In the T-DXd arm: ORR: 60.3%; Median PFS: 16.4 months	Median PFS: 9.6 months with T-DM1 versus 6.4 months with lapatinib/capecitabine; Median OS: 29.9 months with T-DM1 versus 25.9 months with lapatinib/capecitabine
Author, year	Modi et al.,[11] 2019	Diéras et al.,[24] 2017
Important clinical benefits	Durable antitumour activity in pretreated (with T-DM1) patients with HER2-positive metastatic BC; a broader anti-tumour activity than T-DM1	T-DM1 significantly prolonged PFS and OS (with less toxicity than lapatinib/capecitabine) in patients with HER2-positive advanced BC previously treated with trastuzumab and a taxane
AE	Potentially serious ILD or pneumonitis; nausea, vomiting, fatigue, hair loss, and myelosuppression (anaemia, neutropenia)	Thrombocytopenia, increased serum aminotransferase levels, diarrhoea, nausea, vomiting, and palmar-plantar erythrodysesthesia
Therapy for the AE	Corticosteroids for ILD (required close monitoring for pulmonary symptoms)	As required, depending on symptoms

ADC: antibody drug-conjugate; AE: adverse events; BC: breast cancer; HER2: human epidermal growth factor receptor 2; CHT: chemotherapy; ILD: interstitial lung disease; OS: overall survival; PFS: progression-free survival; ORR: overall response rate; T-DM1: trastuzumab emtansine; T-DXd: trastuzumab deruxtecan.

TRASTUZUMAB DERUXTECAN: A NEW GENERATION ANTIBODY–DRUG CONJUGATE AGAINST HER2-POSITIVE BREAST CANCER

T-DXd exemplifies a powerful ADC against HER2 that is composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a payload in a form of the cytotoxic topoisomerase I inhibitor.[21]

The main similarities and differences between T-DXd and T-DM1 are summarised in Table 3.[11,22-24] It is important to keep in mind that the payload of T-DXd (a topoisomerase I inhibitor) represents a different type of CHT compared to the one typically applied in patients with HER2-positive BC. This design can contribute to less resistance to such CHT, especially because there are more payload particles per antibody. Moreover, the payload is able to diffuse from the targeted HER2-positive cells and damage the neighbouring tumour cells, causing a desirable 'bystander killing effect.'[11,15,25] The DESTINY-Breast01 (Phase II) trial has investigated T-DXd involved patients with HER2-positive metastatic BC, who had received on average six prior treatments (including trastuzumab, pertuzumab, and T-DM1).[11] Notably, the objective response rate was approximately 61%, the duration of response was almost 15.0 months, and the median PFS was 16.4 months.[11] Moreover, approximately 13% of participants in this trial had previously treated CNS metastases. It should be underscored that PFS was 18 months.[11] This finding suggests that the prior treatment for CNS metastases had not reduced the favourable effects of subsequent T-DXd use.

Adverse effects of T-DXd (e.g., nausea, vomiting, fatigue, hair loss, and neutropenia, which was usually afebrile) were mild.[11] Also, it is encouraging that no clinically significant cardiotoxic effects were reported. However, the most severe treatment-emergent adverse events were interstitial lung disease (ILD) and pneumonitis that developed in 13.6% of the participants (e.g., usually low grade, but in 2.2% it was fatal).[11] Because of potential lung toxicity, patients treated with T-DXd have to be monitored very closely for ILD.[11] In order to mitigate severe respiratory complications, lung scans have been introduced for early detection of any suspicious pulmonary abnormalities. This would make it possible to adjust the dose or terminate the T-DXd therapy and, simultaneously, implement the therapy with corticosteroids.[11] In addition, other questions to be answered by future studies are relevant to the potential use of T-DXd earlier in the BC course (e.g., in the first-line therapy or early-stage BC) or its possible synergistic actions with some other anticancer therapies in the adjuvant and metastatic setting (e.g., agents that spare the lymphocytes or target DNA repair).[11,25] Also, future randomised trials are needed to address the magnitude of benefit of the T-DXd therapy compared to the current standard of care.

CONCLUSIONS

In patients who had progressed even after multiple lines of previous therapy, HER2 as a therapeutic target is still a valid choice. Moreover, recent clinical studies on new therapeutics (e.g., tucatinib, margetuximab, and T-DXd) for patients with HER2-positive metastatic BC have brought some good news for this patient population and their treatment teams. Tucatinib (a selective HER2 TKI) added to trastuzumab/capecitabine combination has improved PFS and OS (compared to placebo and the above combination) in the population of previously treated women with HER2-positive metastatic BC, including those with brain metastases. Similarly, it is expected that margetuximab (Fc domain-engineered anti-HER2 antibody) may represent an innovative therapeutic strategy for patients with HER2-positive metastatic BC, who are low-affinity *CD16α-158F* allele carriers (*FF* or *FV*). In addition, margetuximab may play a role in the earlier stages of BC therapy. However, this possibility needs to be examined in detail in future trials.

Likewise, it should be noted that T-DXd, representing a new generation ADC against HER2, has revealed remarkable anti-tumour activity in patients with HER2-positive metastatic BC, who were heavily pretreated. However, because of some safety concerns such as ILD or pneumonitis, which pose serious risks, vigilant monitoring for signs and symptoms of ILD and immediate therapeutic intervention (e.g., glucocorticoids) are mandatory for the management of such patients. Nevertheless, it is expected that T-DXd may become a 'new standard of care' for patients with advanced or metastatic HER2-positive BC.

Some urgent questions for further research on TKI and ADC in this area are mostly related to the level of clinical benefits of these agents in specific clinical contexts, and the possibilities of their combined applications with other medications in patients with HER2-positive metastatic BC, especially those with progressive brain metastases. Furthermore, studies aimed at detection of predictive and prognostic biomarkers, to guide the individualised diagnostic work-up and targeted treatment of women with HER2-positive BC, represent research priorities. Simultaneously, there is a need for further studies to investigate and validate innovative therapeutics in the most challenging HER2-positive BC management setting.

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Association of Tumour Location and Recurrence in Patients with Non-Muscle Invasive Bladder Cancer

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Abstract

Introduction: Accurate prediction of recurrence is important for patients with non-muscle invasive bladder cancer (NMIBC).

Objective: To study the association of tumour location with recurrence-free survival (RFS) of patients with primary solitary tumours.

Methods: Patients (N=184) with primary, solitary NMIBC (2000–2018). In cases of overlapping areas, the most involved area was selected. Subsequently, the areas were dichotomised into dorsal versus non-dorsal tumours. The dorsal area was defined as the diamond-shaped area bordered by bladder neck, trigone, posterior wall, and orifices. The non-dorsal areas are the lateral walls, dome, and anterior wall. The association of location with RFS was assessed using Cox regression. Median RFS was estimated using the Kaplan–Meier method.

Results: Altogether, 25 (14%) and 69 (38%) patients had a recurrence at 1 year and 5 years, respectively. Median RFS was 103 months. Primary tumours located at the anterior wall were associated with the lowest RFS (median: 74 months) and at the posterior wall with highest RFS (median: 133 months). After dichotomisation, 54% of the patients had a tumour in the dorsal area with a median 1-year recurrence rate of 9% versus 19% in the non-dorsal area. Median RFS in the dorsal area was 133 months versus 48 months in the non-dorsal area (p=0.02). Cox analysis showed worse 1- and 5-year RFS on adjusted analysis (hazard ratio [HR]: 2.41; 95% confidence interval [CI]: 1.07–5.46; p=0.04; and HR: 1.77; 95% CI: 1.10–2.85; p=0.02, respectively) for tumours in the non-dorsal area.

Conclusion: The tumours in the dorsal area appear to have a lower recurrence rate. There was no association with specific tumour location and RFS.

INTRODUCTION

Risk stratification and prognosis estimation is important in patients with non-muscle invasive bladder cancer (NMIBC). NMIBC has a high probability of recurrence and, to a lesser extent, progression into muscle invasive disease at a later stage.[1] Long-term recurrence rates as high as 80% have been reported,[2] and up to 45% of tumours progress.[3] The need for surveillance for tumour recurrence and treatment complications results in high lifetime treatment costs, making bladder cancer the most expensive cancer.[4]

Because treatment of NMIBC is based on prognosis, several prediction systems have been developed to predict short- and long-term risks. The risk tables of the European Organisation for Research and Treatment of Cancer (EORTC) and the scoring model of the Spanish Urological Club for Oncological Treatment (CUETO) are two prediction systems that are currently recommended by guidelines internationally.[1,5] Both systems assess the probability of 1-year and 5-year recurrence and progression based on a combination of clinical and pathological factors.[3,6] Some of the included factors can be regarded as subjective and are operator dependent, i.e., determination of the number of tumours and estimation of tumour size during a transurethral resection (TURBT).[7] The assessment of tumour stage and histological grade is also associated with high interobserver variability.[8,9] Moreover, the prognostic value of these prediction models are limited because the populations on which the models are based were treated differently than recommended by the current standard.[10]

Tumour location is not considered in risk assessments of patients with NMIBC. However, Palou et al.[11] have shown that tumours in the trigonal area are associated with a higher probability of upper urinary tract tumour (UTUC) presence. Indeed, as is mentioned in the guidelines, imaging of the upper tract has to be considered when finding a tumour in the trigone.[1,5] However, the association of tumour location with recurrence-free survival (RFS) has only been studied in a limited number of patients in heterogeneous datasets, with the inclusion of patients with NMIBC and muscle invasive disease or those with multiple tumour locations and/or used both of their primary and recurrent tumours.[12–14] To improve the understanding of the association of intravesical tumour location with RFS, the disease outcome of patients with primary solitary bladder tumours was assessed. The aim of this study was to identify the influence of location of the urothelial cell carcinoma of the bladder on 1- and 5-year RFS.

METHODS

Data Acquisition

This study was approved by the medical ethical committee of the Amsterdam UMC, location AMC (W17_327_#17.380). A database was constructed using the Data Management System (v 3.1.3, T&S innovations, Utrecht, the Netherlands). All patient data of the 840 patients who underwent TURBT between 2000–2018 were retrospectively collected. Patients were given the possibility to opt-out from the study following the Dutch Act on the Protection of Personal Data and Code Good Conduct.

Only patients with primary, solitary, NMIBC urothelial cell carcinoma that were radically resected during the primary TURBT or re-TURBT and did not contain concomitant carcinoma *in situ* were included. If a tumour was upstaged to muscle invasive bladder cancer during the re-TURBT, the patient was excluded. Additionally, patients with a prior or simultaneous UTUC and patients who underwent a radical cystectomy after the first TURBT were excluded from the study. Follow-up was performed according to the European Association of Urology (EAU) guidelines, with the first follow up cystoscopy after 3 months. Therefore, patients with a follow-up period of <3 months were also excluded.

Tumour locations were assessed by retrospectively checking the reports of the initial cystoscopy, operation, and pathology. Locations were characterised using the bladder map of the EAU guideline, with the exception that trigone and bladder neck were grouped together. Tumours located in the urethra were excluded from the study because it was not possible to assess the exact location (pre- or post- sphincteric).

Besides assessing the specific tumour locations, areas were grouped into dorsal versus non-dorsal tumours. The dorsal area was defined as the diamond-shaped area bordered by the bladder

neck, trigone, posterior wall, and orifices. The non-dorsal areas are the dome, anterior wall, and lateral walls. In case of a large tumour spreading out over multiple regions, the most involved area was selected.

Covariates

The association of location with outcome variables was adjusted for patient and tumour specific characteristics. Patient characteristics included age at diagnosis, sex, postoperative bladder rinses, and adjuvant treatment (intravesical chemotherapy/immunotherapy). Tumour specific characteristics included T-stage (based on the pathology report), Grade (based on both the World Health Organization [WHO]'73 and WHO'04 grading system) and tumour size (<3 and >3 cm). Recurrence was defined as a pathologically proven recurrence.

Outcomes

The outcomes were compared for tumour location specific and dorsal versus non-dorsal area. The primary outcome was defined as RFS. Progression was defined as pathologically proven tumours invading the muscularis propria, imaging-proven nodal or distant metastasis, or UTUC.

Statistical Analysis

Kaplan–Meier survival analysis and log-rank test were used for RFS estimates between groups. Patients without recurrence were censored at last follow-up and patients with incomplete follow-up were censored at the last date of observation. Groups were compared using Pearson's chi-square test. The Cox proportional hazard model was used to assess the association of location with 1- and 5-year RFS. Multicollinearity was measured by variance inflation factors. Variables with a statistically significant association with the outcome measures in the unadjusted analyses were considered in the adjusted analysis. These results were only reported when the association was confirmed. Statistical significance was considered at $p<0.05$. All statistical tests were performed using SPSS® (IBM, New York City, New York, USA) (v25).

RESULTS

Baseline Characteristics

A total of 184 patients were included into the analysis with a median age of 67 years (interquartile range [IQR]: 57–74) and 24% (n=44) were female. Tumour stage was Ta in 81% (n=149) and T1 in 10% (n=19) patients. Data of both the WHO'73 and WHO'04 grading systems were collected. WHO'73 grading was divided as follows: Grade 1 was 16% (n=30), Grade 2 was 52% (n=96), and Grade 3 was 29% (n=53). In 3% (n=5) of patients the WHO'73 grade was unknown. The WHO'04 grade was unknown in 33% (n=61) of patients, and 17% (n=31) had a low-grade tumour and 36% (n=66) had a high-grade tumour. For the tumour size, the definition according to the EAU risk stratification was used. In 71% (n=130) of patients the tumour was <3 cm and in 23% (n=43) the tumour was >3 cm. In 6% (n=11) of cases the tumour size was unknown. In 103 (56%) patients postoperative mitomycin (MMC) was given. Adjuvant therapy in the form of MMC was given to 5% (n=10) of patients and 17% (n=32) received adjuvant Bacillus Calmette–Guérin (BCG). The most common tumour locations were the lateral walls (45%, n=82). The median time of follow-up was 68 months (IQR: 39–115). In the total cohort, 25 (14%) and 69 (38%) patients had a recurrence at 1 year and 5 years, respectively. Progression was seen in two (1.1%) and six (3.3%) patients at 1 and 5 years, respectively.

Recurrence-Free Survival Per Tumour Site

In 12 patients the primary tumour location could not be assessed, and they were excluded from the analysis for specific tumour location. Recurrence rates at 1 and 5 years are shown in Table 1. Recurrence rates at 1 year ranged from 0% for patients with a primary tumour within the posterior wall to 50% for primary tumours within the anterior wall (p=0.22). Recurrence rates at 5 years ranged from 20% for patients with a primary tumour within the posterior wall to 50% for patients with a primary tumour within the anterior wall (p=0.67).

Median RFS was 103 months (Table 1). Median RFS of specific tumour locations ranged from 8 months for tumours at the anterior wall to 133 months for tumours at the posterior wall. Because

of the small number of events per tumour location, Cox regression could not be performed.

According to the Kaplan–Meier analysis, specific tumour locations were not statistically significant to be associated with 1- and 5-year RFS (log-rank: p=0.19; log-rank: p=0.43, respectively). No statistically significant differences were seen in recurrence rate and RFS among different adjuvant treatment groups.

Because of the small population, comparison of progression rate per tumour site was not feasible. However, 5-year progression rate was highest in the trigone (25%), made up of only 2/8 patients.

Dorsal Versus Non-Dorsal Area

Tumours in the dorsal area were seen in 54% (n=100) of patients and in the non-dorsal area in 46% (n=84) of patients, of which 9% and 19%, respectively, had a recurrence within 1 year (p<0.05). Recurrence rates at 5-years were 31% and 45% in the dorsal and non-dorsal area, respectively (p<0.05). No differences were observed in tumour grade (WHO'73: p=0.31; WHO'04: p=0.22) and T-stage (p=0.70) between the two groups.

Median RFS was 133 months for patients with a tumour located in the dorsal area, and 48 months for patients with tumours in the non-dorsal area (Figure 1) (1- and 5-year RFS, log-rank: p=0.02; log-rank: p=0.03, respectively). The WHO'04 and WHO'73 showed multicollinearity (variance inflation factor: 3.56), therefore only the WHO'04 grade was used in the analysis. On unadjusted analysis, T-stage (HR: 2.68; 95% CI: 1.18–6.07; p=0.02) and WHO'04 grade (HR: 8.60; 95% CI: 1.99–37.22; p<0.01) were statistically significantly associated with 1-year RFS. Age (HR: 1.02; 95% CI: 1.00–1.04; p=0.03), T-stage (HR: 1.73; 95% CI: 1.01–2.96; p<0.05), and WHO'04 grade (HR: 3.31; 95% CI: 1.17–6.39; p<0.01) were statistically significantly associated with 5-year RFS. Tumour location within the non-dorsal area was statistically significantly associated with worse 1- and 5-year RFS on unadjusted analysis (HR: 2.36; 95% CI: 1.04–5.33; p=0.04 and HR: 1.74; 95% CI: 1.08–2.80, respectively; Table 2).

Table 1: Overview of recurrence rates and median recurrence-free survival for specific tumour locations and dorsal versus non-dorsal tumours (in number of tumours and percentage of recurrence at each location).

	Total number of tumours (%)	1-year recurrence (%)	5-year recurrence (%)	Median regression free survival (months)
Primary tumour location				
Dome	7 (4)	1 (14.3)	3 (42.9)	103
Anterior wall	2 (1)	1 (50.0)	1 (50.0)	8
Posterior wall	10 (5)	0 (0.0)	2 (20.0)	133
Lateral wall	82 (45)	15 (18.3)	36 (43.9)	53
Trigone	8 (4)	1 (12.5)	3 (37.5)	56
Ureteral orifice	62 (34)	5 (8.1)	21 (33.9)	101 (mean)
Prostatic urethra	1 (1)	1 (100.0)	1 (100.0)	4
Overall	184 (100)	25 (14.0)	69 (38.0)	103
Dichotomisation				
Dorsal tumours	100 (54)	9 (9.0)	31 (31.0)	4,063
Non-dorsal tumours	84 (46)	16 (19.0)	38 (45.2)	1,470

In case of overlapping tumour areas, only the main tumour location was taken into account. Proportions may not total 100% as a result of unknown main tumour area.

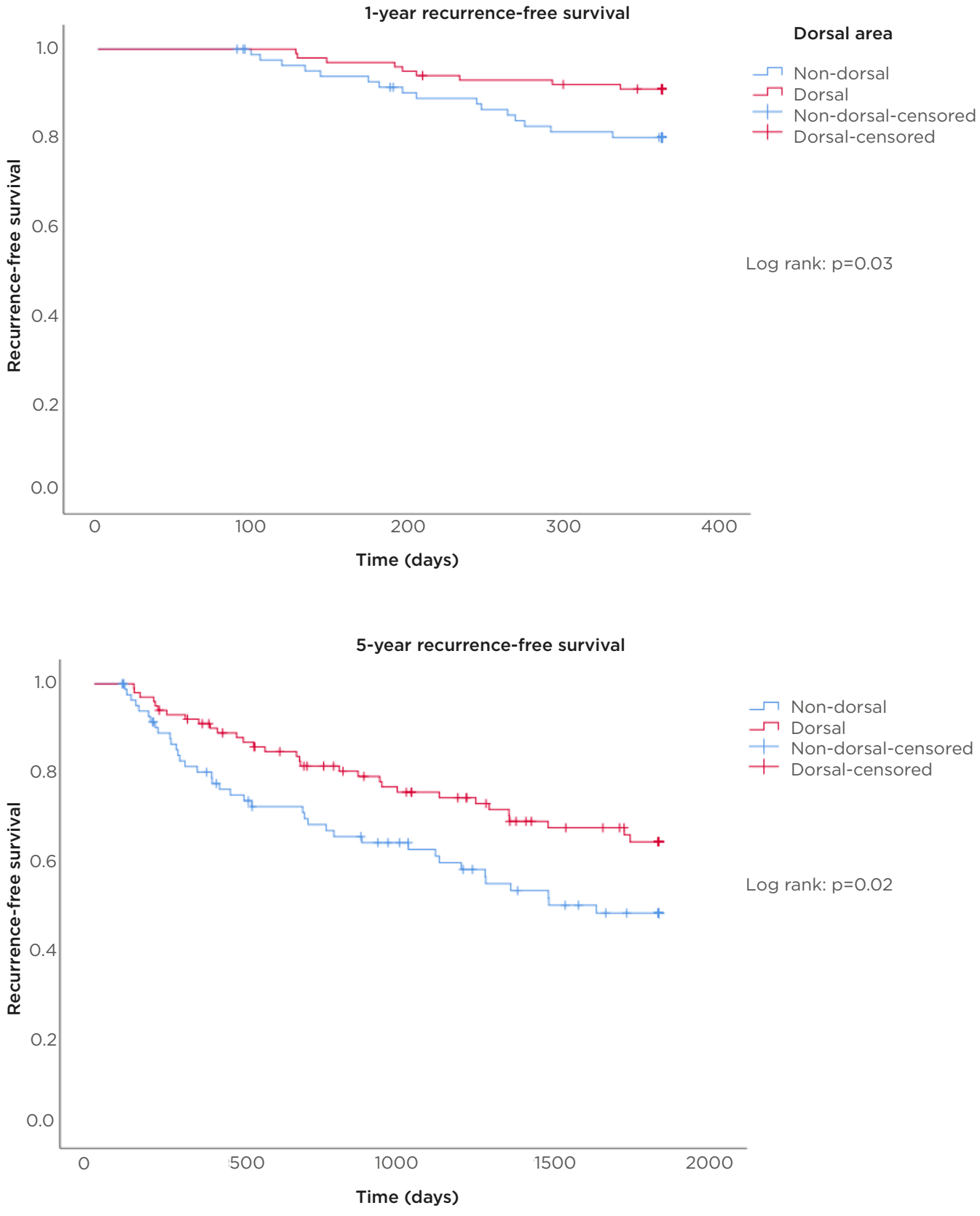

Figure 1: Kaplan–Meier curves for 1-year (top panel) and 5-year (bottom panel) recurrence-free survival based on dorsal and non-dorsal tumour area.

Table 2: Cox regression (unadjusted and adjusted analysis) for recurrence-free survival based on tumours in the non-dorsal area.

Variable	Recurrence-free survival							
	1 year				5 years			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Sex (Male ref)	1.62 (0.70-3.76)	0.26			1.13 (0.62-1.95)	0.67		
Age	0.99 (0.97-1.02)	0.69			1.02 (1.00-1.04)	**0.03**	1.02 (1.00-1.04)	**0.03**
T-stage								
Ta	Ref				Ref			
T1	2.68 (1.18–6.07)	**0.02**	2.75 (1.22-6.23)	**0.02**	1.73 (1.01–2.96)	**<0.05**		
Grade WHO'73								
- Grade 1	0.13 (0.02–1.02)	0.05			0.43 (0.19–0.94)	0.04		
- Grade 2	0.44 (0.19–1.02)	0.06			0.59 (0.35–0.98)	0.04		
- Grade 3	Ref				Ref			
Grade WHO'04 (low-grade ref)	8.60 (1.99–37.22)	**<0.01**			3.31 (1.71–6.39)	**<0.01**		
Tumour size (<3 cm ref)	1.59 (0.64–3.95)	0.31			1.10 (0.61–1.95)	0.77		
Postoperative MMC	0.47 (0.21–1.05)	0.07			0.77 (0.47–1.24)	0.28		
Adjuvant MMC	3.10 (0.93–10.36)	0.07			1.56 (0.57–4.23)	0.39		
Adjuvant BCG	1.84 (0.77–4.40)	0.17			1.54 (0.89–2.67)	0.12		
Tumour location						0.11		
Dorsal	Ref				Ref			
Non-dorsal	2.36 (1.04–5.33)	0.04	2.41 (1.07–5.46)	**0.04**	1.74 (1.08–2.80)	**0.02**	1.77 (1.10–2.85)	**0.02**

BCG: Bacillus Calmette–Guérin; CI: confidence interval; HR: hazard ratio; MMC: mitomycin; ref: reference; WHO: World Health Organization.

The adjusted analysis showed that only the dorsal versus non-dorsal area was significantly associated with a shorter 1- and 5-year RFS (HR: 2.41; 95% CI: 1.07–5.46; p=0.04 and HR: 1.77; 95% CI: 1.10–2.85; p=0.02; Table 2).

In the dorsal area, 1- and 5-year progression was observed in 1% and 3% of the patients, respectively. For the non-dorsal area, progression incidences were 1% and 4%, respectively. Four patients developed an UTUC during follow-up, of which two patients had an initial tumour in the dorsal area and two in the non-dorsal area.

DISCUSSION

This study assessed the association of intravesical tumour location with RFS. The main findings are that tumours located in the non-dorsal area of the bladder were associated with shorter RFS. However, no significant association of more specific tumour locations with RFS was found in this study.

As the recurrence rate of NMIBC is a relevant parameter for the determination of the need and options of adjuvant treatment, several risk prediction systems have been constructed.[3,6] In these nomograms, different clinical and pathological parameters related to recurrence rates are assessed. The primary location of the tumour is not a parameter in these prediction systems. Over time, only three studies have studied the association of tumour location with recurrence.[12,15,16] Mulders et al.[15] prospectively studied 371 patients with NMIBC. They identified bladder neck, prostatic urethra, posterior wall, and trigone separately as regions associated with a shorter recurrence-free interval. Vukomanovic et al.[16] studied a group of 74 patients with T1 high-grade NMIBC, which they divided into patients treated with TURBT and BCG versus TURBT alone. For patients treated with BCG, recurrence was more common when having a tumour in the bladder neck, whereas in patients treated with TURBT alone, tumours in the lateral walls and orifices were associated with recurrence. Segal et al.[12] analysed a group of 278 patients with T1 high-grade NMIBC and found that tumours located in the trigone were associated with shorter RFS on adjusted analysis. The main weakness of these three studies is the low number of events per tumour location, making the statistical models unreliable.[17] Similarly, the dataset was too small to assess the association of specific tumour location with RFS. However, this study found a higher recurrence rate and a shorter RFS in patients with a tumour in the non-dorsal area in contrast to the previous studies.[12,15,16]

Only a small number of studies have studied the influence of intravesical tumour location on progression.[18,19] Kobayashi et al.[18] found, in a population of 297 patients with NMIBC, tumours within bladder neck to be significantly associated with progression, whereas Weiner et al.[19] showed that tumours in the dome were statistically significant and associated with advanced stage at the time of radical cystectomy. The sample size of this study was unfortunately insufficient to assess the association of tumour location with progression.

To the authors' knowledge, this is the first study to determine the association of intravesical tumour location with RFS, including only patients with primary, solitary NMIBC. Most studies that considered the relation of tumour location with recurrence have used heterogeneous datasets, including recurrent and multiple tumours. However, both variables have been significantly associated with lower RFS.[3] In comparison with the EORTC, this study population did receive postoperative MMC, or adjuvant BCG or MMC if indicated. The main weakness of this study is the retrospective character, which may contribute to a lack of standardisation and tumour location description. Although adequate documentation of tumour location by using a bladder diagram has proven to reduce the recurrence rates,[20] in this dataset several patients were excluded due to a missing description of tumour location. Another variable that should have been taken into account is the surgical experience of the surgeon performing the TURBT. A TURBT performed by an experienced surgeon has shown to decrease the recurrence rate.[21,22] The surgical reports did not clearly state the exact role and amount of supervision when a resident was present during the TURBT, therefore this variable was not included into the analysis. Moreover, the different molecular subtypes of bladder cancer were not accounted for. As for muscle invasive bladder cancer, NMIBC has comparable subtypes which influences outcome.[23] Finally, due to the limited sample size, the number of events per variable was limited. Therefore, performing a Cox regression

analysis on specific tumour locations would have induced an overestimation of the significance.[17] Because the number of patients was limited, the number of variables that could be taken into account in the multivariable analysis was also limited. Therefore, this study may not be enough to present final conclusions. Dichotomisation of the data made it possible to assess the HR of the dorsal and non-dorsal tumours. Because the trigonal area is often difficult to define, the bladder neck, trigone, orifices, and dorsal area were grouped together.

The current risk stratification models use variables that are highly susceptible for interobserver variation and are unable to correctly predict recurrence rates.[10] Consequently, external validations demonstrated low concordence-indices.[24] Therefore, the search for better predictors is ongoing. However, since the areas within the bladder are also susceptible for interobserver variation, the use of the intravesical tumour location as a suitable characteristic for risk stratification is also debatable. Because the bladder is a spherical organ, areas within the bladder are hard to define.

Several mechanisms of recurrence have been described.[13] Tumour seeding is a well-known mechanism, where tumour cell implantation occurs after trauma of the urothelial layer following thermal or mechanic injury.[25,26] This knowledge has led to the introduction of instillation of postoperative chemotherapy to induce tumour cell lysis.[14] Field cancerisation may imply that micro tumours already exist during primary TURBT. Since the whole bladder is exposed to the same carcinogens, genetically unrelated tumours arise in different parts of the bladder.[27] As a result, new tumour formation is also scored as recurrence.

Several reasons for the possible relation of the non-dorsal tumour location and recurrence can be hypothesised. Most likely, inadequate resection plays an important role in the shorter RFS. Tumours in the non-dorsal area are somewhat more difficult to assess during cystoscopy, complicating radical TURBT. Moreover, during TURBT a rigid cystoscope is preferably used, which ensures less visibility of the non-dorsal side compared to a flexible cystoscope. This may cause incomplete TURBT. To overcome this problem, additional techniques might be considered to evaluate adequate resection, such as narrow band imaging[28] or photodynamic diagnosis.[29] Other mechanisms of action, for example those related to the flow of urine, which induces differences in contact time of the bladder wall areas with carcinogenic substances within urine, may also play a role in the recurrence rates of these tumours.

Risk stratification is important to enable comparison of outcomes and standardisation of treatment and follow-up. However, external validation of the EORTC and CUETO shows low concordance-indices for both risk tools.[10] A possible explanation is that both tools are based on research data of >20 years ago and does not reflect the current standards of treatment. Therefore, it was hypothesised that tumour location within the bladder could be an additional parameter. These results may imply that TURBT techniques for a tumour in the non-dorsal area needs to be improved and an active follow-up is required for tumours in this area. A prospective study is needed to deliver a more powerful analysis that would be able to give an update of the existing risk stratification models.

CONCLUSION

This study has demonstrated that a primary tumour within the non-dorsal area is significantly associated with a shorter 1- and 5-year RFS. A significant association of more specific tumour locations with RFS was not found. The findings warrant further, preferably prospective, investigation into the role of intravesical tumour location on the outcome of patients with NMIBC.

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Phosphate and Oxysterols May Mediate an Inverse Relationship Between Atherosclerosis and Cancer

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Abstract

The peer-reviewed literature has reported an inverse relationship between atherosclerosis and cancer for almost 100 years, but no causative mechanism has been established to explain this puzzling relationship. More recent research has reported an association between tumourigenesis and phosphate toxicity from dysregulated phosphate metabolism, and an association has also been reported between atherosclerosis and cholesterol oxidation products or oxysterols. The present review article synthesises these research findings and proposes that an inverse relationship between the associated risk of cancer and atherosclerosis may be mediated by tumourigenic and atherogenic dietary patterns containing inverse proportions of dietary phosphate and oxysterols. Low-fat animal-based foods generally have reduced cholesterol and oxysterol levels and relatively higher protein and phosphate levels, and dietary patterns containing these foods are associated with reduced atherosclerosis risk and increased cancer risk. By comparison, full-fat animal-based foods are higher in cholesterol and oxysterols and relatively lower in protein and phosphate, and dietary patterns containing these foods are associated with increased atherosclerosis risk and reduced cancer risk. Fruits, vegetables, and plant-based fats generally have lower phosphate levels and no cholesterol, and dietary patterns associated with increased amounts of these foods, such as the Mediterranean diet, reduce risk for both cancer and cardiovascular disease.

INTRODUCTION

"If it's not one thing, it's another" is the sardonic title of an article by Li et al.[1] which describes a puzzling inverse relationship between cancer and atherosclerosis. Observing that atherosclerosis is a major causative factor in cardiovascular disease, Li et al. identified that cardiovascular disease and cancer are the two leading causes of morbidity and mortality in developed nations. A recent 2019 analysis showed that cancer has surpassed cardiovascular disease as the leading cause of death in high-income nations.[2] While it may seem surprising that the associated risk of one of these diseases goes up as the other goes down, even more surprising is that no cause has been established to account for this inverse relationship, which has remained an unsolved mystery for decades. Li et al. noted that observations of the inverse association of cancer and atherosclerosis extend back as far as over half a century ago, but similar observations

extend back even further than that.[1] Elkeles[3] reviewed the research of early 20th century pathologists, including Busch in 1924, Casper in 1932, Sjoeval and Wihman in 1934, and Wegelin in 1935, all of whom observed a very low frequency of advanced arteriosclerosis in cancer cases.

More recently, a prospective study that followed 5,262 elderly people for over 12 years found that deceased participants with symptomatic atherosclerotic disease, including coronary disease and atherosclerotic stroke, had approximately 30–40% reduced mortality from cancer compared to deceased participants without symptomatic atherosclerotic disease.[4] Another analysis of 2,370 autopsy reports over 14 years found that cancers of the pancreas, breast, and colorectum, as well as lymphomas/lymphoid leukaemia and sarcomas had strong inverse correlations with atherosclerosis.[5] One modern theory proposing a plausible explanation for the inverse association of cancer and atherosclerosis suggests that the administration of statins might increase the associated risk of cancer; however, a recent review of the literature suggested that statins were more likely associated with a decreased cancer risk.[6] Furthermore, statins were obviously not in use during the early decades of the 20th century when an inverse relationship between cancer and atherosclerosis was first observed. Another explanation for the inverse relationship of these two diseases proposed that chemotherapy lowered atherosclerosis in cancer patients, but Li et al. dismissed this proposal as unsubstantiated and inconsistent with the known pathobiology of atherosclerosis.[1]

Li et al. conducted an analysis of cancer and atherosclerosis based on 1,024 autopsy reports from Brigham and Women's Hospital in Cambridge, Massachusetts, USA, and the researchers conducted a second analysis from the database of the Harvard Catalyst Shared Health Research Information Network; both analyses confirmed a significant inverse relationship between cancer and atherosclerosis.[1] The explanation offered by the researchers speculated upon a difference in patient propensity toward inflammatory properties, arguing that an inflammatory immune response appears more directly associated with atherosclerosis than with cancer. The researchers' hypotheses might help explain lower atherosclerosis among cancer cases, but it does not explain reports of lower cancer among atherosclerosis cases. Furthermore, the researchers' proposed explanations only account for a potential difference in disease mechanisms from a pathophysiological perspective, without considering a wider range of causes and factors associated with increased disease risks from an epidemiological perspective.

Shared modifiable risk factors, including smoking and poor nutrition, are associated with increased risks for both cardiovascular disease and cancer.[7] Smoking tobacco is a risk factor associated with smoking-related cancers as well as atherosclerosis; however, there was a strong inverse association of nonsmoking related cancers and atherosclerosis in an analysis of 2,101 deceased patients.[8] Aside from smoking, the current review article investigates poor nutrition as a risk factor for cancer and atherosclerosis, and proposes that different dietary patterns containing inverse ratios of phosphate and oxysterols, which are correspondingly associated with increased risks for cancer and atherosclerosis, may provide a novel hypothesis that explains the inverse associated risk of cancer and atherosclerosis.

OXYSTEROLS AND ATHEROSCLEROSIS

The following is a brief summary of the association of oxysterols and atherosclerosis, based on a more detailed review of the existing research literature.[9] Atherosclerosis is associated with serum levels of low-density lipoprotein cholesterol (LDL-C).[10] As atherosclerosis develops, a lesion grows within the inner or intima layer of the arterial vascular wall.[11] The inner layer of the vascular wall is lined with endothelial cells which form a barrier that normally regulates selective permeability of certain biomolecules from the blood plasma, but this permeability becomes dysregulated in cardiovascular disease.[12] Endothelial cells are lined with membranes formed by a phospholipid bilayer which contains cholesterol molecules that strengthen the membrane.[13]

Oxysterols are cholesterol oxidation products that originate from endogenous and exogenous sources, including dietary sources of cholesterol that have undergone oxidation through processing, preparation, and storage.[14]

During the formation of oxysterols, oxidation changes the molecular structure and polarity of cholesterol, which creates packing defects in the vascular endothelial cell membranes as oxysterols enter into the phospholipid bilayer and do not line up properly compared to normal cholesterol.[15] Packing defects from oxysterols eventually increase endothelial cell membrane permeability to protein from the blood plasma.[16] This pathophysiological mechanism could explain unregulated permeability of serum LDL-C into the subendothelial space of the arterial wall, with subsequent LDL-C oxidation by immune cells and eventual formation of foam cells and an atheroma which extends into and blocks the lumen of the arterial vessel.[17]

In vitro experiments have demonstrated that oxysterols alter endothelial barrier permeability compared to normal cholesterol,[18] and atherosclerosis in the aortas of rabbits increased dramatically when the rabbits were fed oxysterols.[19] Although further research is needed to investigate the pathophysiological mechanism described above, clinical evidence continues to link oxysterols with atherosclerosis. For example, elevated serum levels of oxysterols in patients were associated with increased risk for atherosclerosis and cardiovascular disease.[20,21]

Conventional dietary guidelines to reduce atherosclerosis, according to the Therapeutic Lifestyle Changes programme of the National Heart, Lung, and Blood Institute (NHLBI) in the USA, recommend reducing saturated fat to no more than 7% of calories and cholesterol to no more than 200 mg/day.[22] More recently, the 2015 Dietary Guidelines Advisory Committee of the USA Department of Agriculture (USDA) and the U.S. Department of Health & Human Services (HHS) issued a scientific report that is less restrictive of cholesterol intake.[23] However, neither of these guidelines mention oxysterols, nor are oxysterols included in nutrient databases of foods.

Of relevance, symptoms of angina rapidly regressed in patients prescribed a vegan diet which contained no cholesterol, and presumably no oxysterols, but symptoms returned when dairy and eggs were added to the diet.[24] In the first controlled clinical trial of a dietary intervention that reversed coronary heart disease, Ornish et al.[25] used a vegetarian diet with small amounts of nonfat milk and egg whites, which contain little and no cholesterol, respectively. However, a more recent study found that stroke rates in vegetarians and vegans were 20% higher than in meat eaters,[26] although the researchers could not identify causative dietary factors. Salt intake is associated with stroke in countries like China.[27] Investigations should determine if vegans and vegetarians consume excessive salt in soy sauce, tamari, salted nuts, seeds, nut butters, processed snacks, exotic seasonings like Himalayan salt and sea salt, and high amounts of salt in baked grain products[28] and processed meat alternatives.[29]

A review examining the association between below-normal vitamin B12 status and cardiovascular health in vegans suggested that normal B12 levels might have a cardioprotective effect.[30] A limitation of the reviewed studies is that changes observed in cardiovascular surrogates, flow-mediated endothelium-dependent dilation and carotid intima-media thickness, may not translate to actual cardiovascular events. Additionally, there are many vegan foods available that are fortified with vitamin B12, and the researchers suggested that vegans monitor their vitamin B12 status "to reap the full benefits of cardiovascular disease prevention in plant-based eating styles of vegan diets."[30] Having reviewed evidence implicating dietary oxysterols in atherosclerosis, the next section of this article examines the leading cause of mortality in high-income nations: cancer, and its association with dysregulated dietary phosphate.

PHOSPHATE TOXICITY AND TUMOURIGENESIS

As risk factors for cancer increase through the global spread of Western lifestyles and an ageing population, cancer is projected to increase to 22.2 million new global cases in the year 2030.[31] Substances that are identified as carcinogenic in laboratory analyses do not always progress to cancer in real life,[32] implying that other cancer growth factors are involved in tumourigenesis. Schipper et al.[33] suggested that cancer promotion is linked to dysregulated metabolic pathways which may be reversible. A recent review[34] supported the role of dysregulated dietary phosphate metabolism in the promotion and progression of tumourigenesis, which may be modified by a low-phosphate diet.

Phosphate is formed from the essential micronutrient phosphorus, and inorganic phosphate in the body is normally regulated by endocrine communication between an axis of organs consisting of the kidneys, skeletal system, parathyroid glands, and intestines.[35] If this axis becomes burdened, phosphate metabolism becomes dysregulated and extracellular and intracellular levels of phosphate may accumulate, leading to a harmful condition known as phosphate toxicity. Evidence suggests that excess phosphate may accumulate in the tumour microenvironment. For example, compared to normal cells, cancer cells from the ovaries, lung, breast, and thyroid overexpress sodium–phosphate cotransporters,[36,37] which allow cells to absorb and sequester large amounts of inorganic phosphate from the tumour extracellular microenvironment. Tumour cells of the lung and colon were observed to contain levels of inorganic phosphate that were up to twice as high as normal cells.[38] Excess inorganic phosphate was found to increase biogenesis of ribosomal RNA, which stimulates protein synthesis and promotes cancer cell growth.[39] Using animal models, researchers found that high levels of dietary phosphate increased growth of skin cancer[40] and lung cancer,[41] activating cell-signalling pathways involving PI3K, protein kinase B, and mTOR.[42] Progression of cancer in metastasis has also been linked to high concentrations of phosphate in extracellular tissue.[43]

Higher serum phosphate levels were positively associated with cancer in adults,[44,45] except in females with reproductive cancers, possibly related to a shift of high serum phosphate levels into rapidly growing reproductive tissue. Of relevance to the present article, a ketogenic diet reduced tumours in experimental animals[46] and in patients with brain cancer.[47] A sample ketogenic diet used to medically treat children with epilepsy provides a 4:1 ratio of fat g to nonfat g.[48] Extrapolated to a diet sufficient in calories for an adult, the low-phosphate level of the ketogenic diet lies below the recommended dietary intake of 700 mg of phosphorus per day for an adult. Nevertheless, despite benefits associated with reducing cancer risk, the high-fat ketogenic diet has also been associated with arterial wall dysfunction in children and adults with epilepsy.[49]

ATHEROGENIC AND TUMOURIGENIC DIETARY PATTERNS

The preceding literature review provides evidence that an atherogenic dietary pattern is high in cholesterol, saturated fat, and oxysterols, and a tumourigenic dietary pattern is high in phosphate as well as protein. Dietary phosphate is closely correlated with dietary protein, with approximately 12–14 mg phosphorus for each g of protein.[50] Therefore, as the macronutrient ratio of protein increases in a dietary pattern, phosphate often also increases.

Figure 1 compares a proposed inverse ratio of phosphate and oxysterols in atherogenic and tumourigenic dietary patterns. Note that as the public is encouraged to consume more low-fat and nonfat foods, which reduce the associated risk of atherosclerosis, the macronutrient proportion of proteins and phosphate increases in the diet, thereby increasing the associated risk of cancer linked to high phosphate intake. Inversely, as the public consumes a greater proportion of animal-based foods high in saturated fat, cholesterol, and oxysterols, the associated risk of atherosclerosis increases while the lower macronutrient proportion of protein and phosphate in the diet reduces the associated risk of cancer.

FUTURE PREVENTION OF CANCER AND ATHEROSCLEROSIS

An optimal solution to the dilemma of an inverse association between atherosclerosis and cancer might be to lower dietary intake of both phosphate and oxysterols by increasing dietary intake of fruits, vegetables, and plant-based fats, as in a Mediterranean dietary pattern.[51] A plant-based dietary pattern is associated with lower cardiovascular disease risk and mortality in middle-aged adults.[52] Dietary guidelines for cancer prevention from the American Cancer Society (ACS)[53] and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)[54] also emphasise a whole-foods plant-based dietary pattern with limited consumption of refined grain products and processed meat. In addition, the ACS guidelines provide advice on properly balancing strict vegetarian or vegan diets with vitamin B12, zinc, iron, and calcium to meet the special needs of premenopausal women and children.

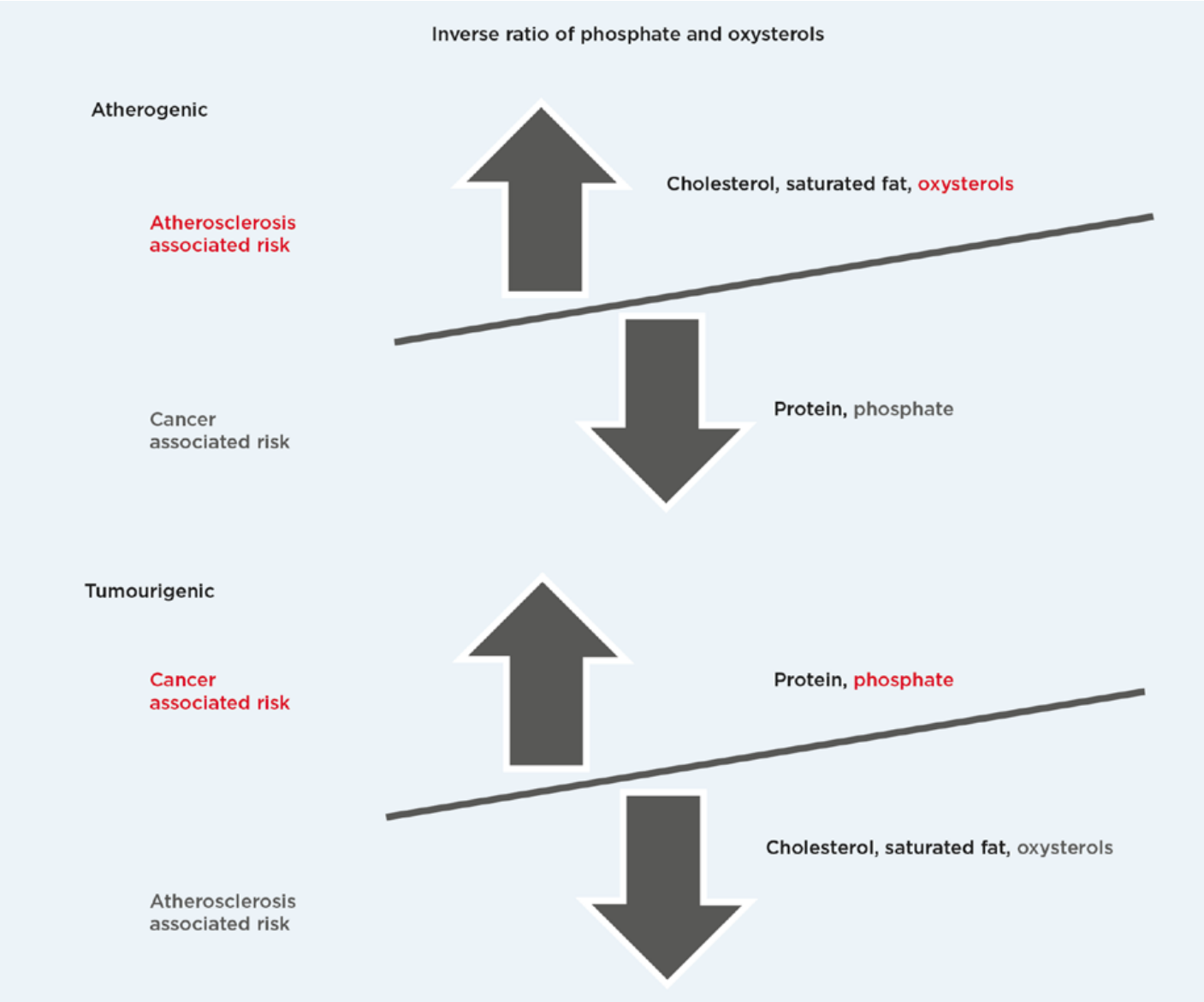

Figure 1: Dietary patterns.

Proposed inverse ratio of phosphate and oxysterols in atherogenic and tumourigenic dietary patterns.

Specific cancer sites associated with different dietary factors are also mentioned in the ACS guidelines, such as cancers of the breast, colorectum, endometrium, and other organs. Tumourigenic properties of excess phosphate is an overlooked dietary factor that may be involved in many of these specific cancers, and more research is needed to investigate the effects of excess phosphate by specific cancer site. In addition, many specific food items such as full-fat meats, dairy, and eggs have high levels of animal protein and phosphorus in addition to high levels of fat and cholesterol, thus increasing the associated risk of both cardiovascular disease and cancer in investigations that include these foods. Nevertheless, the overall dietary pattern, not any particular food, could be the determining factor in the inverse association between atherogenic and tumourigenic diets.

Table 1[55] shows the low phosphorus content of selected fruit and vegetables compared to grains, legumes, and animal-based foods.[55] A recent meta-analysis of 95 studies found that intake of fruit and vegetables was associated with significant reductions in cardiovascular disease and cancer.[56] The researchers observed dose-response reductions in diseases associated with daily combined fresh fruit and vegetable intakes of up to 800 g for cardiovascular disease and 600 g for cancer.

Table 1: Phosphorus in selected food items.

Food item	Phosphorus (mg/100 g)	Food item	Phosphorus (mg/100 g)
Pineapple	8	Potato	57
Grapefruit	8	Date	62
Apple	11	Broccoli	67
Pear	12	Whole milk	84
Fig	14	Green peas	108
Orange	14	Wholegrain pasta	110
Cantaloupe	15	Tilapia	170
Grapes	20	Chicken breast	174
Banana	22	Whole egg	198
Celery	24	Sirloin	209
Tomato	24	Chickpeas	252
Carrot	35	Lentils	281
Romaine	35	Black beans	352
Kale	55	Cheddar cheese	455

Adapted from U.S. Department of Agriculture, Agricultural Research Service.[55]

This amount of fruit and vegetables is double the 400 g currently recommended by the World Health Organization (WHO)[57] and the World Cancer Research Fund (WCRF).[58]

Plant-based dietary fats, like olive oil in the Mediterranean diet, have also been associated with lower cancer and atherosclerosis risk.[59] Of relevance, oils obtained from plant-based foods are generally stripped of the mineral content found in whole foods, so these oils often contain little or no phosphorus. In addition, cholesterol is lacking in plant-based foods, providing little chance for the formation of cholesterol oxidation products in plant-based oils. Whole foods such as nuts, seeds, coconuts, and avocados contain moderate to high amounts of phosphorus. But because these plant-based foods are also high in fat and calories, their overall phosphorus caloric density, or phosphorus per calorie, is relatively low, especially compared to the very high phosphorus caloric density of lean flesh foods, nonfat dairy, legumes, and grain products.

CONCLUSION

This article proposes a novel hypothesis suggesting that the answer to the nearly century-old riddle of an inverse relationship between atherosclerosis and cancer may be explained by inverse proportions of phosphate and oxysterols in atherogenic and tumourigenic dietary patterns. Furthermore, evidence linking reduced associated risks for cancer and cardiovascular disease with plant-based dietary patterns, especially diets abundant in fruits and vegetables with moderate amounts of plant-based fats, infers that a substantial change in current dietary patterns of developed nations is necessary for the future prevention of cardiovascular disease and cancer.

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Nasopharyngeal Rhabdomyosarcoma: A Rare Malignancy Incidentally Found in a Middle-Aged Male with a Diagnostic Dilemma

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Abstract

Nasopharyngeal rhabdomyosarcoma is a rare tumour of the paediatric age group that emerges from embryonal mesenchymal cells. Presented here is a case of a 54-year-old male of Asian ethnicity with a notable history of weight loss, lack of energy, anal fissure, and haematochezia. After the incidental finding of a lytic lesion following imaging, the patient underwent an extensive work-up to rule out malignancy and increased uptake on nasopharynx was found, which was biopsied to diagnose a poorly differentiated tumour, having desmin and myogenin positivity on immunohistochemistry. Metastatic work-up showed extensive bone marrow invasion apart from multiple lytic bone lesions throughout the body. The patient was started on vincristine, actinomycin D (dactinomycin), and cyclophosphamide (VAC) protocol chemotherapy and was followed-up until two cycles were completed, with no evidence of disease remission.

INTRODUCTION

Rhabdomyosarcoma (RMS) is an infrequent and aggressive malignancy that emerges from embryonic mesenchymal cells all around the body, including sites devoid of striated muscles.[1] RMS has an unknown aetiology as genetics, chemical hazards, viruses, and environmental factors have all been considered a cause of pathogenesis.[2] In 1958, Horn and Enterline classified RMS into four histological classifications: alveolar, pleomorphic, embryonal, and botryoid. The embryonal subtype is the most frequent in children (50–60%), the alveolar subtype is the most common subtype seen in adolescents until the age of 25, and the pure pleomorphic subtype occurs merely in adults.[3] RMS is the third most common extracranial tumour in children after neuroblastoma and Wilms' tumour, respectively, and frequently arises within the nasal cavity

and paranasal sinuses of the paediatric population.[4] Incidence per annum of RMS in children is reported at 4.3 cases per million.[1] It follows a bimodal distribution in the general population, with peak occurrences between 2 and 4 years and 12 and 16 years, respectively.[5] RMS demonstrates a significant predisposition for Caucasians and commonly occurs in males.[6] Comparatively, RMS occurs less frequently in adults.[1] Soft tissue sarcomas constitute <1% of all adult malignancies, and RMS accounts for 3% of all soft tissue sarcoma.[7] Adult RMS do not show a propensity for males, as observed in paediatric patients, and occur primarily in the extremities.[3] Furthermore, its occurrence in adults in the head and neck area is extremely rare.[4] RMS of the head and neck region is divided into three perceptible groups: the orbital group, parameningeal group, and other head and neck location group.[7] Among the parameningeal group, the nasopharynx is the most commonly reported site.[7] Parameningeal lesions have the worst prognosis because of the difficulty in diagnosis; associated complications, i.e., central nervous system involvement; and operative complexity.[7]

CASE PRESENTATION

A 54-year-old male of Asian ethnicity presented with a notable history of weight loss, lack of energy, feverish feeling for almost 8 months, and complaints of lower back pain, fever, and generalised weakness for 1 month. He denied any cough, haemoptysis, abdominal pain, alternating bowel habits, melaena, haematochezia, urinary incontinence, urinary dribbling, hesitancy, flank pain, or haematuria. On further inquiry, he was noted to have occasional nasal blockage and rhinitis, and now has predominant complaints of haematochezia. He described months of episodic, severe pain on defecation associated with small volumes of fresh blood per rectum. Given the history, he was managed with antipyretics, nutritional supplements, a high fibre diet, hip baths, and topical ointments keeping the probability of anal fissure in view.

Physical examination results were considered normal, except that the patient was febrile with a temperature of 99 °F, and systemic examination was also unremarkable with no lymph nodes palpable and no bone tenderness reported. Ears, nose, and throat examination showed a deviated nasal septum towards the left side and rectal examination was deferred by the patient because of severe pain in the perineum; therefore, an MRI scan of the pelvis was recommended. Laboratory work-up revealed a haemoglobin level of 9.8 g/dL; total leukocyte count of 10.1 cells/μL, with a neutrophil count of 54% and lymphocyte count of 39%; mean cell volume of 92; platelet count of 46 cells/μL; erythrocyte sedimentation rate of 120 mm/hour; C-reactive protein level of 52 g/dL; serum ferritin level of 2,000 ng/mL; lactate dehydrogenase level of 1,091 international units/L; creatinine phosphokinase level of 266 international units/L; serum creatinine level of 0.9 mg/dL; and normal serum immunofixation and serum protein electrophoresis results. The differential considerations included initially were Pott's disease, multiple myeloma, Crohn's disease, or underlying malignancies including colorectal cancer, lymphoma, and chronic lymphocytic leukaemia.

The pelvis MRI ruled out perianal abscess, fistula, and intestinal mass and provided a diagnosis of anal fissure, but also showed multiple infiltrative lytic bone lesions in the sacrum, acetabulum, and lumbar and sacral vertebrae (Figure 1). An immediate skull X-ray (Figure 1) and lumbosacral spine X-ray were also carried out, which showed punched out lesions within the skull, but the lumber and sacral spines appeared normal (Figure 2). Pott's disease was attributable to the patient's history of lower back pain, weight loss, fever, generalised weakness, and raised erythrocyte sedimentation rate, but it was ruled out on radiological imaging. The patient was managed conservatively for anal fissure, and further work-up for malignancy was planned after ruling out multiple myeloma. Further work-up included urine Bence Jones protein and bone marrow biopsy; there was no trace of Bence Jones proteinuria. PET-CT demonstrated a mass in the right nasopharynx extending to the right maxillary sinus and a metastatic right cervical lymph node, and further revealed increased uptake in the thoracic lumbar vertebrae, sacrum acetabulum, right scapula, and the left 10th rib. Biopsy of the nasopharyngeal mass exhibited RMS of anaplastic (undifferentiated) variety with immunohistochemical stains positive for desmin and myogenin (Figure 3).

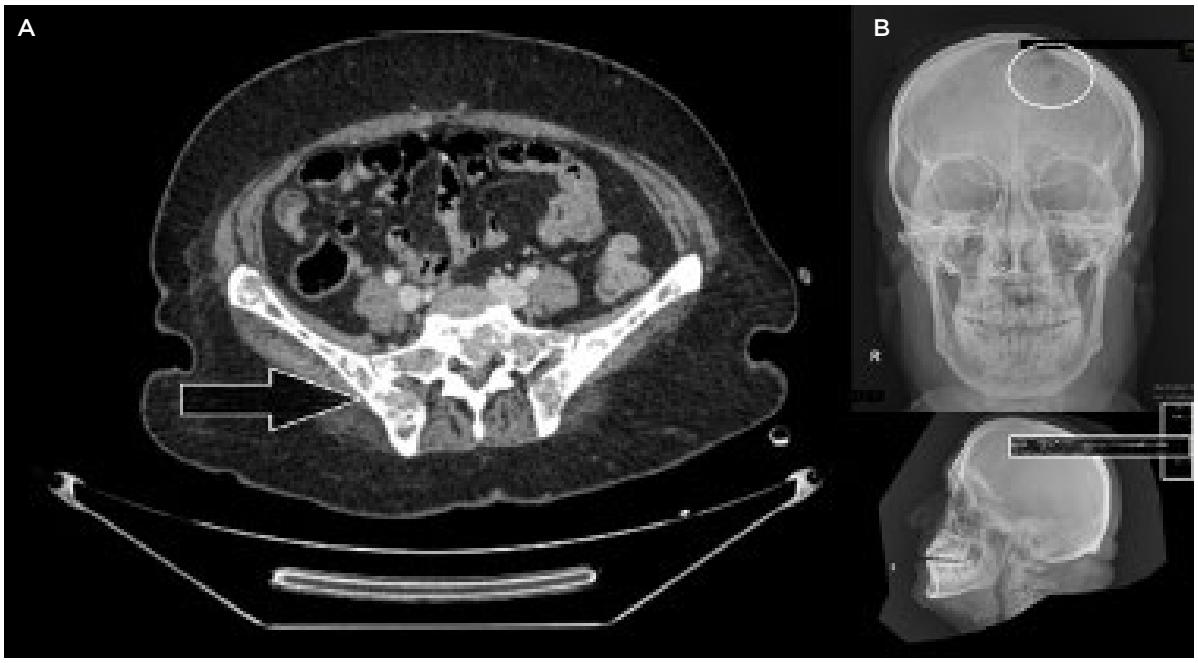

Figure 1: Lytic bone lesions over the pelvic girdle (A) and skull (B).

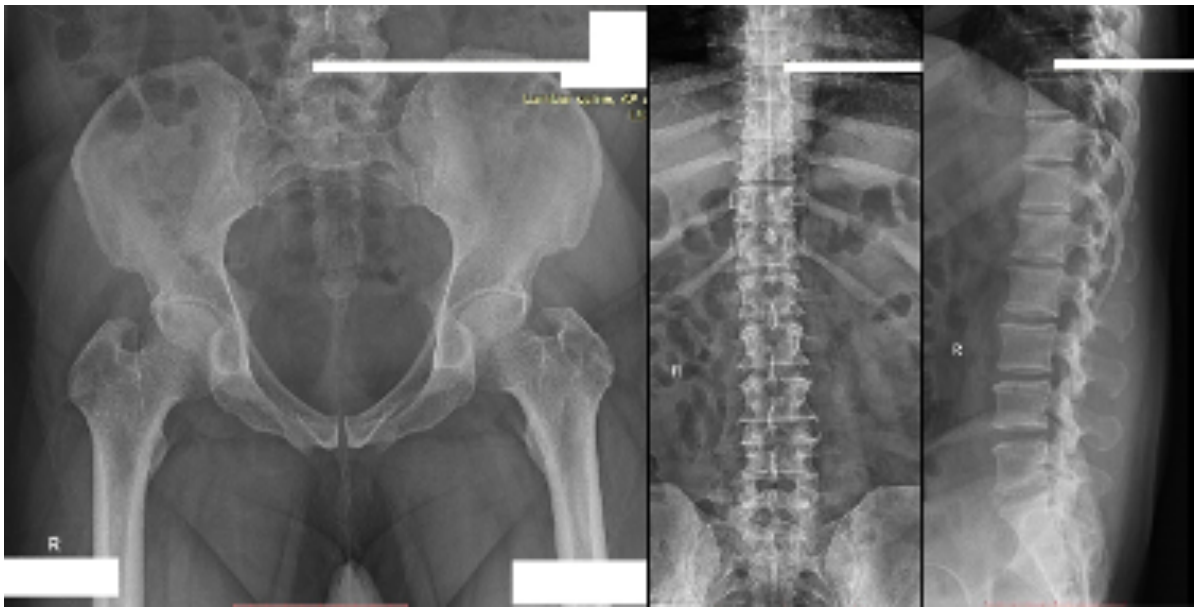

Figure 2: Normal lumbosacral spine and pelvic X-ray.

The histopathological differential diagnosis included small round blue cell tumours and pleomorphic sarcomas. Because of the weak positivity of CD117 and placental alkaline phosphatase, and to exclude a possibility of germ cell neoplasm (another differential diagnosis), a large panel of immunohistochemical stains were used; however, because of the nasopharyngeal location of the tumour and crisp positivity of desmin and myogenin, the diagnosis of embryonal RMS was made. Bone marrow biopsy was conclusive for metastatic infiltration, exhibiting a hypocellular specimen and clumps of non-haematopoietic cells.

Gross: Specimen is received in a single container as "Nasopharyngeal mass" specimen comprising multiple, irregular, greyish, soft tissue pieces that collectively measure 1.0x1.0x0.6 cm in aggregate. Entirely submitted in a single cassette.

Microscopic features: Sections examined revealed multiple polypoidal fragments of respiratory mucosa covered by stratified squamous columnar ciliated epithelium and shows patchy areas of surface ulceration. Underlying tissue mucous secreting glands mixed inflammatory infiltrate. At places foci of neoplastic lesion are present. Cells are arranged in trabeculae. The cells are shown to have moderate amounts of cytoplasm, nuclei show moderate to marked pleomorphism with coarse chromatin and inconspicuous nucleoli. Special stains for glycogen (periodic acid–Schiff +/- diastase) is positive.

The sections were stained with the panel of the following immunohistochemical stains and neoplastic cells showed the following reactivity pattern:

CD20	negative
CD3	negative
CKAE1/AE3	negative
S100	negative
Tdt	negative
CK5/6	negative
CK7	negative
P40	negative
CK8/18	negative
Cyclin D1	negative
MUM 1	negative
Melan A	negative
Desmin	strong positive
Myogenin	strong positive
CD117	weak positive
PLAP	weak positive
LCA	negative

CD4	negative
CD8	negative
CD34	negative
CD138	negative
CD30	negative
Synaptophysin	negative
Chromogranin	negative
CD68	negative
MPO	negative
ASMA	negative
Caldesmon	negative
Oct 34	negative
CD56	negative
EMA	negative
CD99	negative
Alk protein	negative
P63	negative
Cytokeratin	negative

Conclusion: Nasopharyngeal mass: biopsy
Morphological and immunohistochemical features are in favour of rhabdomyosarcoma.

Figure 3: Nasopharyngeal mass biopsy immunohistochemistry report.

A large panel of immunohistochemical stains were used. Owing to the weak positivity of CD117 and placental alkaline phosphatase, germ cell neoplasm was also considered in this case; however, because of the nasopharyngeal location of the tumour and crisp positivity of desmin and myogenin, the overall features were in favour of rhabdomyosarcoma. Strong clinical and radiological correlation was advised.

According to the TNM classification, the tumour was classified as T3 (tumour grown into the sinuses and/or bones nearby), N2 (spread to nearby lymph nodes), and M1 (distant metastasis), stratifying the patient to Stage 4 disease. The patient was referred to the oncology department for palliative chemotherapy and was started on the VAC protocol chemotherapy regimen for metastatic RMS (vincristine 1.4 mg/m^2/dose, dactinomycin 1.5 mg/m^2/dose, cyclophosphamide 1,500 mg/m^2) for every 21 days cycle.[8,9]

After two cycles, the patient attended a follow-up visit with the disease still progressing and a haemoglobin level of 11.5 g/dL; total leukocyte count of 4.5, 60% neutrophils and 27% lymphocytes; and a platelet count of 38 cells/μL. The follow-up period was limited because of the patient's ongoing chemotherapy. After two sessions of chemotherapy, the patient was lost to follow up.

DISCUSSION

With the advent of immunohistochemistry, electron microscopy, and molecular genetic studies, the histological diagnosis of RMS has remarkably ameliorated.[3] Using these techniques, the tumour cells of the RMS express desmin, muscle-specific actin, and myoglobin in well-differentiated tumour cells.[3] Poorly differentiated tumour cells do not stain these agents; here vimentin was strongly positive. Other newly used markers include myoblast determination protein 1 and myogenin antibodies, as was the case in the described patient.

Regardless of the age and gender of a patient with RMS, the signs and symptoms depend on the tumours' origin and its invasion into abutting structures.[3] The time between the onset of symptoms and diagnosis averages from 1 week to 9 months.[2] While superficial tumours may be asymptomatic or present with a tender mass, deep tumours cause vague symptoms and often significantly increase in size before being brought to medical recognition.[5] Tumours arising in the paranasal sinuses, nasal cavities, mastoid, and nasopharynx present with symptoms of nasal obstruction, rhinorrhoea, and recurrent otitis media.[5] Paranasal sinuses are the most common primary site.[10,11] RMS of sinus and nasal origin in adults present with local pain, epistaxis, nasal obstruction, otorrhea, deafness, and sinusitis, and advanced cases usually present with cranial nerve palsies.[3,12] Symptoms of ophthalmoplegia and decreased vision as a result of direct invasion of the orbital apex have been reported in cases of nasopharyngeal RMS.[12] Microscopically, these tumours appear pink, fleshy, and soft, while no variation exists between types except for the botryoidal variant.[10] RMS is equivalent to teratoma, as microscopic tissues present evidence of cartilage, bone, and other bodily tissues.[13] Microscopically, the embryonal type shows increased cellularity, containing several undifferentiated mesenchymal cells and the presence of myxomatous changes.[4] In contrast, the alveolar type shows small circular rhabdomyoblasts, arranged in nests or cards, separated by connective tissue trabeculae and focal locations of alveolar architecture.[4] Metastasis via intracranial spread or to distant locations is the most common cause of death.[14]

RMS are high-grade tumours with local belligerence and a strong propensity to metastasise; hence, are considered a 'systemic disease' given the swift development of metastatic spread.[5] RMS metastasises through direct tissue invasion, a haematogenous route, and by involving the lymphatic system.[6] They differ from other forms of sarcomas by showing an increased predilection to metastasise via lymphatic channels.[13] RMS of the palate spreads to the deep cervical nodes, causing them to have a rubbery consistency, while atrophy and central necrosis tend to occur in the larger metastatic nodes.[15] Nasopharyngeal RMS tends to grow rapidly and infiltrate the skull base or central nervous system.[14] The direct invasion route poses a distinctive danger to the meninges, especially when the tumour inhabits the nasopharynx.[6] The absence of anatomical confines in nasopharyngeal tumours allows its spread via this particular method, decreasing the effectiveness of surgical management.[14] Evidence for meningeal involvement can be evaluated by assessing cranial nerve functions and signs of raised intracranial pressure.[6] Less than one-quarter of the patients with nasopharyngeal RMS have apparent distant metastatic disease at diagnosis, with >50% of these patients having only a single site of metastatic disease, typically in the lung.[14] Haematogenous spread of the tumour has a preference for the bone marrow and lungs.[6] Another unique distant site of RMS metastasis is breast tissue, with only seven formerly reported cases worldwide.[16]

The most significant prognostic factors affecting the outcome of patients with RMS are the age of the patient, site of the tumour, stage, and pathological subtype. Patients >10 years or <1 year of age have a worse prognosis. In contrast to other tumour locations, parameningeal RMS has the worst prognosis.[5] When considering histological subtypes, the alveolar subtype is notorious for metastatic disease, leading to an

unfavourable prognosis compared to other types. A relapsing disease of RMS has a bleak survival rate that ranges from 5–15%.[5]

Before the introduction of antineoplastic drugs, the main modality of treatment for RMS was surgery with poor survival rates, i.e., 25% 5-year survival.[5] Thereafter, the introduction of multi-agent chemotherapy protocols resulted in a significant increase in long-term survival rates i.e., 70% 5-year survival.[5] The present-day treatment regime of RMS includes chemotherapy, radiotherapy, and surgical management.[17]

The commonly chosen radiotherapy technique for paediatric RMS has originated from the Children's Oncology Group (COG) trials ARST 0331, ARST 0431, and ARST 0531, respectively.[14] Treatment is given according to the planning target volume (gross tumour volume + 1 cm = clinical target volume).[14] The planning target volume may change in accordance with the anatomy and normal tissue endurance, especially organs at risk. The inclusion of lymph nodes depends on their pathological status. This method recommends radiotherapy doses of 50.4 gray in 28 fractions at 1.8 gray per fraction to the isocentre, using 6 MV photons and a CT scan-outlined plan.[14] Treatment should be done daily, 5 days per week in a total of 5.5 weeks[4] and external beam radiotherapy is an essential part of therapy. The radiation field covers the nasopharynx and neck completely. In paediatric patients, the dose is dependent on the patient's age, and other significant factors include dose per fraction, total dose, percentage volume of organ receiving dose, chemotherapy, surgery, and comorbidities i.e., hydrocephalus and diabetes.

With increasing benefits and the use of radiotherapy, long-term use complications are becoming more apparent.[14] Complications of radiotherapy include sensorineural deafness, endocrine manifestations, cranial nerve palsies, cataracts, retinopathy, growth disturbance, and occurrence of secondary malignancies within the radiation field. Morbidity from radiotherapy may be astronomical and varies on the frequency and dose of radiation. Dental abnormalities are a major concern for long-term survivors, including microdontia, hypodontia, and xerostomia. Current approaches in radiotherapy are aimed at enhancing the rate of tumour control and reducing overall complications. The administration of radiotherapy has become better with the use of CT and MRI, producing far greater image resolutions.[14,18] Concomitant use with MRI improves the precision of radiotherapy, as MRI can better depict soft tissues and oedema. Radiation is more efficacious and less harmful if it is delivered conforming to the shape of the tumour. Intensity-modulated radiation therapy is based on the guidelines of conformation and converging higher radiation doses to regions within the tumour while reducing the dose to surrounding physiological critical structures.[14] Regardless of the tumours' location and stage, every patient with RMS will receive chemotherapy at some point in the treatment course as a fundamental element of treatment.[5] Although debate exists about the optimal chemotherapy regimen, the most important difference in treatment strategy relates to the technique and timing of local treatment. Complete surgical resection with negative margins grants the best chance of controlling local disease and decreases the local relapse rate, recuperates the overall survival, and may help avoid radiotherapy altogether.[5]

There can be many comparisons drawn between the presented case and the previous scientific literature.[7-9,12,15,16] The major consideration is the location of the tumour, its characteristic immunohistochemistry, and bone marrow invasion of tumour cells, in this case leading to cytopenia. As was also evidently effective in two previous case studies, VAC protocol chemotherapy for metastatic RMS was administered to the patient.[8,9] The patient had RMS in the head and neck region (i.e., nasopharyngeal RMS), which are exceedingly rare, with poor prognosis.[3] Hence, it should be considered as a separate clinical entity and require distinct management from that of paediatric patients because there are possible discrepancies between RMS in adults and children.[19] Major histological subtypes include embryonal, alveolar, pleomorphic, and spindle cell/sclerosing RMS, which was traditionally included as a variant of embryonal but it is now considered as a separate spindle cell/sclerosing RMS subtype in the latest World Health Organization (WHO) classification (2017), and the botryoid is considered a variant.[20]

CONCLUSION

The described case showcased a rare malignancy; the patient presented with nonspecific complaints of anal fissure and was diagnosed incidentally on a pelvis MRI with multiple lytic bone lesions, which provided a clue for the metastatic disease. Further work-up was carried out and the patient was diagnosed imminently with nasopharyngeal RMS. The unusual site and age of the patient contributed to the novelty of this case, with a guarded prognosis.

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Adaptations and Advancement of Biologic Immunotherapy in the Management of Immunologically Cold Solid Malignancies

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Abstract

Contemporary breakthroughs within cancer immunotherapy are frequently cited amongst the most promising of therapeutic directions for medical oncology and perioperative solid tumour management. However to date, the efficacy of treatment of immunologically derived therapeutic modalities is limited to a few highly selective malignancies, exemplified by leukaemia or renal cell carcinoma. Many solid tumours exhibiting low immune activity, i.e., immunologically 'cold', such as highly aggressive pancreatic cancers, have correspondingly become regarded as inappropriate for prospective immunotherapeutic modulation. Standard approach in these tumours therefore relies upon early-stage identification and curative surgical resection, an identifiably imperfect option in both progression temporality and deterrence of metastatic disease.

Fundamentally predicated upon the therapeutic activation of existing systemic immune resources, selectively towards malignant transformed cellular subpopulations, current cancer immunotherapy heavily utilises monoclonal antibody checkpoint inhibitors (i.e., PD-1, PDL-L1, CTLA-4) influencing resultant upregulation of physiologic immune activation pathways. These correspondingly enhance immunologic function and interfere with carcinogenesis. With ongoing development in the scientific understanding of complex tumour microenvironment interactions and subclonal heterogeneity, increasingly promising investigations have developed. These include the effective management of low immune activity cold solid tumours with original immunogenic cofactor therapies as well as immune modulation in conjunction with co-operative chemotherapeutic, radiological, or surgical intervention.

Advancements in novel combination immunotherapies as well as innovative downstream management courses offer great optimism for the applicability of emerging cancer immunotherapy to prospective treatment of cold tumours. This review comprehensively analyses and discusses notable current research directions in the field and underscores future directions for continued scientific progress alongside relevant clinical applications.

INTRODUCTION

Increased awareness has emerged regarding the critical role of immunotherapy within translational cancer management and personalised medicine. Encompassing notable developments such as widely adaptable monoclonal immune checkpoint antibodies, donor immune cell transfusion, and direct cytokine incorporation have brought about significant advancements in effective noninvasive clinical management opportunities for a spectrum of cancers. Fundamental to the majority of current cancer immunotherapy modalities is the adaptation of pre-existing host immune resources to selectively detect and eliminate carcinogenesis, resulting in enhanced T-lymphocyte infiltration (TIL) of solid tumour tissues.[1] This cascading process induces malignant cell apoptosis and parent tumour necrosis, accompanied by marked reduction in aggressive invasion as well as metastatic behaviours *in vivo*.[2] Therefore, modern cancer immunotherapy heavily predicates upon clinical modification of cancer cells' erroneous 'elimination, equilibrium, escape' lifecycle components wherein growth transitions uncontrollably from physiologic to pathologic patterns through avoidance of natural immunologic growth-inhibiting mechanisms. Under healthy conditions, several immune checkpoints, PD-1, PD-L1, and CTLA-4, downregulate immune responses to prevent autoimmunity and systemic exhaustion. Relevant to the development of cancer treatments, immune checkpoints are of value for therapeutic targeting in the form of inhibitory antibodies (immune checkpoint inhibitors [ICI], such as ipilimumab, anti-CTLA-4, pembrolizumab, anti-PD-1, durvalumab, and anti-PD-L1), as induced checkpoint interferences allow for expanded antagonism against cancer cell functions (Figure 1).[3-5]

Whereas patient-centred immunotherapy outcomes have been demonstrated for many haematologic malignancies and immune-active 'hot' solid tumours including lung and breast cancer subtypes,[6] counterpart cold tumours have concurrently become progressively recognised for poor response to immunologically based therapy. This is exemplified via intrinsically poor TIL infiltration as well as being immunologically ignorant and therefore expressing lower levels of relevant checkpoint receptors or even targetable biomarkers including major histocompatibility complex class I.[7] However, cold tumours demonstrate alternative populations of less therapeutically utilised immune infiltration by myeloid progenitors.[8] A significant and contentious debate revolves around whether cold immunologic tumours, such as primary pancreatic and prostate cancers, may prove to be realistic targets for cancer immunotherapy. This review provides a comprehensive discussion of current literature into such cold tumour immunotherapy and evaluates its applicability, perceived limitations, and future directions.

MODERN MANAGEMENT AND EMERGING MODALITIES

As a foundation for point-of-care therapeutic guidelines, distinction between hot and cold tumours relies on the Immunoscore® classification, a robust and standardised system based on T-cell (CD3+/CD8+) prevalence at the centre of the tumour and exterior invasive margin.[9] It is scored from I0–I4, with I0 indicating low infiltration at both measured locales and therefore characterising cold tumours. Immunoscore has demonstrated to be more accurate than pathologic tumour staging as well as clinical differentiation status, nuclear atypia, or lymphovascular invasion severity at predicting both patient prognosis and immunotherapeutic response.[10] By convention, I0–I1 are considered cold tumours, I2 neutral, and I3–I4 immunologically hot. Furthermore, marked decreases in immunotherapy effectiveness within solid tumour treatment correspondingly occur below the I2 tumour Immunoscore threshold.[11-13] Importantly, this scale does not differentiate between causes that may result in differing levels of tumoural TIL infiltration such as fundamental deficiency of tumour-associated antigens, defective antigen-presenting cell recruitment, or substandard T-lymphocyte costimulation with activation upon antigen presentation.[14] Furthermore, intra-Immunoscore (i.e., I2) differences in longitudinal outcome and tumour behaviour by geographical T-cell distribution remain under evaluation.[15,16]

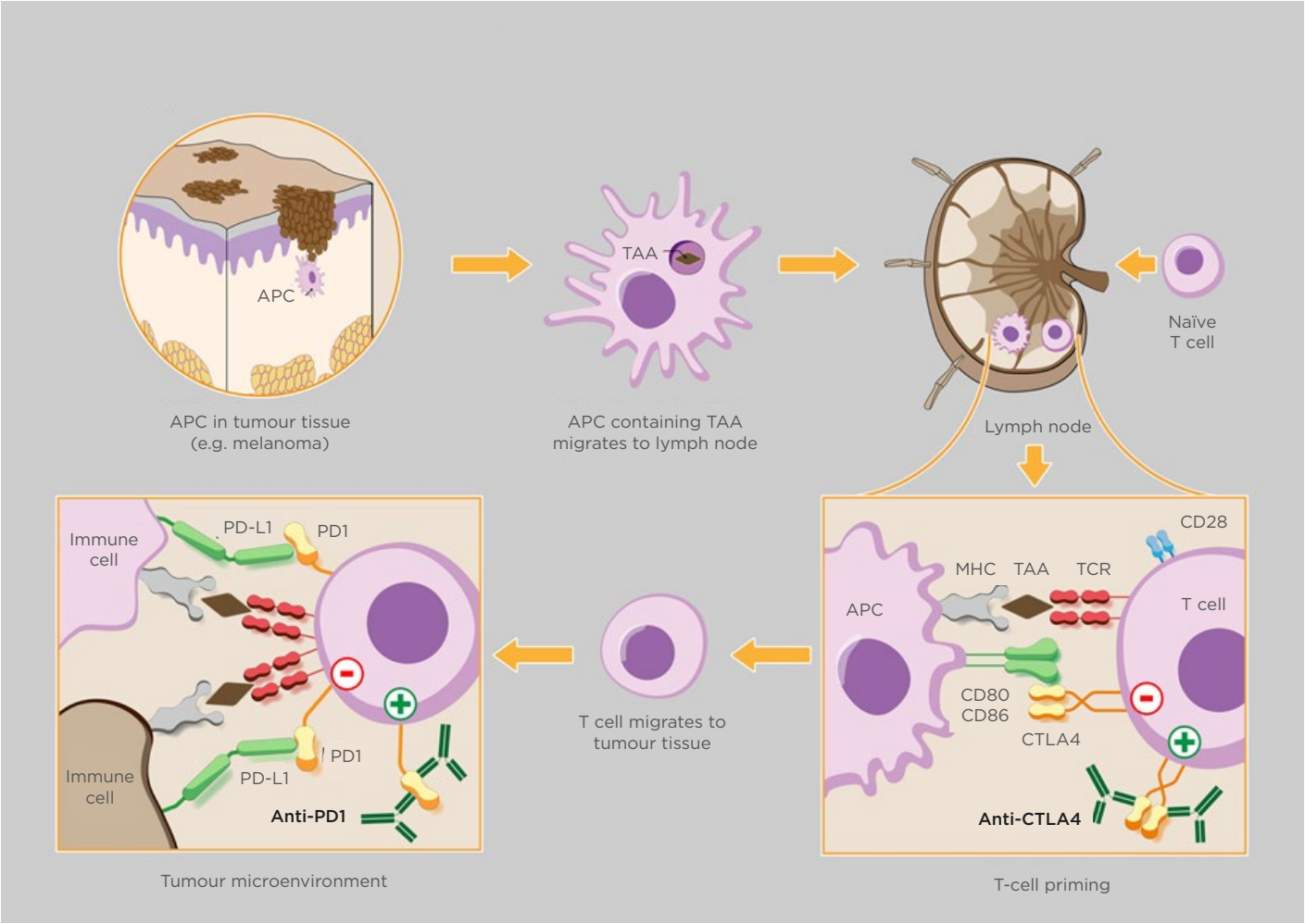

Figure 1: Model of cancer therapy by inhibition of negative immune regulation (CTLA-4, PD-1).

Cancer immunology by downregulation of physiologic immune checkpoints (i.e., CTLA-4, PD-1) therapeutically enhance host immune system responses to malignant tumorous cellular growth. Implementation of CTLA-4/PD-1 inhibitors improve activation of T cells against tailorable tumour-associated antigens which consequently encourages carcinogenic apoptosis alongside reduced neoplasia.

APC: antigen-presenting cell; MHC: major histocompatibility complex; TAA: tumour-associated antigen; TCR: T-cell receptor.

Adapted from www.hegasy.de.[3]

In vivo efficacy of cancer immunotherapies relies heavily upon host immune system adaptation as well as the sustained presence of baseline anticarcinogenic immunology. Factors which increase immune function (i.e., pro-TIL inflammatory modulators or high infiltration) or immune knowledge of tumour markers therefore generally improve treatment response, whereas corresponding deficiencies (i.e., immunosuppression or low TIL-populated microenvironments) produce inhibited effects of treatment. Classification of cold tumours by Immunoscore (I0–I1) has been shown to strongly correlate with poor clinical outcomes and predictably reduced patient response to immunologically-derived treatments (both $p<0.001$).[17,18] Interest in immune-nonresponsive solid tumour management has therefore focussed upon the introduction of targetable factors or stimuli into a fundamentally silent immunologic landscape, which may in turn establish foundations upon which immunomodulation may be efficaciously introduced[19-21] (Figure 2).[22]

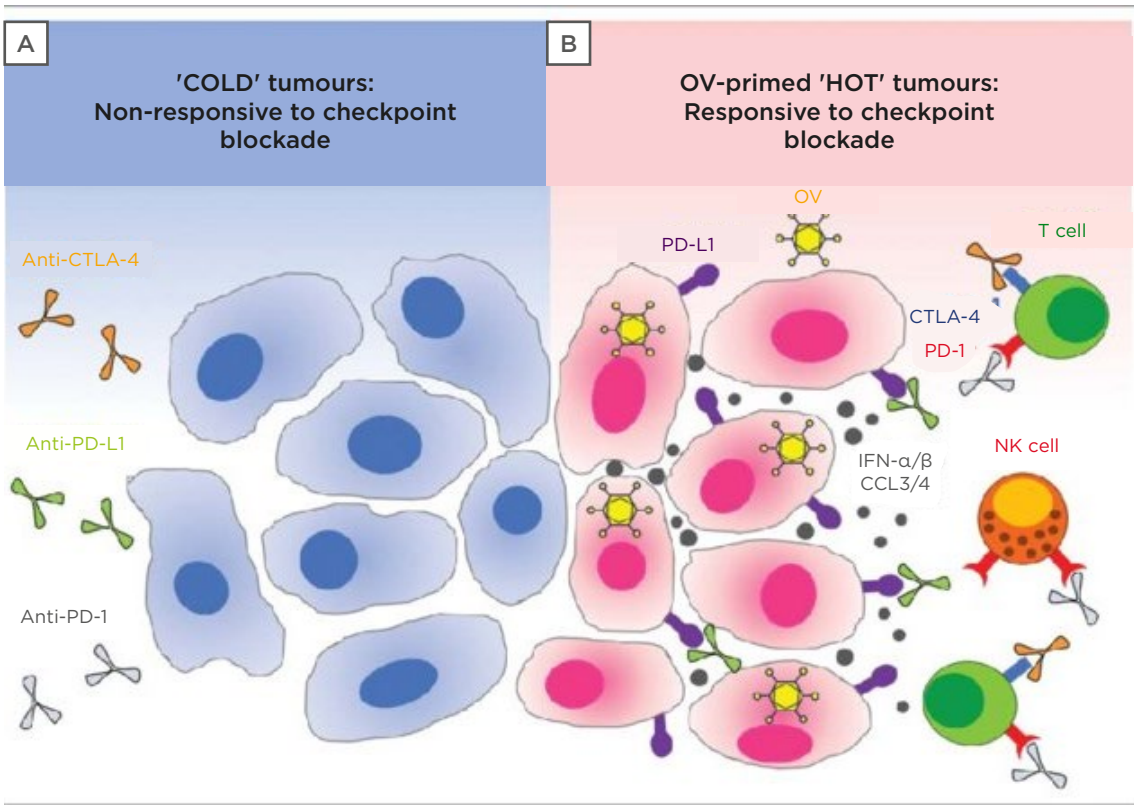

Figure 2: Therapeutic potentiality of cold tumour immune response by oncolytic virology.

'Cold' solid cancer tumour cells exhibit low immunologic targetability and corresponding responsiveness to immunotherapeutic modulation given low cell-surface protein expression (**A**). Clinical implementation of oncolytic viruses (**B**) may modulate local and systemic tumour cell behaviours, including enhanced immune receptor availability, leading to positive immunotherapy applicability.

IFN: interferon; NK: natural killer; OV: oncotherapeutic viruses.

Adapted from Gujar et al, 2018.[22]

These treatment approaches are categorised into the following overarching means of immune facilitation and provocation: combination chemotherapy, radiotherapy, immunostimulation or direct oncolytic virotherapy, and the novel peptide-based cancer 'vaccines'.

Combination Chemotherapy and Immunotherapy

Clinical inquiry into methods of cooperative, dual chemo- and immunotherapy to stimulate cold solid tumour immunogenicity represents a prominent and longstanding direction of interest. Trials in this subsection of pharmacotherapy occur predominantly between expansion of recognisable tumour cell adjuvanticity and antigenicity. Literature suggests that high mutational burden and intratumoural heterogeneity project poor immunotherapy prognoses[23,24] and evolving data informs utility of artificial 'neo-antigens' which may be presented through direct genotoxic chemotherapeutic courses (i.e., cyclophosphamide) and reliably produce downstream changes in immune relevance through increased tumoural antigenicity.[25] By broadly inserting drug-induced precursor DNA lesions to neoplastic cell populations, physiologic cascades including the well-researched cGAS-STING-IP3 pathway are hypothesised to upregulate local tumour immunogenicity, allowing formerly cold tumours to be more efficaciously targeted by present standardised immunomodulatory pathways.[26] Ongoing trials[27-29] introducing direct pharmaceutical cGAS-STING-IP3 hyperactivity (investigative drug ADU-S100) alongside immunotherapy (pembrolizumab) are similarly recipients of interest attributable to preliminary

data suggesting high efficacy against diverse cold lymphomas, primary otolaryngologic lesions, and secondary metastatic lesions.[30]

Noted limitations across animal models with concerted efforts to singularly increase tumoural antigenicity via neo-antigens revolve around unpredictable levels of induced neo-antigen epitope expression, which given commonly moderate-to-low prevalence correlate to modest effectiveness.[31] This presentation derives from clinical reality that many DNA-damaging chemotherapeutic agents act upon mature cancer cells, which leads to only mitotic daughter cells receiving an introduced mutation for immune generation. Mutation rates for chemotherapeutics aimed at increasing antigenicity within established solid tumours are therefore low in comparison to the initial replication processes of the same cancer. This is because uncontrolled growth would likely have gone through hundreds of rounds of replication by the time of drug-influenced DNA damage.[32] Overall neo-antigen efficacy and prevalence, regardless of chemotherapeutic toxicity and dosage, by result inherently remain less appreciable than that of baseline hot solid tumours in regard to the aforementioned challenges in clonal proliferation. An additional challenge is that mature tumours also contain a significant proportion of non-dividing, fully mature cancer cells. Chemotherapeutic genotoxicity in these tumoural components would essentially produce no immunogenic benefit and, given their abundance, many chemotherapeutic induction courses for immune treatment remain considerably limited in effect size and consistency. Nonetheless, unpredictable antigenicity improvements from numerous chemotherapeutic agents may concurrently influence adjuvanticity, the secondary activation of apoptotic or tumour necrosis pathways, through exocytosis of damage-association molecular patterns. Simultaneously, concentrated local apoptosis of tumour cells may induce a systemic IFN-α immune response, resulting in heightened recruitment of CD4+/CD8+ memory and cytotoxic T cells. A replicated pre-clinical finding in murine models[25,33] has instigated considerable interest in the practicality of commonly used anticancer anthracyclines, taxanes, or oxaliplatin among others as immune-instigating co-therapy.[34]

Epigenetic Medicine

Alongside traditional cancer pharmaceuticals, the application of fledgling epigenetic agents toward upregulation of cold tumour antigenicity as well as presentation pathways has *in vitro* shown to enhance the penetrance of therapeutically utilisable immunogenic markers. Through demethylation of silenced antigen codons common to tumours clonally selected for immune resistance, DNA methyltransferase inhibitor drugs (i.e., decitabine) have been reported in literature to introduce open transcription frames correlative to subsequent tumour production of highly immune active and targetable peptides.[35] Additionally, a majority of currently available epigenetic drugs (DNA methyltransferase inhibitors and histone-lysine N-methyltransferase EZH2 inhibitors) are well-replicated as being able to significantly reduce silencing of intratumoural TH1-response cytokines, a process that heavily regulates CD8+ T cell infiltration associated with impaired patient prognoses.[36] Therefore, without inducing detectable chemotherapeutic damage into host systems or tumour cells directly, epigenetic drugs and demethylating agents at present appear to nonetheless carry significant promise in cold cancer immunotherapy supplementation. Currently, multiple early stage clinical trials are examining the safety profile and pharmacodynamics for numerous proposed epigenetic-inclusive combination regimens.[37,38] Prominent trials include the EMERGE trial[39] (Phase II) for gastrointestinal cancers, investigating anti-PD-L1 immunotherapy with domatinostat, a novel class 1-selective histone deacetylase inhibitor hypothesised to increase cold gastrointestinal tumours' immunogenicity and successive susceptibility to follow-up checkpoint inhibition.[40]

Radiation Oncology and Direct Stimulatory Immunotherapy

Perhaps a more direct procedure for inducing immunogenicity suitable for immunotherapeutic targeting lies in radiotherapy that utilises ionising radiation directed at controlled tumour cell immunogenic cell death. Via elaborated mechanisms within which temporal homogeneity of tumour cell apoptosis may expand toward systemic anticarcinogenic benefit,[41] immunogenic radiotherapy coupled with ICI is currently

regarded with optimism for control of varied cancers. These include trials ranging from systemic metastatic disease to treatment of resistant cold neoplasms.[42,43] Through high-dose radiation of aggressive cold malignancy such as pancreatic-head or non-small-cell lung carcinoma,[44,45] integrative radio- and immune- combined therapy in animal models have exhibited the capacity to cause systemic immune upregulation more systemically than localised chemotherapy precursors.[46] In practise, this indirect systemic augmentation suggests the capacity to concomitantly protect against localisable primary metastases as well as reduce the severity of secondary malignancies both known and yet undiscovered. Precise mechanisms of reliably generalised immune protective effects remain under investigation, although some recent studies suggest that exaggerated post-treatment increases cold tumour-specific CD103+/CD141+ murine and human protein, quantities which are relatively less scarce in these CD3+/CD4+/CD8+ immune-ignorant tumoural populations.[35]

Emerging work into the dynamic interplay of tumour microenvironments with systemically administered tailorable immunotherapies has yielded encouraging findings. Through combination regimens of localised immune response stimulatory agents (i.e., inactivated viral vaccine), an early-phase clinical trial which co-administered anti-PD-1 antibody (pembrolizumab) has reported productive utility for the transformation of low immune activity neoplasms into more targetable levels of immune infiltration and drug modifiable expression.[47,48] Contemporary investigation demonstrating strong consistency and reliability of these preliminary findings have lent further value to this particular line of research.[45] However, to date there remains the need for prospective Phase III trials to assess macroscopic interrelationships and rare adverse effects between locally stimulating viral administration alongside concurrent immune intervention. Additional clinical clarification in key areas yet undetermined and inherent to the described treatment combinations include whether patient demographics, disease stage or determinable genotypic (mutational degree) variation, and medical history with potential comorbidities may influence prognosis from these dual treatment courses.[49]

Anticarcinogenic Virotherapy and Neoadjuvant 'Vaccination'

Outside of immune response-provoking effects for viral vaccine introduction into the cold tumour microenvironment, interdisciplinary investigations delineate that engineered oncolytic viruses may play a role in the efficacious immune elimination of mutated tumour cells.[50] Whereas the direct resultant effect of oncolytic viruses often involves cytotoxicity and highly specific cancer cell death locally comparable to chemotherapy and radiotherapy, literature has suggested more stable and prolonged systemic immunogenicity from viral oncolysis. This is through mechanisms including but not limited to ICD instigation, DAMP exocytosis, and viral activation of antigen-presenting cells (major histocompatibility complex Class II) all of which combine to upregulate host immune functionality[51] (Figure 3).[52] Infected cancer cells within immunologically cold tumours, which frequently confer considerable challenges for antibody checkpoint inhibitors or other traditional immunotherapy methods, have also been shown to be more reliably targeted by antitumour antigen-specific T-lymphocyte driven immune reactions in animal models. This is hypothesised as a result of systemic immune recognition resources being able to recognise oncolytic viruses, if not markers on infected host tumour cells themselves. Mediated elimination of both components consequently has demonstrated desirable tumour-reducing outcomes in preliminary research.[53] More recently, advanced melanoma and squamous metastatic disease management trials[54,55] utilising oncolytic viruses alongside pembrolizumab (PD-1 inhibitor) and talimogene laherparepvec (a melanoma- and sarcoma-specific ICI) have generated considerable interest as a leading example of novel anticarcinogenic dual immune-virotherapy. Initial results have indicated satisfactory patient treatment safety and moderate improvements in participants' prognoses and disease progression, which is especially important given the high aggressiveness in both melanoma and secondary squamous tumour behaviours.[35]

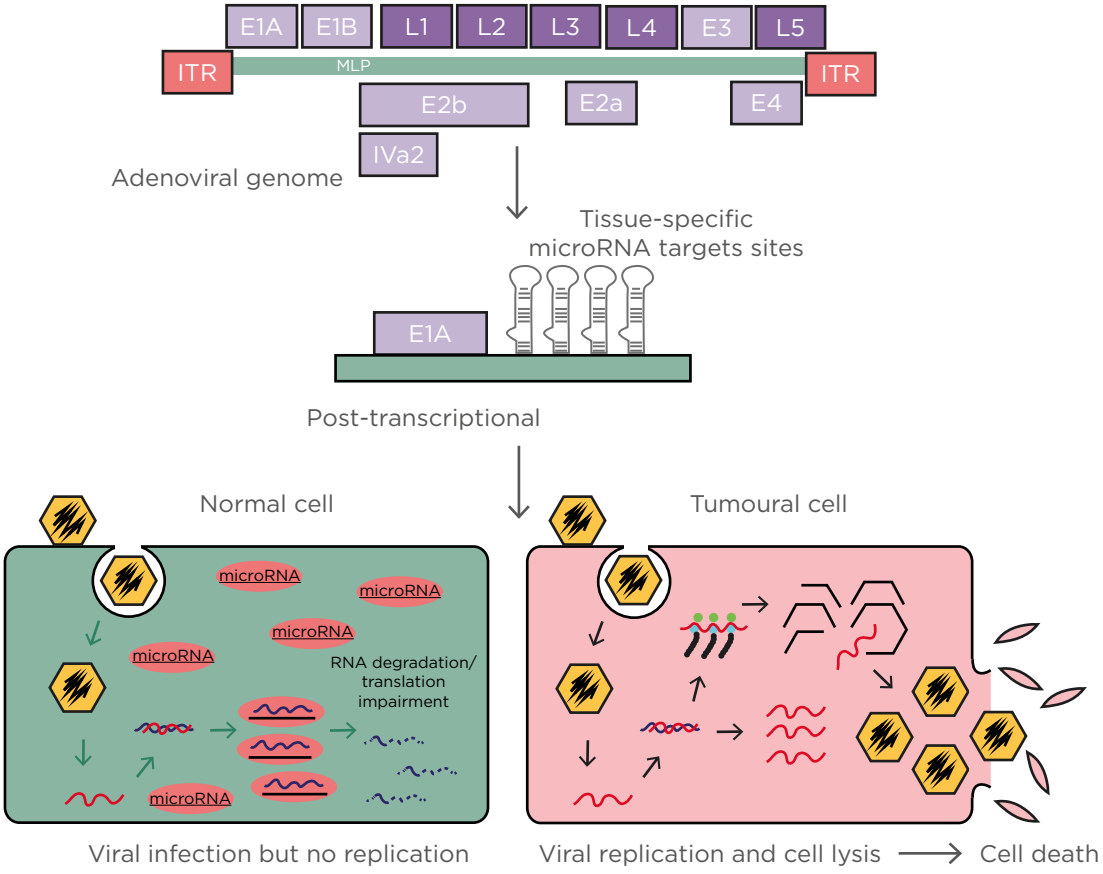

Figure 3: Oncolytic adenovirus controlled by microRNA response element.

Representative depiction of oncolytic adenovirus *in vivo* function and target cellular subpopulation selectivity, relative to independent and supportive cancer immunotherapy applications. Infected cells may influence both local tumour cell lysis as well as systemic upregulation of immune function and tumour targetability through induced release of pro-immunogenic pro-inflammatory factors.

Adapted from Bofill-De Ros, 2010.[52]

Recent biological methods of tumour antigen expansion have increased the attention for the synthesis and patient personalisation of so-called cancer vaccines, where samples of allogenic inactivated target tumour antigen may be tailored and presented to host immune resources prior to the induction of more standard immunotherapeutic methods.

Extensive modern trials encompassing GVAX (pro-GM-CSF) for pancreatic and prostate cancer[56,57] demonstrate a significant increase in host recruitment and tumour infiltration of CD8+ T-lymphocytes, with correspondingly significant increases in patient survival and disease state ($p<0.02$) alongside PD-1 inhibition.[58,59] Whereas large-scale follow-up remains vital to elucidate applicability of cancer vaccines as a means of augmenting low levels of foundation immune response to cold tumours, ongoing studies strongly suggest such vaccinations may co-transform nonresponsive cold cancer populations towards TIL-inflammation through direct effect while also expanding checkpoint inhibitor functionality through multiplication of relevant special-effector T-lymphocytes.[60] However, difficulties to practising fully-personalised cancer vaccination alongside immunotherapy endure, which outside of practical implications in resource or time investment is further constrained by advanced disease realities such as patients' deficient T-cell function and incomplete response to initial vaccination.[61]

DISCUSSION AND FUTURE DIRECTIONS

Immunologic intervention is frequently cited as being amongst the most adaptable and promising of treatment options in modern oncology, broadly applicable to the management of a wide array of cancers. However, appropriate knowledge on adaptation and application of constituent methodologies ranging from CAR T cells to oncolytic viruses and novel vaccines remain relatively underdeveloped and an emerging field of inquiry. Further challenged by varying degrees of tumoural immune activity seen within solid malignancies, especially regarding more robust immunomodulatory therapies in non-solid tumour cancers. While the clinical effects and expected adverse events of CAR T therapy to target immunomodulatory tumour antigens such as CD19 alongside adaptability with immune costimulatory domains CD28/CD137 are largely well-characterised in conditions such as diffuse large B-cell lymphoma,[62] current applications and suitable targets within solid tumours, particularly those challenging immunologically cold malignancies for which CAR T might intuitively prove most beneficial, remains under investigation and its perceived effectiveness still to be well-demonstrated.[63,64]

As outlined in this review, ongoing clinical trials on traditionally cold and less immunogenic solid tumours emphasising co-operative combination therapies and immunogenic interactions suggest that translational and personalised cancer immune interventions contain considerable therapeutic value in the realm of solid tumour management. Of further importance is that immunotherapy for solid tumours, unlike haematologic and primary systemic malignancies (i.e., lymphoma), may not exclusively exist as curative in intent. Strong evidence indicate that the gold standard for patient prognosis across many solid tumour cancers is early-stage curative resection, considering the high relapse-free cure rates;[65,66] substantial value may also be derived out of cold tumour immunotherapy as an opportunity for surgery-supportive perioperative care. In illustration, where for non-Hodgkin's lymphoma a moderately effective immunotherapeutic response achieved by CAR T infusion may prove only useful for control of disease spread but accompanied by major adverse outcomes with long-term use, the same level of efficaciousness in primary pancreatic cancer could produce previously nonresectable growths (i.e., caused by staging or aggressiveness profile) into the tumour staging range for clinical consideration of operation.[67] In cold immunologic tumours management, combination approaches may expand the patient and disease profiles associated with treatable characterisation and, through the broadening of operative suitability classification, could provide marked benefits toward epidemiologic cure rates for many cancers.

Against alternative nonsurgical methodologies such as chemo- and radiotherapy for nonsurgical management alone, across limited published studies, immunotherapy has demonstrated slightly reduced systemic side-effect profiles with no significant increases in either patient adverse event frequency or serious adverse event severity.[68,69] A reasonable expectation would therefore persist in the fact that with greater flexibility and biomarker identification ability within immune-based treatment regimens, more control and minimisation may be exerted on behalf of patients undergoing cancer treatments, which is presently cited amongst the leading instigators for patient cancer therapy nonadherence.[70] That is not to indicate that long-established anticancer methodologies such as chemo- and radiotherapy no longer have a valuable freestanding niche in the arsenal of cancer treatment options in light of immunotherapeutic medicine progression. Outside of combination therapies to provoke ICD, early systematic treatment of diagnosed malignancies through alternative mechanisms may also reduce the pathologic intratumoural selection of immunologically cold clones less responsive to both physiologic control processes as well as inducible immunotherapy.

Major challenges to generalised adaptation of current immunotherapeutic techniques remain prominent. These encompass the management of patient autoimmunity, side effects through greater modifiable therapeutic selectivity, and a reduction in therapy-associated immunotoxicity. Moving forwards, investigation of cancer immunotherapy's efficacy and tolerability in early-stage disease is of critical importance given the presently limited data. Clinical intuition suggest that existing immunostimulatory modalities likely demonstrate more favourable findings in advanced tumour stages (the

concurrent focus population of most available trials) given that patient immunocompromise reduces baseline physiologic antitumour defences whilst also limiting host immunotoxicity potential,[71-73] a major barrier against greater onco-immunology translation. The rise of generalised hyperimmunity (i.e., allergies) and autoimmunity particularly in first-world nations[74,75] additionally requires clarification upon the future manifestation and clinical role of onco-immunology, specifically in relation to side-effect profile severity and incidence during treatment, upon widespread adaptation.

Pragmatically, continued research and proposed practise of highly individualised precision oncotherapeutics must necessitate scalable and encompassing genetic and immunotherapeutic biomarker repositories. Because of the extreme complexity of tumour microenvironment interactions as well as local-to-global immune relationships, only through accurate and exhaustive bioinformatics databases would bench-to-bedside management guidance prove truly attainable. Likewise, valid reservations remain regarding current practicality and cost-benefit of effectively inducing clinical immunogenicity within less-responsive tumours, ignorant to direct immunotherapeutic intervention. Concerns regarding the practicality and cost-benefit analysis of relatively ICI-dependent modern immunotherapy to cancers with inherently low mutational loads (i.e., forms of pancreatic cancer, which subsequently reduces effectiveness of any ICI antibodies), physiologic barriers to combination drug therapy penetration (i.e., immune- and chemotherapeutically derived drug entry into the central nervous system through the blood-brain barrier[76]), or still-unknown mechanisms for significant observed deviations in patient response given disease status to combination immunotherapy (either baseline or acquired therapy resistance not previously noted)[77-79] require proactive exploration.

CONCLUSION

This review of current literature and clinical trials critically analyses and identifies potential current avenues of clinical utility for immunotherapy in the treatment of immunologically cold solid tumour neoplasms. In spite of nascent efficacy data and directly translatable clinical value for immunologically derived approaches independently, it is the position of this paper that combination treatment guidelines incorporating means of immunogenicity induction followed by targeted immunotherapeutic ICI remain realistic and of critical importance for sustained investigation. As a complement to early detection and surgical resection, immunotherapy demonstrates the exciting concurrent capacity to inform perioperative management of solid tumours as neo-adjuvant care, while also potentially proving curative for malignancies with identifiable and therapeutically targetable markers. This provides a wide scope of application that includes the potential to treat resistant tumours traditionally regarded as being immunologically cold. With the continued identification and functional clarification of further immunologically relevant cellular antigens and receptors as well as tumour microenvironment interrelationships, long-established boundaries in tumour characterisation alongside associated therapeutic evaluation are increasingly less definite.

A profession-wide shift of healthcare towards personalised medicine and translational therapeutics is now constrained in the realm of immunologically cold solid tumours by a persistent inability to effectively identify and target such neoplasms accurately. Numerous ongoing efforts to clinically induce immunogenicity for consequent immune intervention through chemotherapy, radiotherapy, vector, and vaccine-based modalities are promising but unfinished. Meaningful progress in these fronts will require accompanied advancement in the scientific community's understanding of tumour microenvironment interactions as well as clonal heterogeneity, an ambitious order that will require considerable sustained research. Nonetheless, given the many avenues of potential immunotherapeutic management presently under exploration as well as their apparent untapped clinical potential, eventual introduction of adaptable immunotherapies effective and versatile to both traditionally hot and cold immune activity tumours with therapeutic success still appears a generally reasonable expectation. Combination and novel cancer immunotherapy, by extension personalised medicine of the future, carry great applicability and clinical promise for the efficacious treatment of diverse, challenging malignancy subtypes inclusive of resistant solid tumours exhibiting low immune responsiveness.

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