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EMJ Oncology

Review of ESMO Congress 2022

Editor's Pick

Identifying the Best Ki-67 Cut-Off for Determining Luminal Breast Cancer Subtypes Using Immunohistochemical Analysis and PAM50 Genomic Classification

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Welcome to *EMJ Oncology* 2022, which offers an engaging review of this year's Congress of European Society for Medical Oncology (ESMO) that took place in Paris, France, and featured key developments in the field. It has been an amazing year of progress in oncology. We have seen progress on many fronts including clinical trials on melanoma and non-small cell lung cancer, among others.

Attending this year's congress was an exciting experience and provided us with great insights both in clinical and translational research such as a study demonstrating that air pollution can induce IL-1β release in cells with *EGFR* mutations to drive lung cancer development in non-smokers.

Among our coverage of the congress is a summary of a session discussing the personalising of immunotherapeutics in non-small cell lung cancer and how these can be applied to special populations. Other developments highlighted include a study on the use of tumour organoids from multifocal metastatic colorectal cancers for personalised oncology, and a study including the use of liquid biopsy for early detection in lung cancer.

We are also proud to present a number of articles featuring engaging insights in the field, from a study focusing on determining the optimal cut-off that could differentiate between luminal tumours using Ki-67 as the independent differentiating factor, to an unusual case report of primary pleural schwannoma.

Thank you to everyone who brought this issue together with special thanks to our contributors, reviewers, and Editorial Board. We look forward to seeing everyone again next year in Madrid, Spain. Until then, enjoy reading *EMJ Oncology!*

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Foreword

Dear Colleagues,

I am thrilled to present the latest issue of *EMJ Oncology*, focusing on the European Society for Medical Oncology (ESMO) Congress 2022, which took place between the 9th–13th September in Paris, France.

My Editor's Pick is an excellent paper by Escala-Cornejo et al., which discusses the best Ki-67 cut-off for determining the luminal breast cancer subtypes using immunohistochemical analysis and PAM50 genomic classification. The study involved genomic testing using PAM50 of samples from 143 females diagnosed with early-stage luminal breast cancer.

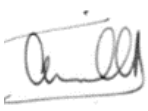
A captivating article by Saad et al. provides insights on colorectal cancer in pregnancy, as the increasing choice of having children later in life is leading to an increase in rates of colorectal cancer. The authors discuss the presentation, anatomical location, and pathogenesis of the disease, as well as the challenges that come with diagnosis and treatment.

Limula et al.'s case review discusses the use of dual immunotherapy in patients with a history of organ transplant, presenting a 58-year-old patient with a history of renal transplant who was diagnosed with a relapse *BRAF*-mutant melanoma, and who showed good response to dual immunotherapy treatment and graft tolerance.

Further content features a case report by Cherem-Kibrit et al., reviewing primary pleural schwannoma; a case study by Khan et al. discussing thyroid papillary carcinoma and hyperthyroidism; and a congress review featuring highlights from the ESMO Congress 2022.

This journal also features an infographic explaining the ESMO recommendations for the diagnosis and staging of metastatic non-small-cell lung cancer, and an interview with Carlos Caldas, Clinical Scientist and Senior Group Leader at the Cancer Research UK Cambridge Institute.

I sincerely thank all Editorial Board members, authors, reviewers, and interviewees who have contributed to this issue. I hope you enjoy reading this inspiring journal.



Ahmad Awada

Head of the Oncology Medicine Department,
Jules Bordet Institute, Brussels, Belgium

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ESMO 2022

Review of the European Society for Medical Oncology (ESMO) Congress 2022.

Location: Paris, France, and online
Date: 9th–13th September 2022
Citation: EMJ Oncol. 2022;10[1]:10-18. DOI/10.33590/emjoncol/10128767. https://doi.org/10.33590/emjoncol/10128767.

THREE years after the last in-person European Society for Medical Oncology (ESMO) Congress, the 2022 congress welcomed nearly 23,000 participants in Paris, France, as well as 5,000 online. The purpose of the congress was a celebration of being back together, and of collaboration between all healthcare professionals wanting to improve survival times for patients. During the opening ceremony, Solange Peters, President of ESMO, said: "For ESMO, there was never going to be a return to normal. The only way we know is forward."

In their introduction, Peters highlighted the importance of sustainability in oncology, and how ESMO aims to help achieve this. First, through a qualified medical workforce, by nurturing oncologists' professional development and supporting them in their daily practice. Next, ESMO aims to promote prevention, thereby minimising overall impact of cancer on healthcare resources. Up to half of cancers are deemed preventable. Through adequate prevention and screening initiatives, the absolute number of cases can be lowered and early diagnosis enabled, leading to shorter, less intensive treatment courses. Finally, sustainability can be achieved by caring for the environment in which we operate, contributing to a healthier world. Peters emphasised that the goal is to reduce cancer incidence. It is expected that there will be over 30 million cancer cases worldwide by 2040 (there are currently 19 million). Therefore, sustainability will be critical to ensure the best care possible for patients in the future.

Scientific Co-chairs Charles Swanton and Fabrice André introduced the congress programme, which was constructed to achieve a better understanding of the disease in order to provide better care for patients with cancer, while also caring for sustainability. The focus was on science that impacts patients on a daily basis, rather than virtual science. Major challenges in oncology were integrated in the ESMO programme, including early detection and prevention of cancer; treatment de-escalation thanks to molecular analysis; drugs developed from biotechnologies and impact on infrastructures; molecular medicine to develop new drugs; the impact of new drugs in under-represented populations; and topics needing more attention, such as survivorship and artificial intelligence.

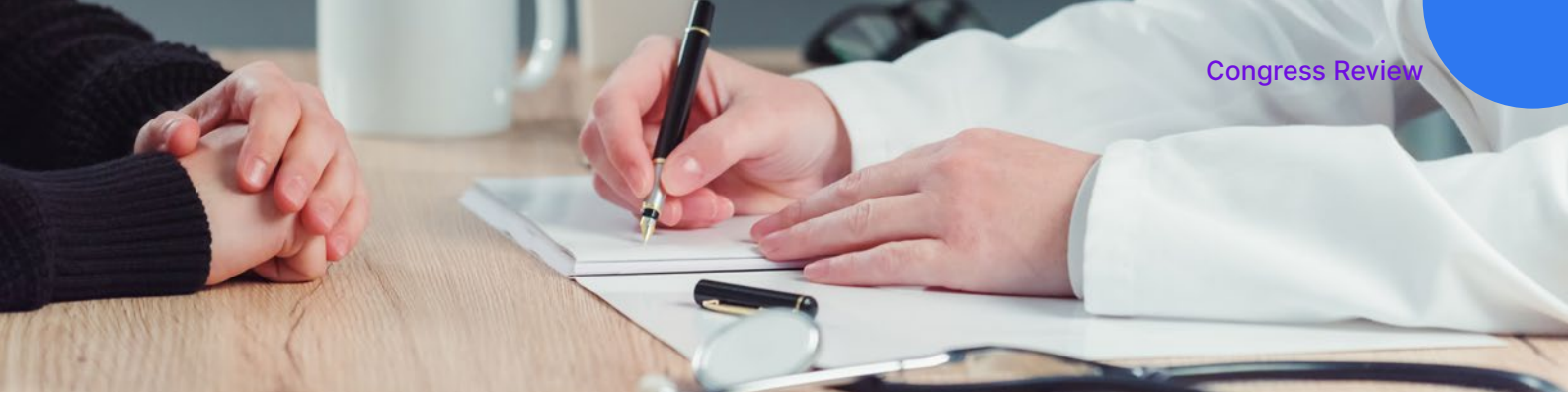
Amanda Psyrri, Chair of the ESMO nomination committee, handed out four awards at the opening ceremony. The first, the ESMO Award, was granted to Karim Fizazi for outstanding contributions to the development of medical oncology, particularly

their contribution to prostate cancer research. Next, Samra Turajlic was awarded the ESMO Award for Translational Research for exceptional achievements in translational research, including their work on cancer evolution, especially in kidney cancer. The third, the Women for Oncology Award, was presented to Fatima Cardoso, for their significant support of the career development of women in oncology, and becoming a role model to a whole generation of women working in oncology. Finally, Bernard Escudier was presented the ESMO Lifetime Achievement Award, for their lifelong commitment to clinical cancer research and education, particularly their achievements in renal cell carcinoma, immunotherapy, and on new therapeutic strategies. During the award ceremony, the recipients from 2020–2021 were also given the opportunity to receive their awards in person.

Peters concluded by saying: "It is also a matter of ensuring that the fruit of the work we do here, our past and future victories in treating cancer more effectively, do not slip permanently out of the reach of patients in the coming year."

"It is also a matter of ensuring that the fruit of the work we do here, our past and future victories in treating cancer more effectively, do not slip permanently out of the reach of patients in the coming year."

The EMJ team was delighted to attend this event, and is looking forward to attending next year's ESMO congress on the 20th–24th October in Madrid, Spain. Read on for our highlights and reviews of this year's congress. ●



Non-Small-Cell Lung Cancer Could Be Treated with Anti-programmed Death-Ligand 1

ANTI-programmed death-ligand 1 could be used to treat patients with non-small cell lung cancer (NSCLC). A Phase II IPSOS study, which compared single-agent chemotherapy to first-line atezolizumab in patients with NSCLC, was presented at ESMO Congress 2022. It is the first randomised clinical trial to evaluate single-agent immunotherapy in patients with poor prognosis.

The researchers randomised patients with locally advanced or metastatic NSCLC without driver mutations 2:1 to single-agent vinorelbine or gemcitabine in 3/4 weekly cycles, or atezolizumab 1,200 mb intravenously every 3 weeks. The participants were ineligible for first-line platinum-doublet chemotherapy, due to comorbidities in patients aged 70 or over, and due to poor performance status (PS). Atezolizumab improved median overall survival significantly, and these benefits were seen across all subgroups, including PS, histology, and programmed death-ligand 1 expression levels.

This confirms data from the PePS2 trial of pembrolizumab monotherapy in patients with NSCLC and PS of 2, as the median overall survival with atezolizumab is similar. It also confirms that immunotherapy is effective for patients 70 years or over with a PS ≥2 and comorbidities. Lizza Hendriks, Maastricht University Medical Center, the Netherlands, remains cautious, as the question remains of who will benefit from this. They stated: "For relatively stable patients, immunotherapy could be an option, but we must also remain realistic that it will not work for everyone." It is unclear exactly why the patients involved in the trial were not eligible for platinum-doublet chemotherapy. Furthermore, it is unclear what type of patients they were. Hendriks explained that the PS ≥2 can have multiple causes, including the cancer but also comorbidities. This makes it difficult to determine what the optimal management strategy is.

They also said: "It would be interesting to see details of the tumour burden (low tumour burden is often associated with better outcomes with immunotherapy) and comorbidities of patients involved in the trial or how stable they were in terms of PS prior to study enrolment." They concluded that the patients who will benefit from the treatment, as well as biomarkers, need to be identified in order to understand the impact of this study on clinical practice. ●

"Atezolizumab improved median overall survival significantly, and these benefits were seen across all subgroups, including PS, histology, and programmed death-ligand 1 expression levels."

Could Sotorasib Improve Progression-free Survival in Pre-treated *KRAS* G12C-mutated Non-small Cell Lung Cancer?

ACCORDING to the results of a Phase III study presented at the ESMO 2022 Congress, sotorasib improves progression-free survival (PFS) compared to docetaxel in pre-treated patients with *KRAS* G12C-mutated non-small cell lung cancer (NSCLC). The study involved patients with *KRAS* G12C-mutated NSCLC that had disease progression following platinum-based chemotherapy and a checkpoint inhibitor. Sotorasib is an oral, irreversible *KRAS* G12C inhibitor, that is approved for the treatment of pre-treated adults with *KRAS* G12C-mutated advanced NSCLC. However, the aim of this study was comparing sotorasib versus docetaxel in KRAS G12C-mutated NSCLC. Comparative studies allow researchers to gain further insight of the disease and therefore accelerate the approval of use in other countries; currently, it has been approved by the U.S. Food and Drug Administration (FDA).

The study participants showed a response of sotorasib versus docetaxel (hazard ratio: 0.66; 95% confidence interval [CI]: 0.51–0.86; p=0.002) after a median follow up of 17.7 months (LBA10). One-year PFS rates were 24.8% for sotorasib and 10.1% for docetaxel and PFS benefit was consistent across subgroups. Furthermore, an objective response rate (ORR) was also remarkably higher with sotorasib (ORR: 28.1%; 95% CI: 21.5–35.4%) than with docetaxel (ORR: 13.2%; 95% CI: 8.6–19.2%; p<0.001); and disease control rate was 82.5% versus 60.3%, respectively.

> **"These results, while supporting a new treatment option, confirm that further improvements are highly sought."**

The study lead, Antonio Passaro from the European Institute of Oncology (IEO), Milan, Italy, stated: "Sotorasib previously received accelerated FDA and conditional [European Medicines Agency] EMA approval in the same setting based on ORR data from the single-arm Phase I/II CodeBreaK 100 trial, but a comparative evaluation was needed to improve the understanding of this molecular-driven disease and move forward the approval in countries where sotorasib is not yet reimbursed."

"These results, while supporting a new treatment option, confirm that further improvements are highly sought after for this specific molecular-driven patient population, and different kinds of combinations are under evaluation in both treatment-naïve and pre-treated settings," Passaro concluded.

Promising New Data Around Antibody–Drug Conjugates

ANTIBODY–drug conjugates (ADC) data shows promise in patients with advanced solid tumours, according to new study data that was presented at the ESMO Congress 2022. The data highlights encouraging safety profiles and responses in individuals with heavily pre-treated malignancies.

Employing a 'Trojan horse' strategy, ADCs use an antibody, which is attached to a chemotherapy agent, that directly targets tumour cells. A Phase I/II dose-finding study of 147 patients with advanced solid tumours unselected for B7-H3 selection received 4.8–16.0 µg/kg of DS-7300. In patients with small-cell lung cancer, 11 out of 19 (58%) had a partial or complete response, with a median duration response of 5.5 months. Further, patients who had received an average of five prior lines had a disease control rate of 71.4% and response rate of 32.0%. While no new safety profiles were reported, more patients in the high-dose cohort had Grade ≥3 treatment-emergent adverse events (TEAE) during a shorter median treatment period than patients on a lower-dose.

The preliminary results of a Phase I dose-escalation and dose-expansion study of zanidatamab zovodotin (ZW49), an ADC, was also presented. Comprised of a bispecific *HER2*-directed antibody and proprietary auristatin toxin, ZW49 was used to treat 77 patients with heavily pre-treated *HER2*-positive cancers (gastro-oesophageal: 27%; breast: 22%). TEAEs were seen in 91% of patients, largely Grade 1 or 2; however, 12% of patients had Grade ≥3 TEAEs. Confirmed objective response rate was 31% and disease control rate was 72% in 29 evaluable patients on ZW49 2.4 µg/kg once every 3 weeks, with two dose-limited toxicities being reported in one patient, which was also observed in one patient on 1.75 µg/kg once a week.

Andrew Furness from the Royal Marsden NHS Foundation Trust, London, UK, and Institute of Cancer Research, London, UK, believes that ADCs show great promise. They noted: "It will be interesting to discover if next-generation ADCs can be developed that are conjugated to treatments other than chemotherapy." ●

"Employing a 'Trojan horse' strategy, ADCs use an antibody, which is attached to a chemotherapy agent, that directly targets tumour cells."

Can Addition of a Tyrosine Kinase Inhibitor Reduce Progression of Renal Cell Carcinoma?

THE COSMIC-313 trial, presented at ESMO Congress 2022, showed that adding cabozantinib, a tyrosine kinase inhibitor, to dual checkpoint inhibitor therapy, significantly prolonged progression-free survival, but increased toxicity. COSMIC-313 is the first trial to show this, and it proves that the triplet regimen can prevent early progression of the disease.

> **"The combination of cabozantinib, nivolumab, and ipilimumab reduced the risk of progression of renal cell carcinoma by 27%, compared with nivolumab and ipilimumab."**

The double-blind, randomised trial included 550 patients with untreated intermediate- or poor-risk advanced renal cell carcinoma. The patients received nivolumab and ipillimumab every 3 weeks for four cycles, then nivolumab every 4 weeks for up to 2 years. The participants were randomised to placebo and cabozantinib according to disease risk and region, and progression-free survival was assessed by blinded independent review. The combination of cabozantinib, nivolumab, and ipilimumab reduced the risk of progression of renal cell carcinoma by 27%, compared with nivolumab and ipilimumab. The objective response rates were 43% for the triplet combination and 36% for the doublet combination.

Viktor Grünwald, University Hospital Essen, Germany, stated we still need to see the overall survival data, and balance the efficacy alongside the toxicity of this new regimen, which shows severe side-effects and toxicity-related treatment discontinuations. Only 41% of patients receiving the doublet combination experienced Grade 3–4 treatment-related adverse events, compared to 73% of patients receiving the triplet combination. Furthermore, 5% of treatment-related adverse events led to discontinuation of all components with the doublet regimen compared to 12% with the triplet. Grade 5 treatment-related adverse events occurred in three patients in both treatment regimens, consisting of gastrointestinal haemorrhage, respiratory failure, and hepatic failure in the triplet regimen; and myocarditis, renal failure, and sudden death in the doublet combination arm. These results mirror those of the CheckMate 9ER trial. More research is needed on the toxicity profile of the triplet regimen to determine its future role. ●

Androgen Deprivation Therapy Beneficial Alongside Radiotherapy in Post-operative Patients with Prostate Cancer

ENCOURAGING results from two Phase III trials (RADICALS-HD and PRESTO), evaluating the use of androgen deprivation therapy (ADT) alongside radiotherapy in post-operative patients with prostate cancer, show metastasis-free and biochemical progression-free survival benefits. This data was presented at ESMO Congress 2022.

The PRESTO trial showed that the primary endpoint, biochemical progression-free survival, was significantly prolonged in patients with high-risk biochemically relapsed prostate cancer after radical prostatectomy, by adding ADT to apalutamide (APA), or to APA and abiraterone acetate plus prednisone (AAP). For ADT+APA, the median biochemical progression-free survival was of 24.9 months, versus 20.3 months for ADT, and 26.0 months for ADT+APA+AAP versus 20.0 months for ADT. Furthermore, the median time to testosterone recovery was 3.9 months for ADT+APA, versus 4.0 months for ADT and 4.8 months for ADT+APA+AAP. The most common Grade ≥2 adverse event, hypertension, was less frequent in the ADT arms (19.4%) than in the ADT+APA (23.4%) and ADT+APA+AAP arm (30.4%).

The RADICALS-HD trial, which studied patients having undergone radical prostatectomy and post-operative radiotherapy showed longer time to salvage ADT, and longer metastasis-free survival (MSF), the primary endpoint, in those who received 24 months versus 6 months of ADT (72% versus 78% at 10 years). While 6 months of ADT improved time to salvage ADT, versus no ADT, it did not improve MFS. Outcomes for MFS with 24 months of ADT versus 6 months, were favourable. The study showed no improvement in overall survival.

"The PRESTO trial showed that the primary endpoint, biochemical progression-free survival, was significantly prolonged in patients with high-risk biochemically relapsed prostate cancer after radical prostatectomy, by adding ADT to apalutamide (APA), or to APA and abiraterone acetate plus prednisone (AAP)."

Stephane Supiot, Institut de Cancérologie de l'Ouest and Université de Nantes, France, stated how important these findings are for patients receiving radiotherapy: "The trial results further support the benefit of adding ADT for patients undergoing radiotherapy, but the lack of overall survival benefit of immediate ADT as shown in the DADSPORT meta-analysis (LBA64) can be interpreted that delayed ADT can salvage patients at the metastatic stage." However, they said the findings are not practice-changing yet, as longer follow-up will give more insights into the optimal treatment duration and combinations, as well as toxicity and quality of life.

Results from the First Randomised Study of Peptide Receptor Radionuclide Therapy in Pancreatic Neuroendocrine Tumours

THE FIRST multicentric randomised study to assess the efficacy of peptide receptor radionuclide therapy (PRRT) in patients with advanced pancreatic neuroendocrine tumours has met its primary endpoint.

Presented at the ESMO Congress 2022, results from the OCLURANDOM trial have discovered that progression-free survival (PFS) was longer when patients received the treatment of 177lutetium-octreotate (OCLU) when compared to sunitinib. The study was designed to evaluate the efficacy of PRRT with OCLU in an anti-tumour capacity versus sunitinib, in a cohort of patients with somatostatin receptor scintigraphy-positive unresectable progressive advanced pancreatic NETs.

The patient group of 84 individuals included those who had been previously treated with Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2, and who had documented disease progression within the year prior to the beginning of the study. Patients had a mean age of 63 years, and 52% were female. Forty-two percent had >25% liver involvement; 37% had Ki-67 >10%; 20% had functioning syndrome; and 43% had received two or more lines of systemic therapy. Forty-four percent of patients experienced Grade 3–4 adverse events in the OCLU arm compared to 63% in the sunitinib arm (decreased blood cell count: 12% versus 23%; digestive problems: 12% versus 21%; hypertension: 12% versus 19%; fatigue: 7% versus 12%).

These patients were randomised 1:1 to receive either OCLU (4.0×7.4 GBq infusions every 8 weeks), or sunitinib (37.5 mg per day). Based on a Fleming design hypothesis, the primary endpoint was if 19 or more patients had no disease progression or had not died after the initial 12 months, OCLU was considered an effective treatment for advanced pancreatic NETs.

The study met this primary endpoint, with significantly longer PFS in those patients receiving PRRT with OCLU versus sunitinib. Twelve-month PFS rates with OCLU were 80.5% (33/41 patients; 90% confidence interval [CI]: 67.5–89.9) versus 42% of patients with sunitinib (18/43 patients; 90% CI: 29.1–55.5). Median PFS for OCLU was 20.7 months (90% CI: 17.2–23.7), versus 11.0 months (90% CI: 8.8–12.4) with sunitinib.

Irene Burger, Kantonsspital Baden, Switzerland, commented that the study "fills an important gap, despite some limitations such as the heterogeneity of prior therapeutic regimens." ●

"The study met this primary endpoint, with significantly longer PFS in those patients receiving PRRT with OCLU versus sunitinib."

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Immunotherapy in Non-small Cell Lung Cancer: Current and Future Use

Authors: Katherine Colvin, Editorial Manager

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ESMO 2022

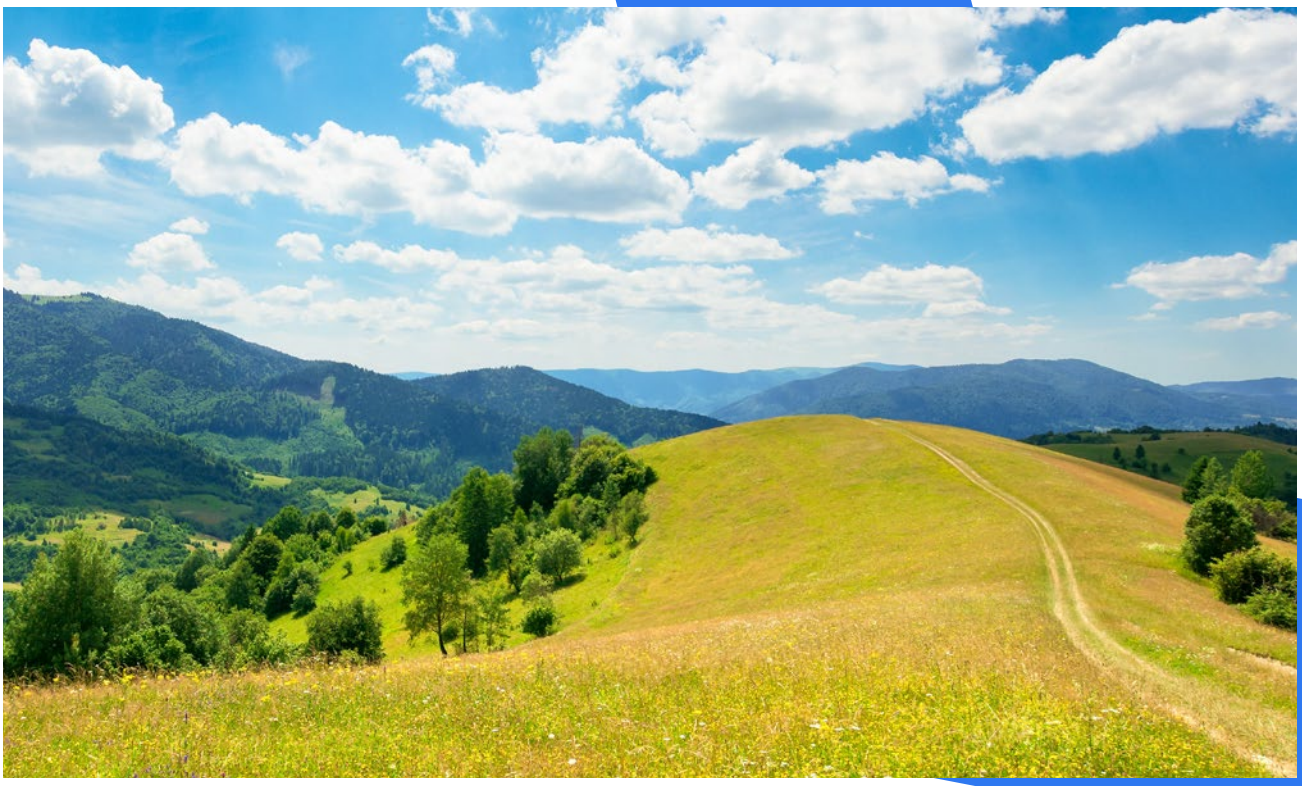
EXPLORING the current state of use of immunotherapies in the treatment of non-small cell lung cancer (NSCLC) and looking to future immunotherapeutic pathways, three expert speakers presented a session at European Society for Medical Oncology (ESMO) Congress 2022, on the 12th of September. The speakers shared insights on personalising current uses of immunotherapeutics in NSCLC, the use of immunotherapies in patient populations traditionally excluded from clinical trials, and the immune pathways and strategies that could be utilised in future immunotherapeutic management of lung cancer.

PERSONALISING CURRENT IMMUNOTHERAPEUTIC TREATMENT

Personalised medicine is regularly practised in the management of NSCLC; however, this is mostly related to the approximately one-third of patients with specific tumour mutations. For the remaining two-thirds of patients, treatment is "dominated" by immunotherapy, outlined the first speaker, Luis Paz-Ares, Hospital Universitario 12 de Octubre, Madrid, Spain. Paz-Ares discussed data from various studies and analyses to highlight that there are many different genomic biomarkers and aberrations under investigation for use in personalising treatment of NSCLC, but in most cases these biomarkers are not yet ready for clinical use.

Paz-Ares particularly considered programmed death-ligand 1 (PD-L1) expression and the use of programmed cell death protein 1 (PD-1) inhibitor immunotherapies where, for the most part, "benefit is proportionate to the expression in magnitude and in frequency," although they cautioned that this is not "the whole truth," as other factors such as gender and tumour mutational burden (TMB) may have an impact. In immunotherapy monotherapy approaches, PD-1 inhibitors improve survival and progression-free survival where PD-L1 expression is >50%;[1] this is now part of standard practice in these patients. However, this treatment choice is less reliable in patients with <50% PD-L1 expression, as Paz-Ares stated that disease progression is observed in 30–40% of these patients within the first 3 months. To further clarify which patients may benefit from immunotherapy monotherapy, Paz-Ares suggested that TMB may be a valuable marker, as data suggest that tumours with low TMB and high PD-L1 expression may have the best response to immunotherapeutics. In those patients with <50% PD-L1 expression, Paz-Ares noted that the

> **"Immunotherapy has completely changed our opportunities to treat patients with advanced NSCLC."**



data support combination therapy with chemotherapy and immunotherapy.[2] This may be attributable to the impact of chemotherapy "preventing early progression in some patients that would have happened with immunotherapy alone," Paz-Ares explained, although survival benefit still map to PD-L1 expression, and cautioned that patient expectations should be set clearly as for those patients with low PD-L1 expression, 3-year survival with chemotherapy plus immunotherapy is <5%.[3]

To further hone a personalised medicine approach in NSCLC, Paz-Ares suggested that some tumour factors could be incorporated into current management guidelines, particularly PD-L1 expression, and potentially tumour aggressiveness, tumour burden, and TMB. As always, treatment choice should be individualised to consider patient characteristics such as smoking status, gender, and comorbidities, as well as patient preferences and expectations around both side effects and survival. More data are needed that compare one treatment strategy to another, rather than across-trial comparisons, to make the most data-informed treatment guidelines.

IMMUNOTHERAPY IN SPECIAL PATIENT POPULATIONS

Martin Reck, LungenClinic, Airway Research Centre North, German Centre for Lung Research, Grosshansdorf, Germany, continued the discussion by considering the evidence available for the use of immunotherapies in patients from populations normally excluded from clinical trials, including those with chronic infections, autoimmune comorbidities, older age, or reduced performance status. "Immunotherapy has completely changed our opportunities to treat patients with advanced NSCLC," Reck highlighted, noting that immunotherapy in NSCLC has progressed from use in patients pre-treated with chemotherapy to integration into first-line treatment regimens. "We see, for the first time, 5-year survival rates exceeding 25% in patients that we do treat with checkpoint inhibitors."[4] However, a major issue with the real-world value of these findings is that promising data on new and developing use of immunotherapy are often via clinical trials, while <5% of adult patients with cancer are recruited into clinical trials.[5] To further compound the issue, exclusion criteria for clinical trials often reflect

"Reck advocated that comorbidities, age, or reduced performance status should not be hurdles to immunotherapy, but that treatments should be determined within patients' contexts."

many characteristics of patients with lung cancer, such as age >65 years, chronic infections, autoimmune diseases, use of high-dose steroids, and poor performance status. There are data available for several of these exclusion characteristics that suggest the safe and successful use of immunotherapies in NSCLC treatment, but further dedicated studies are needed to inform formal treatment guidelines.

Reck discussed the frequently excluded population of those with chronic infections, particularly highlighting HIV chronic infection in concurrent NSCLC. They noted that HIV infection is associated with chronic inflammation, which increases risk of cancer. Reck outlined study data that show comparable safety and efficacy of immunotherapy in patients with HIV infection compared to those without, specifically noting that immunotherapy treatment did not show a detrimental impact on viral load or cluster of differentiation (CD)4/CD8 counts.[6] For patients with COVID-19 infection and cancer, Reck shared a French study that showed "no deleterious effect of chemotherapy or cytotoxic treatment on outcome of patients who are affected with COVID-19 and cancer."[7] In a meta-analysis comparing the effect of different cancer treatments on both incidence of COVID-19 infection and mortality of COVID-19 infection, immunotherapy was associated with no increased incidence or mortality of COVID-19 compared with other cancer therapies.[8] Chronic infection, therefore, does not seem to be the significant barrier to immunotherapy treatment that clinical trial exclusion criteria suggest.

Currently, 50% of patients with metastatic NSCLC are diagnosed aged >70 years;[9] however, clinical trials frequently exclude patients >65 years. Reck commented on the "theoretical problem" of immunosenescence in older patients, highlighting that patients receiving immunotherapy as second-line treatment have been found to have a similar survival benefit compared to younger populations, without a noted increase in immune-related adverse events,[9] suggesting that immunosenescence does not have a significant impact on treatment effect.

Reck concluded by stating: "We are in the process of removing some of the traditional contraindications [to immunotherapy treatment]," and treatment of lung cancers in these patients should be determined with collaboration of multidisciplinary teams. Reck advocated that comorbidities, age, or reduced performance status should not be hurdles to immunotherapy, but that treatments should be determined within patients' contexts. Further dedicated studies are needed to improve our understanding of treatment performance across different patient populations.

FUTURE AVENUES FOR TREATMENT

While immunotherapies have been a game-changing treatment option in oncology, including in treatment of NSCLC, there are several pathways and mechanisms by which tumours can develop or demonstrate resistance to immunotherapies. Natasha Leighl, Princess Margaret Hospital, Toronto, Canada, outlined several of these resistance mechanisms, and explored the strategies by which immunotherapies could evade tumour resistance. Resistance mechanisms include tumours with 'immune desert' phenotypes, where no T cells can infiltrate; tumour differences in organ

location, which affects metabolomics and T cell infiltration; neoantigen loss, such that T cells do not recognise the tumour cells; defects of antigen presentation; abnormal inflammatory signalling; upregulation of co-inhibitory checkpoints (e.g., cytotoxic T-lymphocyte-associated protein 4); and immunosuppression in the tumour immune microenvironment.[10]

Combinations of therapies, as well as novel therapies, could overcome several of these resistance mechanisms. Leighl described pathophysiological pathways by which various treatment approaches could address resistance, as well as highlighted several ongoing trials investigating these treatment options. Using driving metaphors to illustrate these pathways, Leighl first outlined immunotherapy options that aim to "release the brakes," including treatments targeting inhibitory receptors such as PD-1 and cytotoxic T-lymphocyte-associated protein 4. This strategy could be considered in combination with therapies aiming to "step on the accelerator;" i.e., therapies that act to support receptor activation, including CD137, CD40, IL-2, IL-12, or IL-15. Leighl continued by highlighting treatment approaches that help to "steer the car," in which they noted treatment paths that help modulate the "against-self" adverse effects of immunotherapies, including vaccines, *in situ* vaccination, and adoptive T cell therapy. Finally, Leighl discussed treatment considerations that may "pave the road or smooth the way" by remodelling the tumour microenvironment and relieving immunosuppression, such as therapies targeting regulatory T cells, TNF, tumour-associated macrophages, and vascular endothelial growth factor, among others.

CONCLUSION

Immunotherapy in NSCLC has improved survival for many patients and become a cornerstone of usual management. However, the breadth of patients for whom immunotherapy may be a valuable option can be further understood through more dedicated studies that compare treatment approaches head-to-head, and that specifically include and consider patient populations that reflect the common comorbidities and characteristics of patients with NSCLC. There are also many exciting avenues for other immuno-oncological approaches to treatment under consideration or active study, that are awaited with great anticipation in the road ahead in the management of NSCLC.

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Precision Medicine and Next-Generation Sequencing Diagnostic at European Society for Medical Oncology Congress 2022: The Unbreakable Bond

This article covers symposia that took place from 9th–13th September, 2022 as part of the European Society for Medical Oncology (ESMO) Congress 2022

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Disclosure:	Rolando and Quagliata are employees of Thermo Fisher Scientific and hold stocks in this company.

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Meeting Summary

Returning to in-person for the first time since the COVID-19 pandemic started, the European Society for Medical Oncology (ESMO) 2022 conference was packed with new and interesting data. Highlights include updates from DESTINY-Gastric02 and DESTINY-Lung02 exploring treatment with trastuzumab deruxtecan in different settings, and new and encouraging results for the *KRAS* inhibitors adagrasib and the first-in-class sotorasib in advanced colorectal cancer (CRC) and in previously treated patients with non-small cell lung cancer (NSCLC). Of note, updates from APPLE and INSIGHT2 trials strengthen the application of liquid biopsy for disease monitoring and recurrence, while the PATHFINDER study results opened a fierce debate in the medical community, with many stakeholders suggesting that liquid biopsy is not yet fully ready for prime time in early cancer detection.

Nonetheless, the one thing that everybody agreed on, and was vividly supported by almost all presenters this year, is the unmet clinical need related to molecular profiling of patients with cancer. While targeted next-generation sequencing (NGS), mostly in the form of gene-specific panels rather than whole exome sequencing, has emerged as the absolute game-changer for precision medicine concrete realisation, the medical community urgers investments aimed to build NGS testing capability ultimately enabling oncologists to pick the best treatment path for their patients. At ESMO Congress 2022 numerous studies highlighted the remarkable steps that precision medicine has made during the last year.

HER2: A Phenomenal Success Story that Endures in 2022

Accumulating success continues for trastuzumab deruxtecan, targeting *HER2*, following positive readouts across various indications presented at ESMO, including gastric and NSCLC. In the Phase III DESTINY-Gastric02 trial, investigators reported an impressive overall response rate (ORR) of 41.8%, with 5% of these being complete responses, solidifying trastuzumab deruxtecan journey towards becoming the new standard of care in second-line trastuzumab-pre-treated *HER2*-positive recurrent or metastatic gastric cancer.[1]

For NSCLC, top-line results from the Phase II DESTINY-Lung02 trial support trastuzumab deruxtecan's recent approval in the USA for previously treated patients with unresectable or metastatic NSCLC with *HER2* mutations, approximately 2–4% of all patients with NSCLC, who often present with a poor prognosis. Patients in DESTINY-Lung02 had previously received platinum-based chemotherapy, and data showed a 53.8% objective response rate.[2] These results bode well for the confirmatory Phase III DESTINY-Lung04 trial testing trastuzumab deruxtecan as a first-line treatment for patients with unresectable or metastatic NSCLC harbouring *HER2* exon 19 or 20 mutations and should support its rapid uptake in *HER2*-mutated NSCLC (unpublished data, presented at ASCO Annual Meeting, 3-7 June, 2022).

On the breast cancer front, with more than two-thirds of cases being hormone receptor-positive (HR+)/*HER2*-negative, ESMO brought good news about two different targeted therapies for this subtype. The effect of cyclin-dependent kinase 4 and 6 inhibition with the new drug dalpiciclib was tested in a Phase III trial, DAWNA-2, in the first-line setting.[3] Dalpiciclib nearly doubled progression-free survival (PFS) of patients with untreated HR+/*HER2*-negative breast cancer, regardless of menopausal status, when given with letrozole or anastrozole as a first-line treatment. Moreover, final results from the monarcHER trial demonstrated improved overall survival (OS) with abemaciclib, in combination with *HER2*-targeted therapy (trastuzumab) with or without hormonal therapy compared with chemotherapy plus trastuzumab in patients with HR+, *HER2*-positive advanced breast cancer.[4] These final data suggest that a triple-agent, chemotherapy-free treatment regimen may improve OS in patients with HR+, *HER2*-positive advanced breast cancer, a disease setting in which treatment options are limited.

KRAS: Targeting the "Undruggable," Small Steps but Still a Lot to Do

Focus on Colorectal Cancer

Expectations were nothing but huge at this year's ESMO meeting for *KRAS* inhibitors. Updated results from the Phase I CodeBreaK 101 trial that assessed double combination of *KRAS* and *EGFR* blockade with sotorasib and panitumumab for advanced CRC $KRAS^{G12C}$ positive patients, showed an ORR of 30% of patients and a median response of 4.4 months.[5] In line with these results, updated data from the Phase I/II KRYSTAL-1 study confirmed that adagrasib in combination with cetuximab (double blockade of *KRAS* and *EGFR*) in heavily pre-treated patients results in an ORR of 46% and a median PFS of 6.9 months.[6] Bearing in mind that until recently, *KRAS* was considered an undruggable target, these data reinforce the potential for mutant-selective *KRAS* inhibitors in combination with anti-*EGFR* agents in advanced CRC.

Focus on Lung Cancer

While 3% of patients with CRC have $KRAS^{G12C}$ mutation, around 12% of patients with NSCLC harbour this mutation. Sotorasib was the first therapy to receive approval for the treatment of patients with $KRAS^{G12C}$-mutated NSCLC in May 2021, a notoriously hard-to-treat patient population with high unmet needs. At ESMO, a confirmatory Phase III CodeBreaK 200 trial was presented. Sotorasib met its primary endpoint delivering a significant benefit in median PFS over chemotherapy; however, it failed to show a statistical and numerical benefit in OS.[7] While the Phase III readout should support the uptake of this therapy as the new standard of care and may be enough to secure conversion of its conditional approval to full approval, it is clear that overall, the numerical data for PFS and OS released from CodeBreaK 200 are below expectations. Furthermore, concerns about drug

toxicity will have to be addressed carefully for sotorasib, thus its path forward is still uncertain. The underwhelming numerical results and lack of survival benefit suggest that different kinds of therapeutic combinations may be explored in the near future to significantly impact patients' clinical outcome.

Liquid Biopsy Takes the Scene in Therapy Resistance and Disease Monitoring

Disease Monitoring via Circulating Tumour DNA Makes Sense

Resistance to tyrosine kinase inhibitors (TKIs) of the *EGFR* treatment in advanced NSCLC represents a major therapeutic challenge. The underlying mechanism can be *EGFR*-dependent, including the *T790M* mutation, or driven by independent molecular pathways, like *HER2* and *MET* amplifications.

At ESMO Congress 2022, key updates on the use of liquid biopsies for detecting mutant circulating tumour DNA (ctDNA) that may have a major potential in the clinical space were discussed. For example, the results of the APPLE trial supported that serial monitoring of *T790M* status by ctDNA is feasible in patients with *EGFR*-mutated advanced NSCLC and should be used to drive treatment decisions.[8] This strategy identified 17% of patients with molecular progression before response evaluation criteria in solid tumours progressive disease, leading to an earlier switch in favour of osimertinib. Moreover, ctDNA clearance is an early predictor of favourable outcomes on treatment with gefitinib. Altogether, these results indicate that serial ctDNA assessment comes with a clear clinical value, and may be best utilised for risk-adaptive treatments.

Investigating Resistance Using Liquid Biopsy Has a Clear Potential

Between 15–30% of patients with *EGFR*-mutated NSCLC and treated with osimertinib develop resistance through *MET* amplification, and this is associated with poor prognosis.

The two-arm Phase II INSIGHT 2 study addressed the response to the combination of tepotinib plus osimertinib for patients with advanced *EGFR*-mutated NSCLC with *MET* amplification that recurred after first-line osimertinib.[9] About 425 subjects with advanced *EGFR*-mutated NSCLC were screened for *MET* amplification following progression on the TKI osimertinib. Of these, 25% resulted positive for *MET* amplification via fluorescent *in situ* hybridisation in tissue biopsy samples, 3% were positive by NGS liquid biopsy, and 8% had *MET* amplification with both methods. In the group treated with tepotinib plus osimertinib and with *MET* amplification detected by liquid biopsy, about 50% of participants with at least 9 months of follow-up had a complete or partial response, while the ORR of patients treated with tepotinib monotherapy was only 8.3%. These findings strongly indicate that addressing resistance mechanisms can improve patient outcomes and that NGS-based liquid biopsy testing may untangle unknown resistance mechanisms.

Minimal Residual Disease to Predict Recurrence Benefits from Circulating Tumour DNA Testing

Many are wondering when liquid biopsy will eventually be accepted as a tool to more accurately predict recurrence, especially in CRC. Previous evidence indicated that restricting adjuvant chemotherapy to ctDNA-positive and not ctDNA-negative patients with resected Stage II CRC reduced unnecessary chemotherapy exposure without compromising recurrence-free survival.[10] The new data of the DYNAMIC trial presented at ESMO Congress 2022 showed that post-operative ctDNA analysis was more sensitive than standard methods (intensive imaging via CT scanning) for predicting distant recurrences.[11] Moreover, ctDNA clearance was achieved with adjuvant chemotherapy in 87% of post-operative patients who were ctDNA positive and this predicted favourable outcome (2-year recurrence free survival: 97%) compared with patients without ctDNA clearance (1-year recurrence free survival: 20%). Interestingly, neither post-operative nor post-chemotherapy carcinoembryonic antigen (CEA) levels add prognostic value for patients who were ctDNA negative. In line with these data, the Phase III PRODIGE 13 trial showed a lack of survival advantage with intensive follow-up (CT scan and

CEA) in patients with resected Stage II–III CRC when looking at the whole study population.[12] Therefore, ctDNA analysis allows to distinguish between patients at greater risk of recurrence who may benefit from adjuvant treatment and those at lower risk who could receive surgery alone. The classical marker for CRC, CEA, lacks sensitivity and specificity for recurrence and it will probably be replaced by ctDNA in future. Although for a limited number of specific clinical scenarios, minimal residual disease is making its way into routine clinical practice.

Next Generation Sequencing Is Uniquely Bonded to Precision Medicine, No More Proof Is Needed

On top of key scientific sessions highlighting the value of molecular profiling, a number of industry symposia equally underlined the effectiveness of NGS biomarker testing in driving therapy selection. Despite being an imperative aspect of target therapy access, there are still several challenges to a much broader implementation of NGS into clinical practice, including limited technology access, inequalities in healthcare reimbursement as well a lack of technical expertise, and duly trained personnel. Remarkable examples paving the way to overcome these inequalities have been shown at ESMO Congress 2022, including an update on the European Program for ROutine testing of Patients with Advanced lung cancer (EPROPA), which was presented at the World Conference on Lung Cancer (6th–9th August 2022). This initiative aimed to deliver diagnostic and therapeutic opportunities for underserved patients across Europe, and has demonstrated the feasibility to provide a comprehensive and clinically meaningful NGS-based molecular characterisation for patients with cancer, by means of optimising biopsy material management combined with a markedly reduced diagnostic turnaround time. Indeed, access to biomarker testing and availability of test results prior to first-line therapy has been shown to directly impact patient survival, thus supporting the implementation of ultra-fast in-house NGS testing for better clinical outcomes.[13]

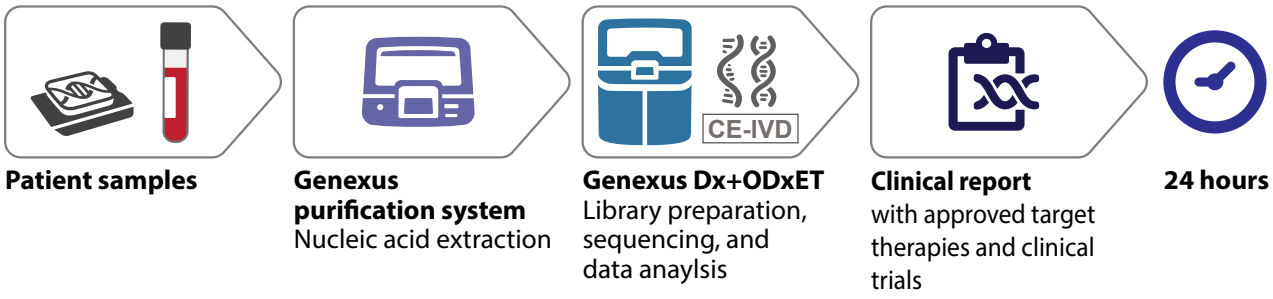
A pivotal example of how to establish a highly automated end-to-end workflow for ultra-fast NGS biomarker testing is ongoing at the Molecular Diagnostic Laboratory of the Hospital del Mar in Barcelona, Spain (Figure 1), and was showcased at ESMO Congress 2022. The overarching aim at the Hospital del Mar is to implement an integrated NGS workflow that provides an assessment of clinically actionable mutations from both tissue and liquid biopsy samples while delivering lab results within just 1 day. Though this might appear to be an ambitious goal, an CE *in vitro* diagnostic compliant NGS technological solution exists nowadays on the market, and can deliver on the promise of ultra-fast simultaneous multiple biomarker testing of actionable genes for therapy selection, ensuring that no patient is left behind.

Liquid Biopsy for Early Cancer Detection: Moving Forward but Not Ready for Prime Time

Despite the ESMO Congress 2022 highlighting the potential of liquid biopsy for disease monitoring and recurrence, its application for early cancer detection or screening is still far from its full clinical implementation.

In the prospective PATHFINDER study, a multi-cancer early detection blood assay used a targeted methylation NGS based test to detect and analyse ctDNA aiming to predict cancer presence 'molecular signals,'[14] i.e., the presence of genomic alterations associated with tumour occurrence. The study included 6,621 adults aged 50 and older who were divided into two cohorts. One group was deemed high-risk if they had a history of cancer but had been disease-free for at least three years, had smoked more than 100 cigarettes in their lifetime, or had a genetic risk of cancer. A cancer signal was detected in 92 individuals. Follow-up ended at 12 months for both groups. Among those who tested positive, cancer was found in 35 people while the other 57 had no detectable cancer. Cancer was confirmed in 35 of these, giving a positive predictive value of 38.0%. This is a drop from the 44.6% figure from the interim cut reported at last year's American Society of Clinical Oncology (ASCO). Conversely, a high (98.6%) negative predictive value was observed; the cancer signal origin prediction accuracy was also high at 88.0%.

Figure 1: Optimal next-generation sequencing workflow for routine diagnostics in oncology.



CE-IVD: CE *in vitro* diagnostic; ODxET: Oncomine Dx Express Test.

Notably, for false positive results, the time to diagnostic resolution for participants was on average 162 days. This extremely long waiting time may cause anxiety and distress in individuals where the multi-cancer early detection signal was detected. The number and types of subsequent tests required for diagnostic resolution, along with the associated costs, are equally concerning. Altogether these results indicate that it is premature to imagine a clear benefit for this technology applied to population-wide screening. Another prominent study presented at ESMO was the PROMISE trial. This is a prospective multicentre case-control study to assess the performance of a multi-omics approach including ctDNA methylation, mutations, and protein biomarkers in the early detection of nine cancer, including CRC, lung, and ovary tumours.[15] Blood samples were prospectively collected from 511 cancer patients and 470 non-cancer controls. Multi-omics model resulted in 98.3% specificity and overall sensitivity of 83.7%, with 71.4% for Stage I cancers and 93.6% for advanced Stage IV tumours. Therefore, sensitivity and specificity of a multi-cancer detection blood test were high for the detection of cancers, and suggest that for future clinical application multi-omics approach may result in higher specificity for early cancer detection.

Takeaway from ESMO Congress 2022: New Drugs Uptake Needs More Patients Testing

It is ever clear from this year's ESMO Congress that the promise of precision medicine will not turn into reality unless a widespread use of molecular profiling for patients with cancer will be eventually implemented at large scale. The pipelines for new therapies associated with specific biomarkers continue to grow steadily, with about 100 new oncology drugs or drug combinations to be launched within the next 3–5 years. Still, as of today, access to testing and thus to new drugs is only a privileged option for a few national healthcare systems, while most are lacking behind. Health policymakers, medical institutions, manufacturers, clinicians, and biomedical researchers, along with patients' associations, have engaged and joined forces, aiming to push for a much broader NGS adoption through global initiatives. Nonetheless, salt and pepper adoption of testing is still the norm.[16] A concrete example lies for instance with poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors is able to achieve impressive clinical results but still missing an accessible and flexible solution for homologous recombination deficiency testing, leading to low adoption rates, and patient leakage. The need to include biomarkers testing readiness in the process of a new drug launch and having sufficient runway to enable laboratories' appropriate preparation is paramount to realise the full value of precision medicine.

Groundbreaking technological solutions are now available to tackle these issues, enabling fast and accurate multi-biomarker testing using NGS panels like never before. Investments in new diagnostic capabilities, from infrastructure to equipment and duly trained personnel, need to be viewed as an integral part to reshape and uplift the cancer care continuum workflow.

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Abstract Reviews

Novel abstracts presented at European Society for Medical Oncology (ESMO) Congress 2022 on the latest research in Oncology.

Tumour Organoids from Multifocal Metastatic Colorectal Cancers for Personalised Oncology

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Keywords: Chemotherapy, colorectal cancer (CRC), functional oncology, genomics, heterogeneity, liver metastasis, living biobank, patient-derived organoids (PDO), personalised oncology, pharmacogenomics.

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BACKGROUND AND AIMS

Patients with colorectal cancer (CRC) have limited systemic treatment options compared to other major cancer types.[1] Tumour heterogeneity is a major cause of treatment failure.

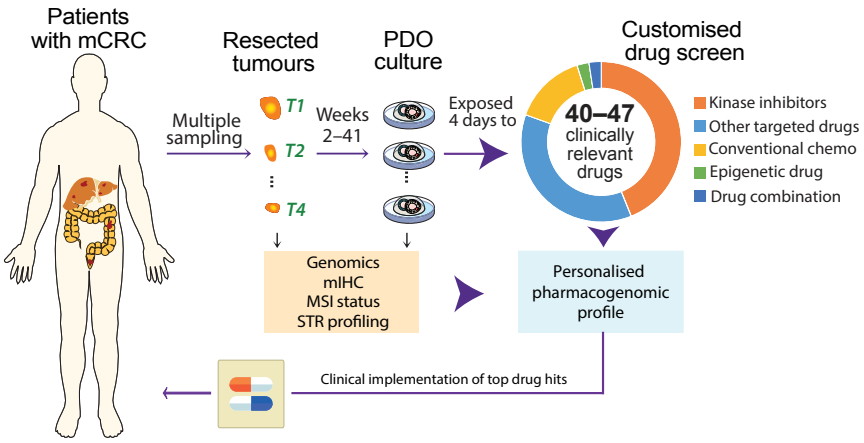
MATERIALS AND METHODS

The authors have generated a living biobank of 208 patient-derived organoids (PDO) from liver metastases of 100 patients treated by hepatic resection for advanced CRC at Oslo University Hospital, Norway. The biobank includes multiple synchronous lesions (n=2–6) from 66 of the patients, and recurrent lesions sampled at hepatic re-resections of four patients. All PDOs have been screened for sensitivity to custom-made and clinically relevant drug libraries for CRC (n=40–47 drugs).[2,3] Subsets of PDOs and corresponding tumour tissue samples have been analysed by multi-omics approaches.[4] The study design is illustrated in Figure 1.

RESULTS

Metastatic lesions from individual patients showed only modest heterogeneity in drug sensitivities with distribution of mean Euclidean

Figure 1: Study design.



Single or multiple metastases were resected from patients with advanced CRC and *ex vivo* PDOs established. Tumour organoids were seeded to pre-drugged plates, followed by cell viability measurements (3D CellTiter-Glo) after 96 hours. Drug Sensitivity Scores were calculated for each drug as a measure of reduced viability. In parallel, gene expression and sequencing of clinically relevant mutations were conducted for pharmacogenomic analyses. Short tandem repeat profiling was performed for all PDOs and their corresponding tissues for authentication.

Chemo: chemotherapy; CRC: colorectal cancer; mCRC: metastatic colorectal cancer; mIHC: multiplexed immunohistochemistry; MSI: microsatellite instability; PDO: patient-derived organoids; STR: short tandem repeat.

distances skewed towards lower intra-patient heterogeneity. Also, there was no correlation between the number of PDOs analysed per patient and their mean Euclidean distances. *TP53* mutated PDOs were generally multidrug-resistant, and *TP53* wild-type PDOs were sensitive to several chemotherapies, including 5-FU, SN-38, TAS-102, and gemcitabine. Furthermore, sensitivity to the PARP inhibitor talazoparib was significantly higher in *TP53* wild-type PDOs, which supports the authors' previous study suggesting wild-type *TP53* activity as a mechanism of response to PARP inhibition in CRC cell lines.[5] A *TP53* mutated PDO harbouring an *ATM* mutation was hypersensitive to PARP inhibition, suggesting that other mechanisms of poly adenosine diphosphate-ribose polymerase inhibitor sensitivity are also involved. Among patients with a lack of sensitivity to standard-of-care drugs for CRC, 7% and 4% presented strong sensitivities towards conventional chemotherapies methotrexate and gemcitabine, respectively. *Ex vivo* drug vulnerabilities from the living biobank are currently being used as a reference basis for an interventional Phase II umbrella clinical study for patients with advanced CRC.

CONCLUSION

PDOs from multifocal liver metastases model pharmacogenomic heterogeneity of advanced CRCs and have strong potential for personalised oncology.

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Does Hepatitis C Independently Increase the Risk of Colorectal Adenoma?

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Keywords: Adenoma, adenomatous polyp, chronic hepatitis C, colon cancer, colon cancer screening, colonic adenoma, colonoscopy, colorectal cancer, hepatitis C, propensity score matching.

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BACKGROUND AND AIMS

Hepatitis C virus (HCV) infection has been associated with extrahepatic malignancies such as colorectal carcinoma (CRC).[1] The majority of CRCs arise from adenomatous polyps, and it is not known if HCV infection influences the growth of these pre-cancerous lesions.[2] This study evaluates the prevalence of colorectal adenomas in patients with HCV compared to the general population, and whether HCV is an independent risk factor for the detection of colorectal adenomas.

MATERIALS AND METHODS

This case-control study included patients who underwent screening colonoscopy at the authors' hospital. Patients were divided into cases (HCV) and controls (non-HCV). Patients with hepatitis B, inflammatory bowel disease, or no biopsy reports were excluded. Colonoscopy findings were stratified on the biopsy results i.e., hyperplastic, adenomatous, CRC, or normal mucosa. Continuous variables were analysed using the Mann–Whitney U test, and categorical variables using the Chi-square and Fisher's exact test with $p<0.05$ were considered statistically significant. After a 1:1 propensity score matching for chronic hepatitis C, a matched cohort of cases and controls was generated. A multivariate regression analysis to compute an odds ratio (OR) for colorectal adenoma detection rate was done.

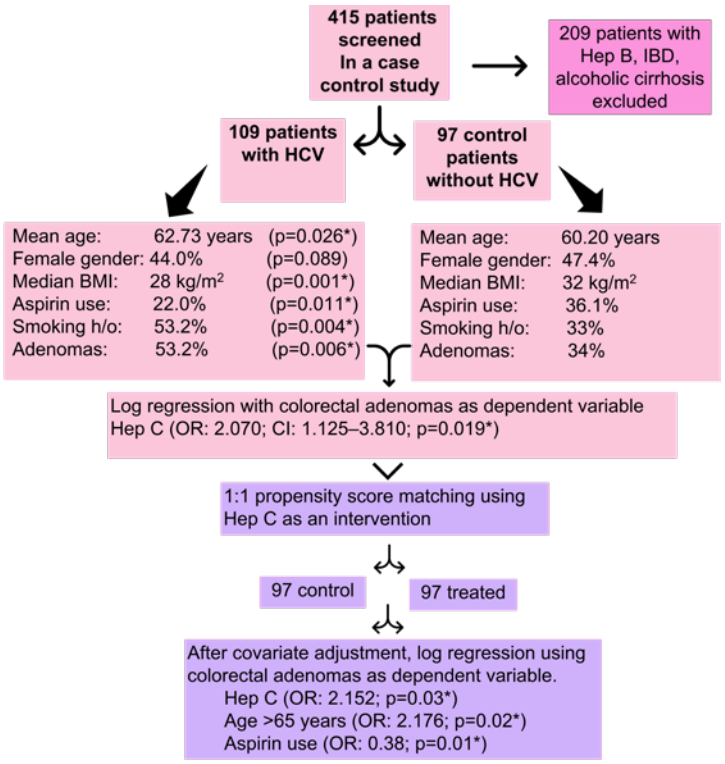
RESULTS

415 patients were screened, of which 109 patients with HCV and 97 controls were included. Descriptive analysis showed that age (p=0.030), BMI (p=0.001), aspirin use (p=0.001), smoking (p=0.004), alcohol use (p=0.010), and adenoma detection (p=0.006) were significantly different between both groups. There were 118 polyps in the HCV group and 78 polyps in the control group, and 97% of the polyps in the HCV group were tubular adenomas. Polyps in the HCV group were arising from the ascending colon in 24.5%, 25% from the sigmoid colon, and 20% from the transverse colon. After propensity matching for HCV, 97 cases and 97 controls were generated. Following covariate adjustment, logistic regression analysis showed that patients with HCV had an OR of 2.06 (p=0.030), and aspirin users had an OR of 0.38 (p=0.010) in having colorectal adenoma (Figure 1).

CONCLUSION

The authors' study shows a significantly higher rate of adenomas in patients with chronic HCV. On multivariate analysis with and without propensity score matching, HCV infection was found to be an independent risk factor for colorectal adenoma. Current guidelines do not recommend earlier screening for CRC for such patients. Prospective studies would be required to assess if treatment of HCV leads to lower adenoma detection rates.

Figure 1: Flowchart of the study.



*Stastistically significant p-value.
CI: confidence interval; HCV: hepatitis C virus; Hep C: hepatisis C; Hep B: hepatitis B; h/o: history; IBD: irritable bowel disease; OR: odds ratio.

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Epidermal Growth Factor Receptor Mutation Testing from Pleural Effusions of Patients with Advanced Lung Adenocarcinoma in Serbia

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Keywords: Epidermal growth factor receptor (EGFR), liquid biopsy, lung adenocarcinoma, pleural effusion.

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BACKGROUND AND AIMS

High incidence of lung cancer in Serbia is derived from high smoking rates, the lack of a nationwide screening programme, and the presence of environmental risk factors.[1] By histology, adenocarcinoma accounts for approximately 50% of all lung cancer cases, with approximately 60% of new diagnoses already in advanced disease stages, where targeted therapies and immunotherapy are indicated. In Serbia, epidermal growth factor receptor (EGFR) mutation testing is still performed on liquid biopsy of patients with lung cancer only by quantitative PCR.[2,3] The aim of this study was to evaluate the efficacy of this approach in pleural effusions of patients with non-small cell lung cancer (NSCLC) at diagnosis and after progression on EGFR tyrosine kinase inhibitors (EGFR-TKI) in Serbia.

MATERIALS AND METHODS

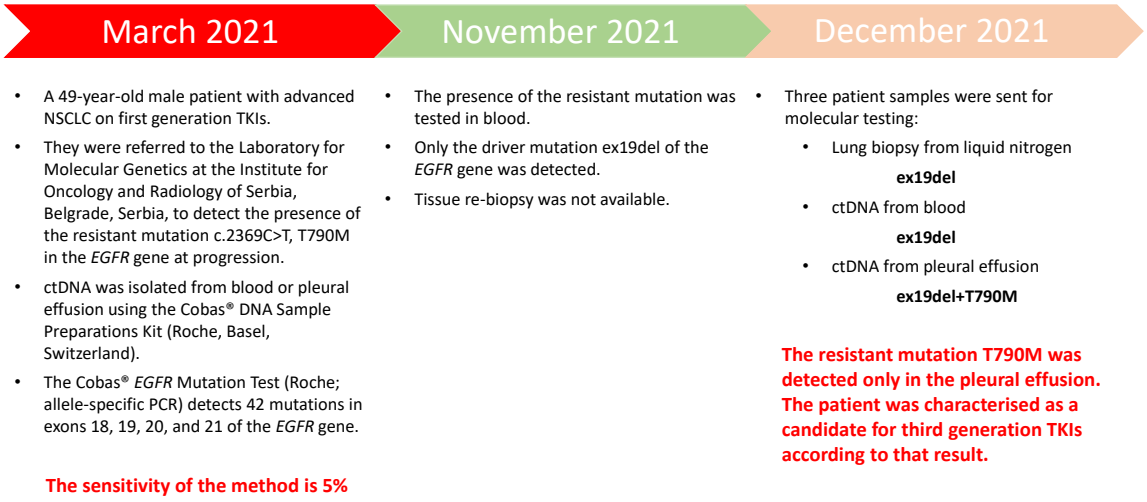
Mutation testing was performed on blood and pleural effusions of patients with advanced lung adenocarcinoma (Stage IIIB or IV; Eastern Cooperative Oncology Group [ECOG] Performance Status 0, 1, or 2) using the Cobas® EGFR Mutation Test (Roche, Basel, Switzerland), which detects 42 mutations in exons 18, 19, 20, and 21 of the *EGFR* gene with sensitivity of 5%.

RESULTS

In the period from 2016–2021, 124 patients were tested at baseline (53% males; 47% females; age range 37–83 years; median 61), and 104 after progression on first line EGFR-TKIs (41% males; 59% females; age range: 34–81 years; median age: 60). At diagnosis, nine mutated samples were detected (7.3%) with a turnaround time of 2 working days, and a 99.2% testing success rate. At progression, an accordance rate of only 67% with the initial driver mutation was observed from blood. The T790M mutation was detected in 34 patients (49% of the mutated samples; 33% of the total), which rendered them eligible for third generation EGFR-TKIs. In the same period, only six samples (4.8%) of pleural effusions were sent to our laboratory along with blood, all from patients at progression. The testing was performed with a turnaround time of 2 working days, a 100% testing success rate, and an accordance rate of 100% with the initial driver mutation. In 50% of concurrently sent samples, the T790M mutation was detected in the pleural effusion, while the corresponding blood sample showed only the presence of the driver mutation (Figure 1).

A 49-year-old male patient with advanced NSCLC on first generation TKIs was referred to the Laboratory for Molecular Genetics at the Institute for Oncology and Radiology of Serbia, Belgrade, Serbia to detect the presence of the resistant mutation T790M in the *EGFR* gene

Figure 1: A Presentation of a clinical case from the Laboratory for Molecular Genetics, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia.



ctDNA: circulating tumour DNA; NSCLC: non-small cell lung cancer; TKI: tyrosine kinase inhibitors.

at progression. The presence of the resistant mutation was first tested in blood, but only the driver mutation ex19del was detected. One month later, three additional patient samples were sent for molecular testing with following results: lung biopsy from liquid nitrogen (ex19del), circulating tumour DNA from blood (ex19del), and circulating tumour DNA from pleural effusion (ex19del+T790M). The resistant mutation T790M was detected only in the pleural effusion. The patient was characterised as a candidate for third generation TKIs according to that result.

CONCLUSION

EGFR mutation testing from pleural effusion has proven valuable as an alternative liquid biopsy sample to blood, for detecting the T790M acquired resistance mutation in patients with advanced NSCLC who progressed on first-line EGFR-TKIs in Serbia. Pleural effusion samples should be considered as a valuable source of genetic material and might be proposed by future guidelines for concurrent EGFR mutation testing alongside blood whenever available.[4,5]

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Assessment of Early Detection by Multi-omics-Based Liquid Biopsy in Lung Cancer: A Prospective Study (ASCEND-LUNG)

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Disclosure: Kou, Cui, B. Yang, Liu, C. Wang, Li, Y. Zhang, G. Wang, X. Yang, Zhou, and Cai are employees of Burning Rock Bioengineering Ltd. All other authors declare no conflicts of interest. This study was supported by the Research Unit of Intelligence Diagnosis and Treatment in Early Non-small Cell Lung Cancer, Chinese Academy of Medical Sciences (2021RU002), National Natural Science Foundation of China (No. 82072566), and Peking University People's Hospital Research and Development Funds (RS2019-01).

Keywords: Cell-free DNA (cfDNA) methylation, early detection, lung cancer, liquid biopsy, multi-omics.

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BACKGROUND AND AIMS

Lung cancer is the leading cause of cancer deaths worldwide, with a global estimation of 2.2 million new cases and 1.8 million deaths in 2020.[1] Low-dose spiral CT-based screening has shown significant mortality reduction of lung cancer in randomised clinical trials. However, the high false-positive results (around 96%) will lead to high rates of overdiagnosis.[2] Liquid biopsy has achieved revolutionary improvements in the early detection of cancers. Here, the authors report the preliminary results of the ASCEND-LUNG trial,[3] a prospective case-control study designed to develop early detection models for lung cancer based on multi-omics assays, including cell-free DNA (cfDNA) methylation, mutation, and tumour proteins.

MATERIALS AND METHODS

Blood samples from eligible participants including 230 cancers were prospectively collected from the Department of Thoracic Surgery of Peking University People's Hospital, Beijing, China, from February 2021 to 15th December 2021. Age-matched non-cancers (n=135) were selected from another study. cfDNA was extracted and sequenced by a customised targeted methylation panel covering approximately 490,000 CpG sites (ELSA-seq, 1000X),[4] and an ultradeep target mutation panel containing 168 genes (35000X; matched white blood cells: 10000X). Sixteen tumour proteins were also detected. Early detection models were developed and validated by the support vector machines algorithm, with five-fold cross validation based on multi-omics.

RESULTS

Three early detection models were developed using the methylation, mutation, and protein data of 158 patients with lung cancer, and 135 non-cancer controls, respectively. The specificities of the models were 98.5% (95% confidence interval [CI]: 95.6–100.0%), and 100.0% (95% CI: 97.8–100.0%). The corresponding sensitivities were 72.8% (95% CI: 65.2–79.1%), 18.8% (95% CI: 12.5–26.8%), and 32.1% (95% CI: 25.0–39.7%). A combined model with methylation and protein data could improve the performance of early detection with a specificity of 98.5% (95% CI: 94.8–99.8%) and a sensitivity of 84.6% (95% CI: 78.0–90.0%). Combining all of the data from the three omics yielded comparable results, with a specificity of 98.5% (95.6–100.0%) and a sensitivity of 83.8% (95% CI: 76.6–90.1%). The sensitivities for Stages I–IV were 81.4% (95% CI: 69.1–90.3%), 94.2% (95% CI: 71.3–99.9%), 90.0% (95% CI: 70.8–98.9%), and 85.7% (95% CI: 42.1–99.6%), respectively.

The robustness of the multi-omics model was not influenced by the clinical covariates including age, sex, or BMI.

CONCLUSION

In this study, the cfDNA methylation lung cancer detection model showed superior performance compared with the models based on circulating tumour DNA mutation or tumour proteins. The multi-omics detection model including cfDNA methylation and protein could improve sensitivity at a considerably high specificity. However, circulating tumour DNA mutation contributed little to the improvement of the detection performance. This study highlights a potential clinical utility of the multi-omics model with cfDNA methylation and protein markers for detecting lung cancer. The enrollment of validation set is ongoing, and is expected to be completed by March 2023.

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MammaPrint® 10-Year Follow Up Results from a German Breast Cancer Cohort Study

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Keywords: Breast cancer, chemotherapy, long-term follow-up, low-risk, lymph node-positive, MammaPrint® (MP), 10-year outcomes.

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BACKGROUND AND AIMS

The MammaPrint® (MP) 70-gene test is utilised in personalised treatment planning for patients with early-stage breast cancer (EBC) with either node-positive or node-negative disease and categorises tumours as high risk (MP-HR; MP index: –1–≤0) or low risk (MP-LR; MP index: >0–+1).[1] A German validation study using samples from the Patients Tumor Bank of Hope (PATH) retrospectively determined the concordance between treatment recommendations based on MP and clinical risk classifications valid at the time of diagnosis. In the PATH study population, MP would have resulted in altered treatment advice for adjuvant systemic therapy in 40% of patients.[2] In this analysis, the authors present the prognostic value of MP at 10 years of follow-up in the PATH cohort.

MATERIALS AND METHODS

Tumour samples from 140 German patients diagnosed with Stage I and II EBC between November 2005 and April 2008 were classified

by MP as MP-LR or MP-HR for distant relapses. Patients were treated based on clinical risk assessment and the St. Gallen guidelines, which were valid at the time of diagnosis.[3] The authors collected 10-year outcome data from 117 patients and assessed overall survival (OS) based on MP risk classification in a retrospective cohort analysis. Differences in 10-year OS according to MP were determined for the following subgroups: lymph node-negative versus lymph node-positive study population; and study population treated with chemotherapy (CT) +/- endocrine therapy (ET) versus ET only. Differences in OS were assessed by Kaplan–Meier analysis and log-rank test.

RESULTS

In the cohort of 117 patients, MP identified 67 (57.3%) MP-LR and 50 (42.7%) MP-HR tumours. The 10-year OS was 93.4% in the MP-LR group and 71.2% in the MP-HR group. The OS in the lymph node-negative population (n=79) was 93.3% in the MP-LR group and 89% in the MP-HR group (p=0.558). The 10-year OS in the lymph node-positive population (n=38) was 93.3% in the MP-LR group and 40.4% in the MP-HR group. Among 117 patients, 95 received adjuvant systemic therapy. Out of 67 patients with MP-LR, 29 (43.3%) were treated with CT and ET and 29 (43.3%) only received ET. The OS in the CT+ET group was 96.3 % and 92.5% in the ET only group, respectively. Within the MP-HR group, 14 out of 50 patients (28%) were not treated with CT. The OS in the CT+ET group was 90.9%, whereas the OS in the ET only group was 61.5% (p=0.052).

CONCLUSION

In the 10-year follow-up of the German PATH cohort, patients with a MP-LR had an excellent OS at 10 years. Survival within the MP-LR group was independent of nodal status and treatment, and in contrast, nodal status and treatment with CT played a significant role for survival in patients with MP-HR.

Considering that treatment planning was at the discretion of the physician, MP could have been of further assistance in treatment planning for 43% (n=29) of patients with MP-LR who were treated with CT, allowing them to forgo this treatment and its associated adverse effects. Similarly, for the 28% (n=14) of females with MP-HR who were treated with ET alone, MP could have provided important information for CT planning.

These results from a German cohort confirm the ability of MP to correctly predict long-term outcomes and to guide treatment decisions. ●

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Autophagy Flux is Induced in Gastroenteropancreatic Neuroendocrine Neoplasms

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Keywords: Autophagy, gastroenteropancreatic neuroendocrine neoplasms, neuroendocrine carcinomas, neuroendocrine tumours.

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BACKGROUND AND AIMS

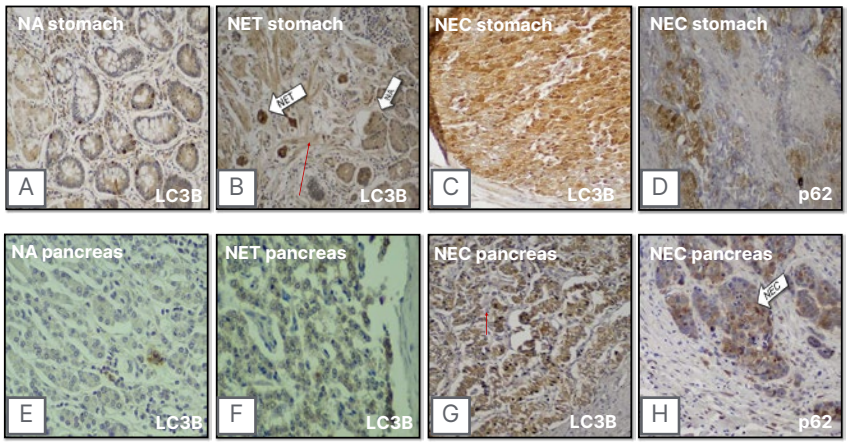
Neuroendocrine neoplasms (NEN) represent a rare heterogeneous group with an increasing incidence, consisting of neuroendocrine tumours (NET) and neuroendocrine carcinomas (NEC), mostly prevalent in the gastrointestinal tract. Cancer stage, tumour grade, mode of treatment, and mainly early diagnosis affect overall survival rate. Their classification is based on their differentiation, grade, mitotic rate, and Ki-67 index status, and according to the latest 2019 World Health Organization (WHO) definitions, NETs are well differentiated, whereas NECs are poorly differentiated.[1] Genetic analysis of NENs deriving mostly from pancreatic cases recognises differences in the mutational profiles between NETs and NECs, but there is still limited understanding on the molecular pathogenesis of the disease.[2]

The molecular mechanism of autophagy is crucial for the survival of cells. However, it holds a dual role in the progression of cancer, as it can either promote tumour survival by ameliorating stress, recycling unwanted proteins, and generation of energy; or suppress tumour survival through apoptosis, necrosis, and inflammation.[3] Various molecules participating in the initiation, nucleation, elongation, or fusion of autophagosome with lysosome, are targeted to study autophagy. The LC3B protein, part of the elongation of the dynamic membrane structure of the autophagosome, is the most characteristic and widely-used autophagy marker, especially in association with the adaptor protein p62/sequestrome 1. Their interaction facilitates autophagic degradation of ubiquitinated protein aggregates in lysosomes.[4,5]

MATERIALS AND METHODS

In this study, autophagy flux was assessed by means of p62 and LC3B protein expression in various GEP-NENs derived from pancreas (n=19), stomach (n=2), small intestine (n=2), and oesophagus (n=1), where existing data are limited. The study was approved by the ethics committee of the Hippokration General Hospital of Athens, Greece. The patient cohort consisted of nine patients with NECs (six male, three females; mean age: 55±7; six pancreas, one stomach, one small intestine, one oesophagus), and 16 patients with NETs (11 male, five female; mean age: 58.69±3.7; 13 pancreas, one stomach, two small intestine). Immunohistochemistry was performed on 5 µm sections of formalin-fixed paraffin-embedded tissue from lesions and normal adjacent tissue. Staining intensity (negative to high: 0–3) was multiplied with the immunoreactive score (0–10%=1; 11–50%=2; 51–80%=3; 81–100%=4) to obtain the final score. Epithelial and stromal cell populations were assessed separately.

Figure 1: Representative immunohistochemical detection of LC3B and p62.



LC3B and p62 in stomach samples **(A–D)** and pancreas samples **(E–H)**: p62 cytoplasmic expression is prominent in NEC lesions **(D and H)**, while LC3B protein expression is significantly increased **(A–C and E–G)** in lesions' epithelium compared to their corresponding stroma (epithelium versus stroma [red arrow]; p<0.001). This pattern is more prominent in NEC lesions (NECs: p=0.018 versus NETs: p=0.016). Magnification: 20x.

NA: normal adjacent epithelium; NET: neuroendocrine tumour; NEC: neuroendocrine carcinoma.

RESULTS

Results were statistically analysed using IBM SPSS Statistics 28.0 (Armonk, New York, USA). Both cytoplasmic and nuclear p62 expression were observed. Expression, mainly cytoplasmic, was higher in NEN lesions compared to their corresponding NA epithelium (0.92±0.4 versus 0.0; p=0.017), in which nuclear expression was prominent (p=0.047). LC3B expression was also induced in lesions compared to NA epithelium, but this difference was not statistically significant (p=0.1), probably due to the limited number of patients. Nevertheless, LC3B protein expression was mainly detected in NENs lesions' epithelium with limited expression in stroma (5.67±0.9 versus 0.47; p<0.001). The difference between epithelium and stroma was more prevalent in NEC lesions (NECs: 7.25±1.5 versus 0.62±0.3; p=0.018) versus NETs (4.67±1.3 versus 0.58±0.3; p=0.016 [Figure 1]).

CONCLUSION

An apparent induction in autophagy was also detected in this study, which includes NENs from various organs of the gastrointestinal tract, and further supports existing data derived from pancreatic NENs.[6,7] However, more data are required, as the number of patients in this cohort was limited. Still, the observed prevalence of autophagy in epithelium compared to stroma in NECs versus NETs might be related to their distinct clinical phenotype, making autophagy a potential candidate for introducing new therapeutic strategies for patients with GEP-NENs.

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Interview

Carlos Caldas

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Q1 What initially sparked your interest in the field of oncology and motivated you to continue researching?

What motivated me, being an internist at heart, was the fact that the molecular biology and genetics revolution would have a first and great impact in cancer medicine. Medical oncology is a specialty for internists who apply molecular understanding of disease to improve the care of patients with cancer. It was obvious to me from very early on that any advances in oncology would come from research into the basic mechanisms of cellular transformation. That egged me on! I wanted to practice as a medical oncologist and to also run a curiosity-driven laboratory research programme to tackle the disease.

Q2 Your research with the Caldas Group focuses on the functional genomics of breast cancer. What was the mission you set out to achieve when this research group was founded?

Our mission was to first characterise in great detail the inter- and intra-tumour heterogeneity of breast cancers. Heterogeneity must be the reason why clinical courses are so diverse! Only with this detailed cancer map can we now move to study tumour dormancy, metastases, and therapy response. We also created patient-relevant models for pre-clinical therapy development. These components will then take us to the ultimate goal: truly personalised precision oncology!

Q3 You also led the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) study. Could you give us an overview of what this project entailed, and summarise the key findings of the study?

I co-led METABRIC with my colleague and friend Sam Aparicio, and we delivered the genomic and transcriptomic landscapes of 2,000 breast cancers with long clinical follow-up. METABRIC has shown us that breast cancer is a constellation of 11 distinct diseases with very different biology, genomic drivers, and clinical courses. The clinical breast cancer community needs to embrace this knowledge to better manage patients, and clinical investigators need also to account for this when designing clinical trials.

Q4 What changes have you brought into effect since your appointment as Chair of Cancer Medicine at the University of Cambridge?

The creation and development of a multi-disciplinary translational programme that integrates multi-omics, pathology, radiology, and novel clinical trials to deliver systems medicine for the benefit of patients with breast cancer. I also created and led the Cambridge Breast Cancer Research Unit at Addenbrooke's Hospital in 2007, and was its Founding Director until January 2020.

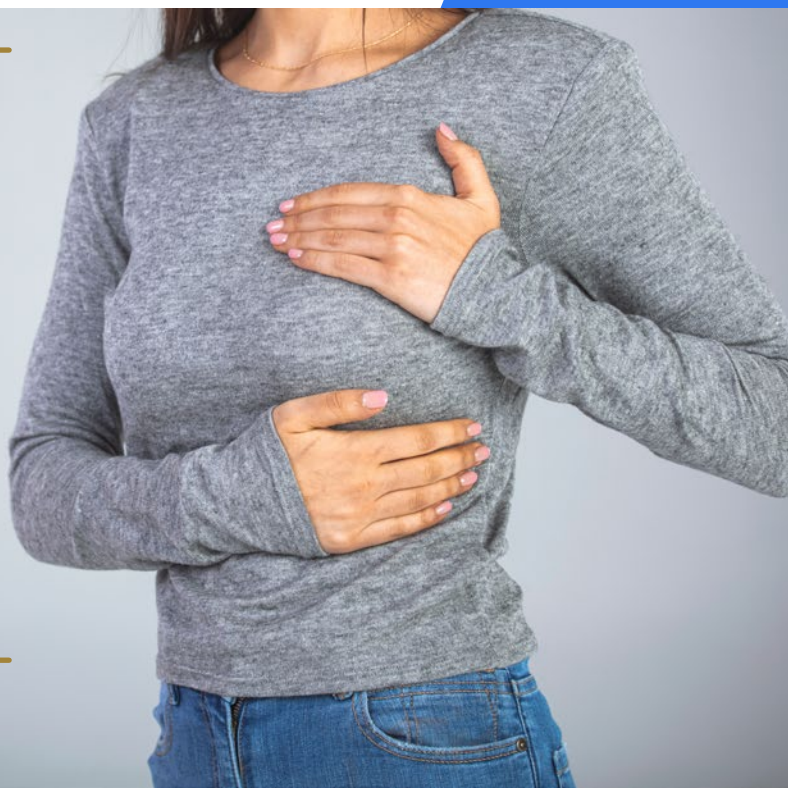
Q5 You until recently led the Cambridge Breast Cancer Programme that you founded in 2016. Has this programme seen much success, and should we expect to see personalised treatment as an option in other forms of cancer?

As I said above, the aims of the translational research programme were to integrate these disciplines to ultimately deliver systems medicine to benefit patients with breast cancer. One of its greatest successes has been the Personalized Breast Cancer Programme (PBCP), which uniquely delivers whole genome and transcriptome sequencing to all consenting patients with both early and advanced forms of the disease in Cambridge. With PBCP, we are empowering National Health Service (NHS) doctors to deliver more targeted and personalised therapies. I am extremely proud that over 850 patients to date have been enrolled in this world-leading and unique programme.

Q6 Over the years practising as an oncologist, how have you seen the field change in terms of advancements to the technology used?

I have witnessed several advances that have had a significant impact on patients, including breast screening, breast conserving surgery and sentinel lymph node assessment, improvements in radiotherapy and hormone therapy, the development of adjuvant chemotherapy, anti-human epidermal growth factor receptor 2 targeted therapy, and genomic medicine.

"It was obvious to me from very early on that any advances in oncology would come from research into the basic mechanisms of cellular transformation."



Q7 There has been interest from many areas of life science and healthcare towards artificial intelligence (AI). Do you believe that there is room for AI in oncology, and will the utilisation of such technologies accelerate research and development?

Both AI and machine learning (ML) will significantly impact oncology in general, and breast cancer medicine in particular. AI has already shown the ability to substantially improve the interpretation and eventual automated reading of screening mammograms. ML was recently shown by my group to be a feasible way to integrate multi-omic data and generate predictors of response to therapy. These examples are just the beginning of what I believe will be a revolution in medicine brought about by big data and its analysis with AI and ML.

Q8 What has been the greatest achievement in your career to date?

I would say two. Firstly, our view of cancers as evolving tumour ecosystems, formed by communities of malignant cells and the many cellular and other components of the tumour microenvironment, constantly being perturbed by therapies and by the immune response. Secondly, another achievement is the role we played in training a new generation of oncologists who understand that tackling cancer requires a detailed characterisation of its molecular underpinnings.

Identifying the Best Ki-67 Cut-Off for Determining Luminal Breast Cancer Subtypes Using Immunohistochemical Analysis and PAM50 Genomic Classification

Editor's Pick

My Editor's Pick is an excellent paper by Escala-Cornejo et al., which discusses the best Ki-67 cut-off for determining the luminal breast cancer subtypes using immunohistochemical analysis and PAM50 genomic classification. The study involved genomic testing using PAM50 of samples from 143 females diagnosed with early-stage luminal breast cancer.

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Abstract

Background: A surrogate classification of breast cancer (BC) molecular subtypes based on immunohistochemistry (IHC) was established at the 13th St. Gallen International Breast Cancer Consensus (SG-BCC). The most controversial point of discussion was the difference between the luminal A and B subtypes. The Ki-67 cut-off that has been used to differentiate these BC subtypes is 14%; however, this cut-off was questioned. This study aimed to identifying the best Ki67 cut-off for determining the luminal BC by PAM50/Prosigna (NanoString Technologies, Seattle, Washington, USA).

Methods: This study included females who were diagnosed with early-stage luminal BC between 2015–2020, and whose samples were subjected to genomic testing using PAM50.

Results: A total of 143 samples were analysed. At the Ki-67 cut-off values of >14%; a correlation of 70.6%, with a sensitivity of 79.1% and a specificity of 55.8%; and a positive predictive value of 75.8% and negative predictive value of 60.4% were observed. When the Ki-67 cut-off was increased to >20%, the percentage of well-classified tumours based on IHC was 76.2%, increasing the agreement by 6.2%. The sensitivity was 93.4%, but the specificity was 46.1%. The positive predictive value was 75.2% while the negative predictive value was 80%, suggesting that IHC has a high probability of diagnosing luminal A and B.

Conclusions: Increasing the Ki-67 cut-off to >20% leads to a better surrogate classification based on IHC and to a higher sensitivity in classifying the luminal subtypes. The authors propose that the cut-off for Ki-67, which is an independent factor, should be globally modified to >20%.

Key Points

1. Advanced techniques such as molecular biology and genome sequencing have altered the way breast cancer is understood. Based on this study, and on subsequent research conducted over the last 20 years, four intrinsic breast cancer subtypes have been characterised: luminal A, luminal B, *HER2*-enriched, and basal-like subtypes, which differ in terms of incidence, risk factors, prognosis, survival, and sensitivity to treatment.

2. The main objective of this study was to determine the optimal cut-off that could differentiate between luminal tumours using Ki-67 as the independent differentiating factor.

3. The study concluded that the specificity and sensitivity that clinicians want to find at the Ki-67 cut-off point depends on the objectives that they want to achieve with the patient. Different clinical factors must guide the clinician, along with the sensitivity and specificity of the Ki-67 cutting method chosen.

BACKGROUND

Over the last few years, advances in molecular biology and genome sequencing have made it possible to identify the genetic alterations that underlie different health conditions, and these advances are particularly important in the field of oncology. Thanks to these advanced techniques, there has been a change in the way a disease as complex and heterogeneous as breast cancer (BC) is understood.[1] In 2000, Perou et al.[2] established a classification of the intrinsic BC subtypes after analysing the microarrays of complementary DNA of 50 genes.[2,3] Based on this study, and on subsequent research conducted over the last 20 years, four intrinsic BC subtypes have been characterised: luminal A, luminal B, *HER2*-enriched, and basal-like subtypes. These entities significantly differ in terms of incidence, risk factors, prognosis, survival, and sensitivity to treatment.[4-6]

Perou et al.'s[2] working hypothesis was based on the idea that the phenotypic diversity of BC is due to the diversity in its expression patterns, which could be studied with complementary DNA microarrays, leading to the establishment of a new molecular taxonomy for BC. This group analysed 65 surgical breast specimens (including tumours and healthy tissues) obtained from 42 females with locally advanced BC who were treated with neoadjuvant therapy. They identified 496 genes with greater expression variability within the different tumour groups, but with minimum variability between the samples of the same patient (intrinsic genes). At this level of gene expression, the tumours could be grouped into the abovementioned subtypes.[2]

The luminal subtypes include oestrogen receptor (ER)-positive tumours, with an expression pattern of the luminal epithelium.[7-9] These tumours are generally low grade, and less than 20% present *TP53* mutations.[10] Within the luminal

cluster, at least two subtypes exist (luminal A and B), which differ from each other in several respects. The luminal A phenotype exhibits high expression levels of ER and ER-related genes, and low expression levels of *HER2* genes and proliferation, including Ki-67. Despite the differences in terms of the number and type of genes analysed in each expression subtype, all results showed that the luminal A subtype has a better prognosis than the luminal B subtype.[11] The luminal B subtype accounts for 20% of all BC cases; conversely, it displays a moderate expression of ER and a lower expression of ER-related genes, with variable expression levels of *HER2* genes and a higher frequency of *TP53* mutations.[12] Several studies have suggested that the prognosis and the 10-year survival rate of these tumours are similar to those of the basal-like subtype.[13]

The *HER2* subtype accounts for 10–15% of all BC cases, and it is characterised by high expression levels of *HER2* and proliferation genes and low expression levels of ER-related genes.[14] In terms of genomic profile, the *HER2*-positive subtype only refers to tumours that do not express ER. They must not be confused with tumours that are *HER2*-positive based on immunohistochemistry (IHC) or on a fluorescence *in situ* hybridisation test or with tumours that express ER, as they are genotypically classified as tumours of the luminal subtype.[15]

The last subtype is called basal-like because of its similarity to the expression of basal myoepithelial cells in mammary ducts. It represents approximately 15% of all BC cases. It is characterised by the low expression levels of luminal and *HER2* genes. This subtype does not correlate with clinical symptoms and is often considered to be a triple-negative phenotype.[16-17]

Based on the 496 genes analysed in the Perou et al's[2] study, and thanks to the microarray and reverse transcription PCRtechniques, Parker et al.[18] simplified the selection of genes in 2009 and reduced it to 45 classifying genes and five control genes, based on which the different intrinsic subtypes were identified. These intrinsic subtypes classified by Perou et al.[2] were subsequently ratified by the study led by The Cancer Genome Atlas (TCGA) project, which analysed over 500 BC cases.[19] This classification of the intrinsic subtypes has some limitations due to the complex methodology involved. For this reason, it was necessary to develop a classification system for clinical analysis based on the surrogate markers detected via IHC, wherein the different types of BC will be grouped into the abovementioned four main intrinsic subtypes. These IHC surrogate markers are ER, progesterone receptors (PR), *HER2*, and the proliferation marker Ki-67.

The most commonly used surrogate classification was established in the 13th St. Gallen International Breast Cancer Consensus (SG-BCC), and this classification demonstrates the correlation of survival and prognosis with the intrinsic BC subtypes.[20] However, out of the four IHC surrogate markers, Ki-67 has disadvantages; to date, the optimal Ki-67 cut-off that could differentiate luminal A and B tumours is unknown, although a cut-off of 14% is currently accepted. Studies on this subject have used cut-off values ranging from 10–30%.[21,22] In other words, there is no fixed value at which the different luminal tumours are distinguished. The clinical guidelines for early-stage BC published by the European Society for Medical Oncology (ESMO) in 2019 proposes a cut-off of 20%.[23]

Different genetic profiles play an essential role in the identification of intrinsic BC subtypes. Not only do they help determine the intrinsic tumour subtype being analysed, but they also make it possible to assess, through the quantification of specific genes and the use of weighting coefficients, the correct adjuvant therapy used in localised BC with a luminal subtype.[24] Several genomic tests used in daily clinical practice have been validated, and four of them (MammaPrint [Agendia, Irvine, California, USA], Oncotype Dx [Genomic Health Redwood City, California, USA], EndoPredict [Myriad Genetics, Salt Lake City, Utah, USA], and PAM50/Prosigna [NanoString Technologies, Seattle, Washington, USA]) are frequently used in the author's centre.[25-28]

Based on the studies published by Perou et al. in 2000,[2] they later presented a risk predictor based on gene expression in 2009. This predictor could be applied relatively easily in clinical practice and could identify the intrinsic subtypes of BC. This predictor is PAM50, and it measures the expression levels of 50 specifically-selected genes that can be analysed using the RNA obtained from formalin-fixed paraffin-embedded

tissues.[29] When the ability of PAM50 to identify the four subtypes was compared with the results of molecular classification based on the microarray of RNA of approximately 2,000 genes from fresh tissue, its accuracy was 93%, demonstrating that the test provides information similar to that obtained from 2,000 genes.[30]

Initially, PAM50 required the use of the genomic quantitative reverse transcription-PCR platform, which allowed for greater clinical applicability; however, the analysis is centralised. In 2001, the nCounter Technology (Nanostring Technologies Inc., Seattle, Washington, USA) made it possible to conduct analyses using degraded RNA without involving amplification, and it can provide results within 72 hours. Moreover, the process is decentralised, meaning tests may be carried out locally. Apart from providing information on the intrinsic subtype of BC, the PAM50 test offers individualised prognostic information based on a predictor known as Risk of Recurrence (ROR),[31] which is a score ranging from zero (best prognosis) to 100 points (worse prognosis). This score determines the risk of distance recurrence after 10 years: low (<10% ROR), medium (10–20% ROR), and high risk (>20% ROR).[32] Given that this test is not centralised, an analytical validation was conducted in three different laboratories. The results showed that the agreement for the intrinsic subtypes was 97–100% and the standard deviation for the ROR score was 0.67–2.90 points (on a scale of 0–100 points).[29] Given the high level of standardisation of the test, it received the 501(k) approval from the U.S. Food and Drug Administration (FDA) in 2013.

Currently, the main indication of the PAM50 test is the prediction of late recurrence of luminal diseases. The prognostic ability of ROR after 5–10 years of monitoring has been retrospectively validated in the ATAC[33] and ABCSG-8 studies.[34] In both studies, the ROR could identify a group of patients who had a risk of <5% after 5 and 10 years of monitoring. In view of these results, the FDA approved the use of PAM50 in 2014 to predict the risk of late recurrence in the luminal subtypes of BC. The lack of availability of PAM50 in all hospital centres has led to the frequent use of surrogate BC classification via IHC. The possibility of obtaining a better classification of luminal BC cases leads to a better choice of adjuvant therapy and prevents the unnecessary use of chemotherapy (CT) as treatment for low-risk tumours. However, this classification does not seem to clearly distinguish between low- and high-risk tumours.

For this reason, this study aimed to determine the optimal Ki-67 cut-off for surrogate BC classification in order to differentiate luminal tumours based on the correlation between the Ki-67 values obtained via IHC and the intrinsic classification based on PAM50.

METHODS

Inclusion Criteria

The authors carried out a retrospective analysis involving pre- and postmenopausal women who were diagnosed with luminal A or B early-stage BC (N0) via IHC and whose surgical samples were subjected to genomic testing using PAM50. The IHC analysis criteria were based on the 13th St. Gallen Consensus, which was published in 2013. The PAM50 study criteria were approved in 2015 by the Health Department of the Regional Government of Castilla y León: resected breast tumour measuring ≤30 mm without lymph node involvement or micrometastatic disease (N0 or N1mi), ER positive and *HER2*-negative, which meets at least one and less than two of the following high-risk criteria: histologic grade (Nottingham score) II; Ki-67 >14% and <30%; PRs >20%; weak or moderate expression of ERs (+/++ or ≤50%).

Definition and Analysis of Statistical Values

In this study, sensitivity is defined as the probability that IHC classifies tumours as luminal A when PAM50 classifies them as such, and specificity is defined as the probability that IHC classifies tumours as luminal B when PAM50 classifies them as such. The positive predictive value (PPV) was described as the probability that PAM50 classifies tumours as luminal A when IHC classifies them as such. The negative predictive value (NPV) was defined as the probability that PAM50 classifies tumours as luminal B when IHC classifies them as such.

A concordance analysis between PAM50 and Ki-67 was conducted and the optimal cut-off

values for Ki-67 was determined using Cohen's κ coefficient and receiver operating characteristic (ROC) curve, respectively. The κ concordance was analysed using the criteria established by Ruiz-Morales and Morillo-Zárate in 2004.[35] The criterion used to select the cut-off based on the ROC curve was the point closest to the upper-left corner of the curve. The 95% confidence interval of the area under the curve was calculated using the method established by DeLong et al.[36] Statistical analysis was conducted using the EZR software (Easy R) v. 1.5.

RESULTS

This study included 143 females with a median age of 54 (32–74) years. The most common histological disease was invasive ductal carcinoma, which was found in 108 patients (75.5%), followed by invasive lobular carcinoma, which was observed in 27 patients (18.9%). Most of the patients (122 out of 143 [85.3%]) had tumours measuring ≤2 cm (pT1) and 21 (14.7%) patients had tumours measuring 2–3 cm long (pT2). Of the patients, 79% (113 out of 143) did not show lymph node involvement, and 21% (30 out of 143) showed micrometastatic disease (pN1mi). All patients had luminal A-like or B-like BC (none of the patients had *HER2*-enriched BC). Within the 6-year follow-up period, none of the patients (0 out of 143 [0%]) showed recurrence after the adjuvant therapy. The general characteristics of the patients are shown in Table 1.

In the IHC classification, 64 tumours (44.8%) were classified as luminal A and 79 (55.2%) as luminal B. In the PAM50 analysis, 91 tumours (63.5%) were classified as luminal A and 52 (36.7%) were classified as luminal B. In 41 patients (29%), the therapeutic decision changed after the PAM50 analysis. In the group that received adjuvant hormonal therapy (HT) as the single treatment prior to the test (n=97), CT was added to the treatment in 27 cases (28%). In the group that received CT plus HT prior to the test (n=46), single HT was decided post-test in 14 cases (39%).

Concordance Between Immunohistochemistry and PAM50

The κ coefficient in the analysis of the global concordance between the IHC surrogate classification and the PAM50 classification was 0.16. The analysis of the diagnostic values for the IHC surrogate markers showed that the concordance rate of the correctly classified cases was 57.7. The IHC surrogate classification had a sensitivity of 55.70, a specificity of 60.78%, a PPV of 68.80%, and an NPV of 46.70%.

When the concordance between IHC and PAM50 was analysed for the Ki-67 marker at the current cut-off of 14%, the κ coefficient was 0.35. The percentage of patients that were correctly classified as having luminal A or B tumours based on Ki-67 analysis was 70.63%. The surrogate marker Ki-67 had a sensitivity of 79.1%, a specificity of 55.8%, a PPV of 75.8%, and an NPV of 60.41%. Compared with the standard classification, Ki-67, being an independent marker, provides a better concordance of 23.42% in differentiating luminal A tumours and a reduced accuracy (lower by 5%) in differentiating luminal B tumours.

When the cut-off for Ki-67 as an independent marker was set at 20%, the κ coefficient was 0.44 and the rate of accurate patient classification was 76.22%, which was 5.60% higher than that obtained at the Ki-67 cut-off of 14%. Moreover, the sensitivity was 93.41% and specificity was 46.15% (sensitivity was 14.3% higher and specificity was 9.65% lower than the results obtained at the Ki-67 cut-off of 14%). The abovementioned results are summarised in Table 2.

The possible influence of PRs on the cut-off point of Ki-67 by IHC was studied. It was observed that the modification of the cut-off points of the PRs in the different points of Ki-67 did not influence the sensitivity and specificity of 14% and 20% in the classification of luminal A and B tumours.

Establishment of the Ki-67 Cut-Off Values with Receiver Operating Characteristic Curve Analysis

The ROC curve for Ki-67, an independent surrogate marker, as determined by IHC is shown in Figure 1. The area under the curve

Table 1: General characteristics of the patients included in the study.

Total patients (n, %)	143 (100%)
Age	54 (32–74)
Sex (M/F)	0/143 (0/100%)
Post-treatment tumour recurrence	0 (0%)
Histology	
Ductal carcinoma	108 (75.5%)
Lobular carcinoma	27 (18.9%)
Mucinous	6 (4.2%)
Papillary	2 (1.4%)
Tumoral size	
pT1	122 (85.3%)
pT2	21 (14.7%)
Lymph node involvement	
pN0	113 (79%)
pN1mi	30 (21%)
HER2-enriched	0 (0%)

F: female; M: male.

Table 2: Summary of the statistical values obtained in the differentiation of luminal A and B tumours.

Biomarker	Agreement (%)	κ	Sensitivity	Specificity	PPV	NPV
Ki-67+PRs	57.7%	0.16	55.7%	60.78%	68.8%	46.7%
Ki-67: 14%	70.6%	0.35	79.1%	55.8%	75.8%	60.4%
Ki-67: 20%	76.2%	0.44	93.4%	46.2%	75.2%	80.0%

κ: Cohen's κ coefficient; NPV: negative predictive value; PPV: positive predictive value; PR: progesterone receptor.

of the ROC curve is 0.78 (95% confidence interval: 0.70–0.85). The Ki-67 cut-off showing the most homogeneous values for sensitivity and specificity was 14% (sensitivity: 79%; specificity: 56%). A Ki-67 cut-off of 10% showed a significant increase in specificity at the expense of a pronounced decrease in sensitivity (specificity: 94%; sensitivity: 43%). The opposite trend was observed when the Ki-67 cut-off was increased to 20%; there was a considerably marked increase in sensitivity with a sharp fall in specificity (sensitivity: 93%; specificity: 46%).

The Ki-67 cut-off values of at least 25% demonstrated a 100% sensitivity. By contrast, the specificity was compromised. At a cut-off of 25%, the specificity was 23% and it progressively decreased with the increase in cut-off value. A 100% specificity was reached when the Ki-67 cut-off was 3%, although the shift in

threshold from 12% to 10% involved an increase in specificity from 56% to 94% and it entailed a decrease in sensitivity from 76% to 43%.

Clinical Implications of the Ki-67 Cut-Off Values

When the Ki-67 cut-off of 14% was applied in the authors' sample, the concordance rate between PAM50 and IHC was 70.6%; 91 out of the 143 patients (70.6%) were classified correctly. Within this group, 72 out of the 95 (75.8%) tumours that were classified as luminal A using PAM50 were correctly classified as such in the IHC analysis, whereas 29 out of the 48 (60.4%) tumours classified as luminal B using PAM50 were correctly classified as such in the IHC analysis.

When the Ki-67 cut-off was set at 20%, the concordance rate between IHC and PAM50 was 76.2% (109 out of 143 patients were classified correctly). The percentage of patients who were correctly classified as having luminal A based on IHC and who were later confirmed with PAM50 was 75.2% (85 out of 113). In the case of luminal B tumours, the percentage of tumours that were correctly classified with IHC was 80% (24 out of 30).

In the authors' sample, the cut-off values below 14% showed reduction in sensitivity, leading to inaccurate classification of luminal A tumours, despite the improvement in the concordance rate for luminal B tumours. Conversely, when the cut-off values were higher than 20%, the increase in sensitivity improved the concordance rate for luminal A tumours. However, the significant loss in specificity entailed the nearly total disappearance of the correct classification of luminal B tumours.

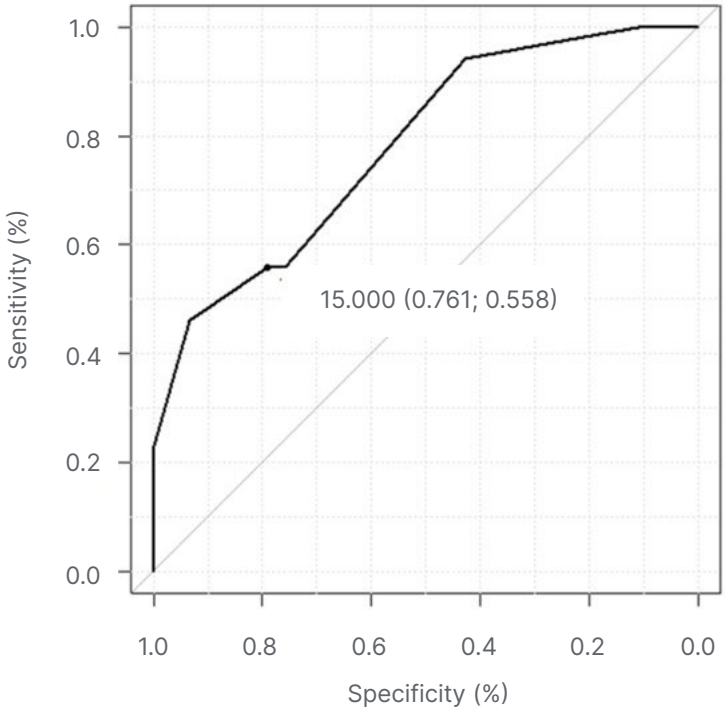
DISCUSSION

In clinical practice, the use of genomic platforms has been essential in the decision-making process in the adjuvant treatment of luminal subtypes of early-stage BC, as well as in the determination of the intrinsic subtypes of BC. The IHC surrogate classification of BC subtypes is a valuable tool when genomic platforms are unavailable. However, the categorisation mechanism of this tool has some shortcomings, particularly in differentiating luminal A and B tumours.

In this study, the authors focused on Ki-67, the most controversial IHC surrogate marker in the literature.[37,38] To determine the optimal cut-off that could differentiate between luminal tumours, the authors assessed the concordance between IHC and PAM50 based on the concordance rate (κ coefficient, relative values, and absolute values) and on ROC curve, globally at first. The concordance rate between the subtypes determined via IHC and the intrinsic subtypes determined using PAM50 was 57.7%. This concordance rate is lower than the published ones, such as those reported by Kim et al.[39] and Fernández-Martínez et al.[40] (61.2% and 70.8%, respectively). The κ coefficient was 0.16, indicating a low concordance between the BC subtype determined via IHC and the true intrinsic subtype. A poor classification of luminal tumours was observed more often in luminal A tumours than in luminal B tumours because, in the authors' sample, the sensitivity was 5% lower than the specificity. These results indicated that the classification of BC subtypes via IHC could not accurately differentiate luminal breast tumours. The need to improve IHC classification has already been mentioned in other studies.[41]

The currently accepted cut-off for Ki-67 as an independent diagnostic marker of luminal BC is 14%. However, the 2019 ESMO 2019 clinical practice guidelines for early-stage BC suggest the use of a cut-off of 20% for Ki-67.[23] In the authors' sample, the κ coefficient was 0.35, indicating a low concordance. Thus, luminal tumours are better differentiated when Ki-67 is used as an independent marker than when PR and Ki-67 are considered together, wherein the differentiation between luminal A and B tumours is poorer in patients with luminal BC (positive expression of hormonal ERs and negative expression of *HER2*). In differentiating luminal tumours, the independent use of Ki-67 provides more accurate results, not only in terms of κ coefficient, but also in terms of the accurate classification of samples (an increase by 12.9%) and in terms of sensitivity (an increase by 23.4% relative to the global classification). In terms of accurate patient classification and sensitivity, the authors found that Ki-67 is a better predictor than IHC surrogate classification for the characterisation of luminal A tumours. The classification of luminal B tumours shows a slightly poorer characterisation derived from a

Figure 1: Receiver operating characteristic curve of Ki-67 as an independent diagnostic marker of luminal breast cancer.



specificity loss of 5%, but this was not reflected in the absolute number of patients in our sample.

This loss of specificity of luminal B tumours is likely to result from a different histological presentation of luminal A tumours. Different genomic or IHC markers that have not been fully characterised at present could make the diagnostic difference between luminal A and B tumours. That is why Ki-67 would be a good marker of IHC for the characterisation of luminal A tumours but not luminal B.

The main objective of this study was to determine the optimal cut-off that could differentiate between luminal tumours using Ki-67 as the independent differentiating factor.[21] In the assessment of different cut-off values via ROC curve analysis, the two cut-off values that showed the best results were 14% and 20%. From a global perspective, when the Ki-67 cut-off was increased to 20% in the IHC classification, more tumours were classified correctly as luminal A; however, the question remains whether this would largely affect a poorer characterisation of luminal B tumours. The increase in the cut-off from 14% to 20% increased the concordance rate by nearly 6% (18 out of 143 patients were correctly classified). Also, the κ coefficient increased from 0.35 to 0.44 (from low to moderate concordance for the differentiation of luminal tumours). This improvement in the concordance rate was accompanied by a significant increase in sensitivity (by over 14%) and in the NPV (by nearly 20%). The 8% decrease in specificity explains the poor classification of luminal B tumours. In the authors' sample, 5 out of the 143 patients (3.5%) were poorly classified. Considering these results, the increase in the Ki-67 cut-off from 14% to 20% led to a better classification of luminal A tumours at the expense of a slightly worse classification of luminal B tumours; however, it does not affect the κ coefficient or the concordance rate.

It is important to note that the proposed new classification, with the elevation of the cut-off point from 14% to 20%, is one more diagnostic tool that helps define patients in luminal subtype A or B. There is a small percentage of patients with luminal subtype B who could be misclassified, so it is important to assess the patient to make a decision on the use of CT adjuvant in these patients. Age, menstrual

status, or the existence of comorbidities in conjunction with the values of immunohistochemistry should be used to help to define what type of complementary treatment patients should receive.

The specificity and sensitivity that clinicians want to find at the Ki-67 cut-off point depends on the objectives that they want to achieve with the patient. Different clinical factors must guide the clinician, along with the sensitivity and specificity of the Ki-67 cutting method chosen. Therefore, it is key to bear in mind that in patients who, due to clinical or tumour factors, might have had a high risk or recurrence, the Ki-67 cut-off point could decrease to 14%, if necessary. Considering these factors, if there are no specific indications that point towards a cut-off point, assessing the specificity and sensitivity of Ki-67 the most optimal cut-off point would be 20%.

The authors' data suggest that it is advisable to increase the Ki-67 cut-off from 14% to 20% in the IHC surrogate classification of BC. However, it is important to consider the sample size. Further studies are needed, given that a larger sample size may validate whether the improved classification of luminal A tumours do not influence the characterisation of luminal B tumours, as seen in the authors' results.

In conclusion, based on the present results, the Ki-67 cut-off at 14% presents the most homogeneous sensitivity and specificity for the classification of luminal A and B subtypes of BC. However, a cut-off value of 20% provides a better classification of luminal tumours because of its higher sensitivity, which leads to a better diagnosis of patients with luminal A tumours. Increasing the Ki-67 cut-off to 20% to differentiate between luminal tumours may prevent unnecessary CT treatments. New studies involving a larger sample are warranted for a prospective validation of this cut-off in order to determine the optimal Ki-67 cut-off.

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The Contradictory Phenomena: Development of a New Life and a Life-Threatening Illness: Colorectal Cancer in Pregnancy

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Abstract

Colorectal cancer (CRC) is a common and lethal disease. Genetic and environmental factors contribute to the development of CRC, with different incidence and mortality rates around the world. Geographic differences appear to be attributable to exposures that are superimposed on a background of genetically determined susceptibility. Globally, CRC is the third most commonly diagnosed cancer in males and the third in females, with 1.8 million new cases and approximately 861,000 deaths in 2018, according to the World Health Organization (WHO). Epidemiologically, it is a disease of the middle-aged and elderly. However, it may occur in young patients, presenting with an aggressive biological behaviour and poor prognosis. Among this young age group are childbearing women, with CRC in pregnancy being rarely diagnosed and reported. Its diagnosis is a challenge to the unaware and, once diagnosed, management options are limited. This study aims to elucidate the presentation, diagnosis, anatomical location, pathogenesis, and treatment options of CRC in pregnancy.

Key Points

1. Colorectal cancer (CRC) in pregnancy is a rare event; however, rates are increasing as risk of CRC is increased in women >40 years and more women are opting to have children later in life.

2. Diagnosis of CRC in pregnancy can be difficult due to wide-ranging presentations of the disease and overlapping symtpoms with pregnancy.

3. Treating CRC in pregnancy presents a unique challenge; a tailored, patient-specific approach is recommended, that considers legal, ethical, emotional, and scientific challenges.

INTRODUCTION

Colorectal cancer (CRC) ranks as the third most common type of cancer in women.[1] Patients aged 50 years and above constitute the highest percentage of patients diagnosed with the disease.[2] Furthermore, women above the age of 40 years are 11-times more likely to have CRC, compared with women aged 30 years and younger.[3,4] Aytac et al.[5] reported a growing incidence of CRC in the younger population; additionally, Khangura et al.[2] concluded that 3% of patients with CRC are under 40 years old. This increase in the incidence of CRC in younger patients translates directly to an increase in incidence during the reproductive age,[5] and therefore during pregnancy.

Despite this, pregnancy-related CRC is an extremely rare disease, with inadequate published data to guide its management. From here, CRC in pregnancy may be considered an independent entity from CRC in the general population. In fact, fewer than 300 cases have been reported in the medical literature,[5] with the first case reported by Cruveilhier in 1842.[6] CRC now ranks as the seventh most common cancer type in pregnancy,[2,7] with a predicted incidence of 0.0076% of pregnancies (one in 13,000),[8] a mean age at diagnosis of 31 years,[7] and an age range of 16 years to 48 years.[9]

PRESENTATION

A substantial similarity exists in the clinical presentation between a pregnancy-related CRC and normal pregnancy, which can delay a timely diagnosis.[1,10] This is particularly true in multiparous women, whose anxiety levels are usually lower compared with women who are pregnant for the first time. Consequently, women who have had at least one previous birth may present later to healthcare providers. With such a wide spectrum of presentation, patients may present with nausea, vomiting, abdominal pain, weight loss, fatigue and anaemia, rectal bleeding, and altered bowel habits (e.g., constipation). From here, what is considered normal in pregnancy may be alarming. For instance, uterine cramps cause abdominal pain, and so may CRC. Furthermore, rectal bleeding is commonly seen in pregnancy and is attributed to pregnancy-related engorged haemorrhoids.[11]

On the other end of the spectrum, and as previously reported by different studies, pregnancy-related CRC can present without a specific presenting complaint.[2,3,12]

DIAGNOSIS

With such a wide spectrum of presentation and overlapping signs and symptoms between pregnancy and CRC, the diagnosis is a challenge. Therefore, healthcare providers should keep CRC in mind when considering differential diagnoses in patients presenting with these overlapping symptoms. Pregnant women presenting with such symptoms must be closely followed up or investigated using paraclinical tests that are safe during pregnancy. Above all, it is vital to investigate further symptoms that are specific, severe, or relapsing.[1,13]

Colonoscopy is considered the gold standard for diagnosing CRC. It also has the advantage of localising the tumour and obtaining tissue biopsy. However, pregnancy is considered a relative contraindication for colonoscopy because of the potential teratogenic medications, placental blood supply insufficiency and the resulting decrease in blood pressure or O_2 supply to the mother, and the risk for placental abruption due to the pressure from manipulation of the endoscope and the change in a patient's position during colonoscopy.[1,5,7,9,10,14] Having said this, it is preferable to proceed with endoscopy when a strong indication or highly suspected case of colorectal malignancy is present. Where possible, the procedure should be delayed until the second trimester.[5,7] It is also advisable to take all of the necessary precautions to minimise procedural risk. Hence, the time during endoscopy must be reduced. Practitioners should also aim to use the lowest possible dose of sedative.[10] Meperidine should be used as a sedative because of its safer fetal profile, O_2 should be supplied to the mother during the procedure to decrease the risk of hypoxia, and gentle abdominal compression should be used to avoid placental abruption.[9,14]

The carcinoembryonic antigen test (CEA) is utilised in pregnancy to follow up on CRC and for prognostic purposes. Unfortunately, CEA levels during pregnancy are usually within the normal limits, and sometimes mildly above the normal limits.[14-16] For this reason, CEA levels cannot

be used to screen for CRC nor diagnose CRC because of their low sensitivity and specificity.[9]

Contrast-enhanced CT is of limited value in diagnosing CRC in general. Its use is also limited during pregnancy because it may compromise fetal well-being.[17,18] Conversely, MRI is believed to be relatively safe in pregnancy. Of note, MRI should be performed without administration of a contrast agent,[13] as the use of these substances has not been approved for the fetus.[12,19] Moreover, gadolinium is considered a teratogenic agent.[10]

ANATOMICAL LOCATION

In the general population, two-thirds of CRC cases arise from the extrapelvic colon.[1,14,16] In contrast, pregnancy-related CRC involves the rectum and sigmoid colon in two-thirds of cases. In fact, it has been reported that approximately 85% of CRC cases in pregnancy are below the peritoneal reflection.[5,7,9,15]

PATHOGENESIS

The pathogenesis of pregnancy-related CRC is complex and not entirely understood. A complex hormonal interaction between oestrogen, progesterone, growth factors, the immune system, and environmental factors is thought to trigger CRC in pregnancy.[20,21] Furthermore, conflicting data are present in the medical literature, especially with regard to the impact of hormonal changes during pregnancy. Some authors reported the expression of oestrogen receptors in 20–80% of CRC cases in pregnancy,[22,23] and progesterone receptors in nearly 50% of cases.[24] However, other authors have not documented similar rates.[25] Having said this, it is believed that the role of hormones in the pathogenesis of CRC in pregnancy is manifested by the higher incidence of CRC in the second and third trimesters, and only one-fifth of patients present during the first trimester of gestation. Furthermore, in a study of over 2,000 women diagnosed with CRC, Arem et al.[26] proved that current use of hormonal replacement therapy is associated with lower CRC mortality risk (hazard ratio: 0.79; 95% confidence interval: 0.66–0.94). Hence, the relation between hormonal exposure and CRC progression should be revisited. Furthermore, Ho et al.[21] proposed an association between growth factors in pregnancy and the development of pregnancy-related CRC. Moreover, it has been found that COX-2 enzymes are essential for normal pregnancy. At the same time, high levels have been detected in many colorectal tumour cells. Thus, it has been postulated that COX-2 inhibitors such as aspirin can alter the course of CRC.[27] In brief, this field has not been adequately explored. Conflicting data exists regarding the pathogenesis of CRC in pregnancy, with complex hormonal interfaces between oestrogen levels, progesterone levels, pregnancy-related growth factors, the immune system, COX-2 enzymes, and environmental factors underlying the development of CRC in pregnancy.[20,21]

TREATMENT

Once diagnosed, the real challenge is treatment. Management requires cautiously individualised strategies after detailed patient counselling. Gestational age and consequently fetal lung maturity, stage of cancer, the role of neoadjuvant chemotherapy and its associated toxicity, the urgency of surgery, and the resulting emotional and physical stress on the mother should all be considered. The main goal is to initiate treatment as soon as possible,[2,19] taking into account the best possible balance for the fetus, and aiming for the optimal neonatal result.[5,9,15,19] From here, the urgency of surgery in combination with the gestational age dictates the management plan. Diagnosing CRC in the first 20 weeks of pregnancy is a rare event, which translates directly into inadequate data on fetal outcomes after surgical resection during this period.[9] With this in mind, and knowing that surgery is the gold standard for treatment of CRC, if imaging suggests a resectable tumour, surgery will be the first-line option.[10] This is particularly true given that postponing treatment can lead to disease progression. Therefore, some case reports recommend aborting the pregnancy, followed by surgical resection.[7,14,15,19] Having said this, cases of colonic resection, including low anterior resection and abdominoperineal resection, have been reported in the first 20 weeks of pregnancy without interfering with the normal pregnancy.[9] On the other hand, pregnancy-related CRC diagnosed after 20 weeks of gestation can be managed by delaying surgery until delivery is an

option in order to save the fetus,[7,14,15,19] keeping in mind the risk of disease progression in view of the proangiogenic state of pregnancy.[10] From here, the balance will be achieving fetal lung maturity and a scheduling delivery between 28 weeks and 32 weeks of gestation.[2,9,10] The patient will then be treated as a non-pregnant individual.[10,14,28]

Moreover, patients presenting with surgical abdomen due to obstructive CRC should be managed as an emergency. Having said this, patients presenting with large bowel obstruction due to CRC early in the course of their pregnancy should be managed surgically.

Surgery includes oncologic surgical resection with two options regarding reconstruction of the gastrointestinal continuity: either by a primary anastomosis or without an anastomosis. On the other hand, patients diagnosed later in pregnancy can be managed by colonic decompression using a loop colostomy, followed by delivery and then an oncologic colorectal resection. For patients with colonic obstruction not requiring urgent surgical intervention, a colonic stent can be used to delay immediate surgery in patients close to term and postpone oncologic surgical resection until after delivery.[29,30]

There may be a need for neoadjuvant chemoradiotherapy, especially considering that a large proportion of patients are diagnosed in an advanced stage because of delays in diagnosis. This also takes into account the fact that 85% of CRC cases diagnosed in pregnancy are anatomically located below the peritoneal reflection,[5,7,9,15] which translates directly to a higher proportion of pregnant patients diagnosed with rectal cancer suitable for neoadjuvant chemoradiotherapy. From here, conflicting data arises regarding neoadjuvant chemotherapy. In fact, some studies proposed that chemotherapy administration during the second and third trimester of pregnancy is safe.[5,7,28] The chemotherapeutic agent of choice for pregnancy-related CRC is 5-fluoruracil (5-FU),[1] especially given that 5-FU is known to have a negligible risk of adverse reproductive outcomes.[31,32] On the contrary, other studies have tackled the risk of spontaneous abortion and teratogenic effect of 5-FU.[5,7,9,15,28] Moreover, oxaliplatin has also been described as being safe.[33] A combined 5-FU, leucovorin, and oxaliplatin (FOLFOX) chemotherapy regimen seems to have been adopted in the management of pregnancy-related CRC. Indeed, there are cases of patients receiving FOLFOX on the 13th week of pregnancy and giving birth to healthy infants.[34] On the other hand, radiotherapy is not advised during pregnancy[7,15,28] because it is associated with lethal damage to the fetus, and may lead to embryonic death, malformation, or growth retardation.[19,28] Furthermore, van Calsteren et al.[35] concluded an overall good outcome of patients diagnosed with cancer during pregnancy, but a high rate of preterm labour induction and consequently a high rate of admission to neonatal intensive care units.[35]

CONCLUSION

Pregnancy-related CRC is a rare event with an expected increasing incidence. This is because more and more women are delaying pregnancy, and also because of the heightened risk of CRC in women older than 40 years of age.[7,32] It appears that there is still much to be studied, especially in the management of this rare entity. Management plans vary widely and pose significant legal, ethical, religious, emotional, and scientific challenges. From here, a tailored patient approach should be adopted by a multidisciplinary team, with accurate diagnosis and prompt treatment as the cornerstone of effective management.

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Dual Immunotherapy in a Patient with Rapidly Progressive Metastatic Melanoma Without Failure of Grafted Kidney

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Abstract

A 58-year-old female presented with a right axillary mass, which was confirmed as Stage IB BRAF-mutant melanoma based on the histology of the resected mass. The patient's history included a left upper arm melanoma that was resected in 2012; an allograft renal transplant secondary to polycystic kidney disease from a deceased donor, which they had undergone in 2009; and immunosuppressive therapy, which they had been on since the transplant took place.

The patient relapsed 8 months after axillary clearance. Dual immunotherapy is the first-line treatment for BRAF-mutant melanoma, but it has been associated with high rates of solid organ graft rejection in systematic reviews. For this reason, targeted therapy with dabrafenib and trametinib was commenced in the first instance, which halted disease progression for 10 months. On progression, dual immunotherapy was again discussed, and the patient fully consented regarding risks of graft loss. They had an excellent treatment response, and their renal graft remains functional.

Key Points

1. This case review discusses a 58-year-old female diagnosed with a relapse BRAF-mutant melanoma on the left upper arm, and a history of renal transplant secondary to polycystic kidney disease. They were treated with dual immunotherapy (IO) and showed excellent treatment response.

2. Dual IO has a better 5-year survival rate than using a single agent in the management of melanoma; however its use is challenging in patients with a history of organ transplant, as high rates of acute graft rejection have been shown in systematic reviews.

Key Points continued

3. The authors concluded that patients with a kidney graft from a deceased donor can be administered dual IO safely, and can achieve good cancer response and graft tolerance. To aid the selection and monitoring of patients with a renal graft, predictive biomarkers for graft rejection following IO would be beneficial.

BACKGROUND

Melanoma is the third most common skin cancer in the UK.[1] Checkpoint inhibitors (CPI) have revolutionised the treatment of melanoma.[2-4] Dual immunotherapy (IO) with anti-cytotoxic T lymphocyte antigen 4 and anti-programme cell death protein 1 agents is associated with improved median progression-free survival.[5,6] Clinical trials with CPIs have typically excluded patients with solid organ transplant due to concerns of organ rejection and loss.[7-9] Several cases of acute graft rejection after the use of CPIs have been reported.[10] This paper details the case of a patient with a renal transplant secondary to polycystic kidney disease and a diagnosis of relapsed BRAF-mutant melanoma, for whom dual IO was used and good treatment response and renal graft preservation were achieved.

CASE PRESENTATION

A 58-year-old female with a medical history of polycystic kidney disease had undergone an allograft kidney transplant from a deceased donor in 2009, and had since remained on an immunosuppressive regime of prednisolone (10 mg, once daily) and ciclosporin (150 mg, twice daily [BD]). The patient then had a left upper arm melanoma confirmed 2 years after the transplant, for which they underwent a complete resection with no residual malignancy. In 2018, the patient detected a lump in their right axilla, but was otherwise well. On examination, the patient was stable, but had a palpable right axillary mass without regional lymphadenopathy. An ultrasound-guided biopsy of the lump confirmed melanoma Stage IB (T2aN0M0). No metastases were found in the staging CT scan.

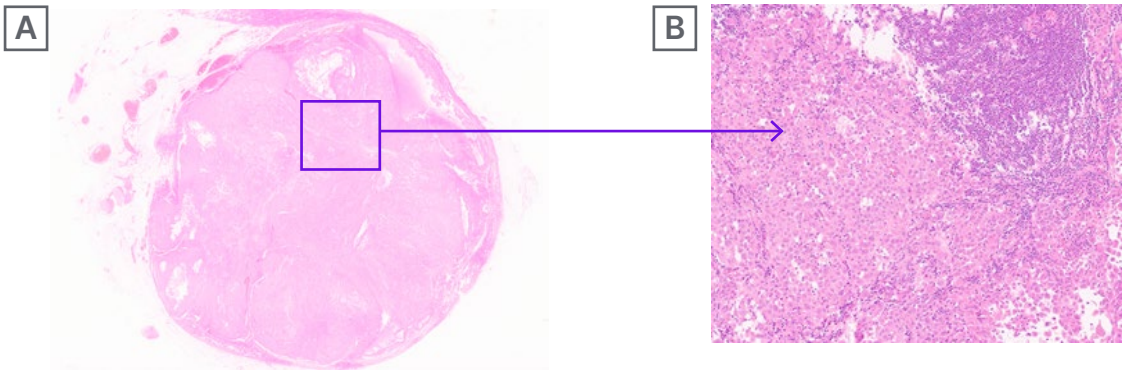
The patient underwent an axillary clearance; no adjuvant therapy was available at the time.

The patient then developed pain 8 months later, and a further right axillary lump was noticed. A restaging CT scan confirmed metastases to the liver and lungs. Biopsy of the left axillary lymph node confirmed BRAF-mutant melanoma (Figure 1). The treatment options available were dual IO, the standard first-line treatment for BRAF-mutant metastatic melanoma, or alternatively targeted therapy with dabrafenib and trametinib. Due to the patient's renal graft and the evidence available regarding graft-rejection risk, the patient was started on targeted therapy as this was thought to have a lower risk of graft loss.[11]

After five cycles of the targeted therapy, a restaging CT scan demonstrated a partial response. However, the patient became acutely unwell with severe back and abdominal pain after 11 months of targeted therapy. CT imaging confirmed extensive disease progression, this time including brain metastases. The patient required admission for symptom control of the rapidly progressive disease. They then gave consent for in-patient dual IO, clearly stating the high risk of graft loss. As a result of the strong evidence of graft loss with the use of IO in systematic reviews, it was anticipated that the patient would likely lose the grafted kidney.[12-15] Single agent IO was considered and discussed with the patient, however, in view of extensive burden of the BRAF-mutant disease and expected poor prognosis, the patient made an informed decision to undergo dual IO with ipilimumab and nivolumab.

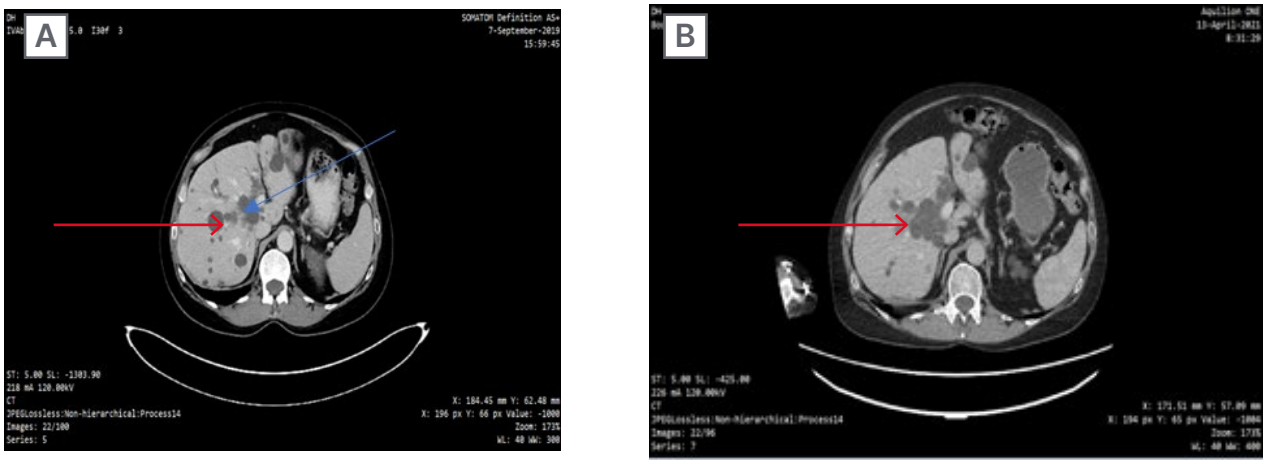
The patient made an informed decision to consent to treatment despite the risks of graft loss and the potential requirement for dialysis, which were highlighted to them. Due to their declining performance status, therapy was commenced as an inpatient procedure with close monitoring of renal function. After discussion with the renal team, the dose of ciclosporin was reduced from 150 mg BD to 50 mg BD,

Figure 1: Microscope images of a left axillary lymph node at x10 magnification (A) and x100 magnification (B).



The box indicates the invasion of the node by BRAF-mutant metastatic melanoma, which can be seen in (B).

Figure 2: Abdominal CT imaging confirming extensive disease, both for pre-dual immunotherapy (A) and for post-dual immunotherapy (B), with visible but not active lesions (indicated by the arrows).

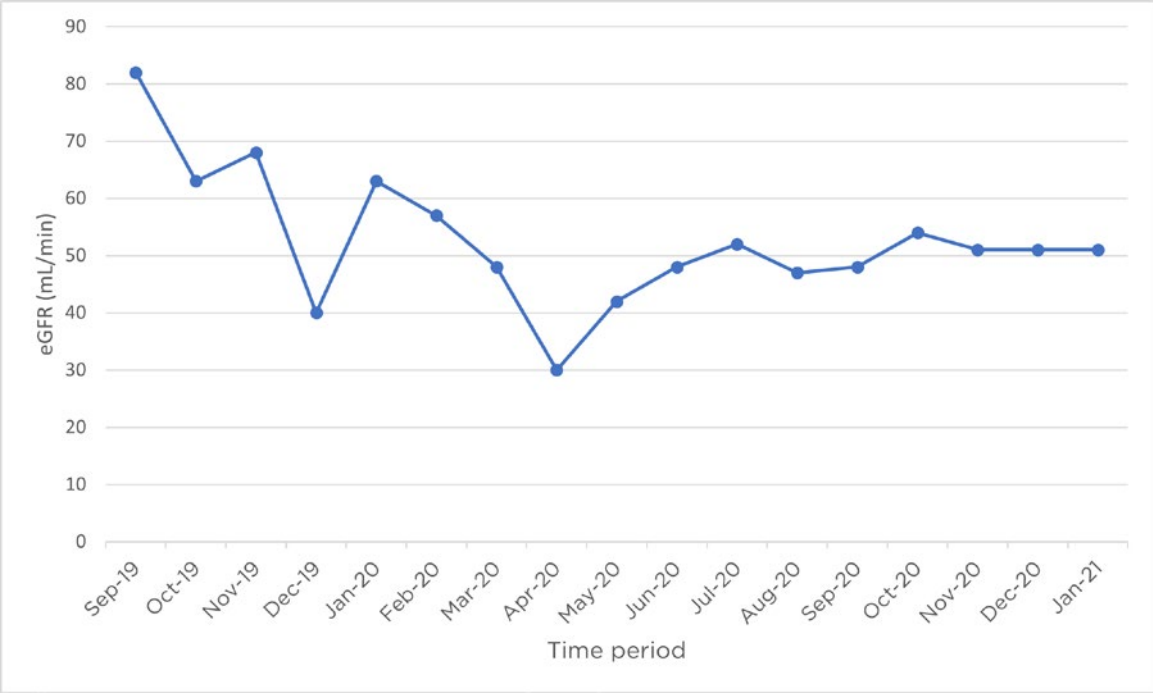


while the dose of prednisolone continued at 10 mg per day. The patient received all four cycles of dual IO (nivolumab plus ipilimumab) and further maintenance doses of nivolumab. The patient also received gamma knife therapy to the metastatic brain disease. They clinically improved after spending some time on the ward and were later discharged. The patient's renal function was closely monitored and remained within acceptable limits (Figure 3).

FOLLOW-UP

CT staging at the end of four cycles confirmed a complete radiological response. The CT scan taken in April 2021 (Figure 2) confirmed a continued response with inactive lesions and graft preservation (Figure 4), and there were no active brain lesions. At the time of writing, the patient was clinically well, and although they tired more easily than before treatment, their pain was improved, they did not require regular analgesia, and they had a Eastern Cooperative Oncology Group (ECOG) performance status of 2.

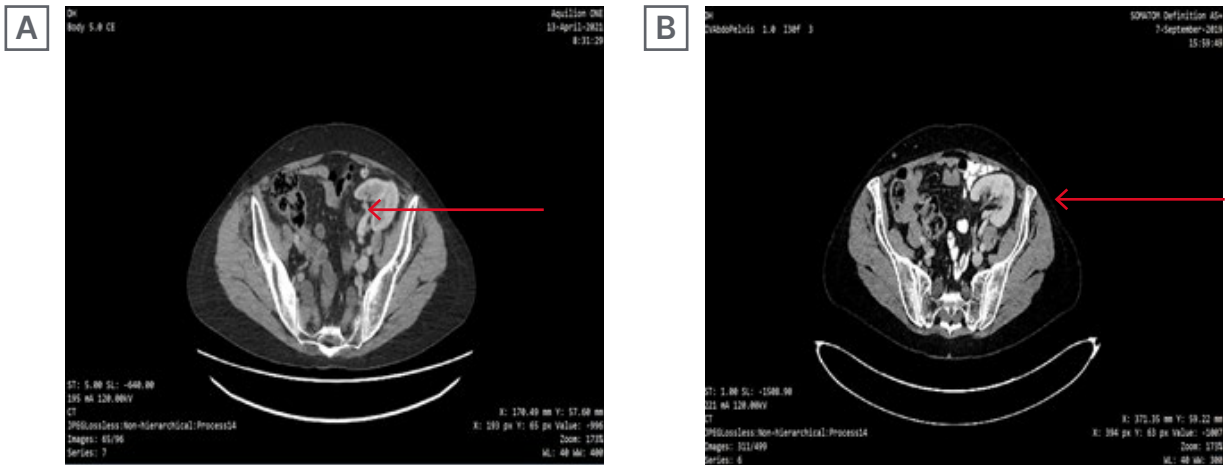
Figure 3: The estimated glomerular filtration rate over time as a guide for the renal function of a patient who had received a renal graft.



The patient was receiving dual immunotherapy for rapidly progressive BRAF-mutant metastatic melanoma. The graph shows an initial decline after commencing dual immunotherapy, but plateaus around 50 mL/min thereafter.

eGFR: estimated glomerular filtration rate.

Figure 4: Anteroposterior abdominal CT scans showing the renal graft (indicated by the arrow) before (A) and after (B) dual immunotherapy.



CONCLUSION

Dual IO in the management of melanoma has been shown to have a better 5-year survival rate than when using a single agent.[7,16-18] The use of dual IO in patients who have had a solid organ transplant remains challenging: systematic reviews have shown high rates of acute graft rejection of up to 81% across all solid organ grafts.[12] In renal grafts alone, rates of up to 48% acute graft rejection have been reported, with a median rejection time of 21 days; therefore, the use of dual CPIs in patients who have had a transplant has been limited.[12,19,20]

This paper outlines the case of a patient with rapidly progressive melanoma for whom dual IO was safely delivered, resulting in complete response. The patient's kidney function remained within acceptable limits, and their renal graft was preserved. The importance of enabling the patient to make informed treatment choices, and of balancing the benefits of therapy with the risks of predictable side effects, is key.[21] Dose modification of immunosuppressive therapy has been demonstrated to be safe, without leading to graft rejection or loss of IO efficacy.

This case demonstrated that dual IO can be safely administered in patients with a kidney graft from a deceased donor, and can achieve good cancer response and graft tolerance. However, predictive biomarkers for graft rejection following IO would aid the selection and monitoring of patients with a renal graft. This case indicated that CPIs can be considered in patients with solid organ grafts and can achieve graft preservation. Patients should receive counselling regarding the potential of graft loss, and close monitoring of renal function is recommended. Dual IO remains the first-line treatment for patients with BRAF-mutant metastatic melanoma. For patients who have received a renal transplant, the optimal sequencing of treatment is yet to be determined.

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Primary Pleural Schwannoma as Incidental Findings: An Unusual Case Report

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Abstract

Schwannomas are neurogenic, benign, slow growing tumours that originate in Schwann's intersecting fascicles of the peripheral nerves. This article reports the case of a previously healthy 51-year-old male, where a 9.0×6.5 cm (3.5×2.5 in) sized pleural mass was found after the patient presented a haemoglobin level of 3.2 g/dL in a blood smear at a routine check-up. The patient had no relevant medical, family, or psychosocial history and presented no relevant symptoms.

After diagnosing and treating a chronic haemorrhoidal disease, the tumour was removed and studied. Demonstrating histopathological and immunohistochemical features of schwannoma, its uniqueness and rarity after successful management of the disease contributes to the medical literature as a histopathologic diagnostic standard and a therapeutic option for future cases of pleural schwannoma.

Sharing the histopathologic features of schwannoma is not common, usually, the available case reports are lacking. The patient was able to recover fully and had no significant or severe complications associated with medical care.

Key Points

1. A schwannoma is a slow-growing, neurogenic, and benign tumour, which originates within the peripheral nerves, on Schwann's intersecting fascicles. They are usually located in the head, neck, and flexor surfaces of the extremities; this case reports a rare case of a pleural schwannoma.

2. Histopathologic reporting of schwannomas notes microscopic Antoni A and B areas in most cases of pleural schwannoma, where Antoni A shows areas of hyper-cellularity with Verocay bodies, and Antoni B represents areas of myxoid hypocellularity exhibiting degenerating changes such as cystic formation, calcification, haemorrhage, xanthomatous infiltration, and hyalinisation.

3. Histopathologic diagnosis should be standard practice, as the histologic differential diagnosis includes spindle cell tumours, such as neurofibroma, leiomyoma, leiomyosarcoma, and calcifying aponeurotic fibroma.

INTRODUCTION

Schwannomas are neurogenic, benign, slow growing tumours that originate in Schwann's intersecting fascicles of the peripheral nerves. Usually, schwannomas are located in the head, neck, and flexor surfaces of the extremities. They are not usually located in the mediastinum and retroperitoneum. Most intrathoracic neurogenic tumours originate in the posterior mediastinum and only 5.4% are in the chest wall.[1]

Approximately 95% of the pleural dependent tumours are malignant, most of which present as a product of metastasis. Needless to say, benign pleural tumours are very unusual and, among them, schwannoma is much less frequent.[2]

To the best of the author's knowledge, around 20 pleural schwannoma cases have been reported in the medical literature to date.

Herein, this article reports the case of a previously healthy 51-year-old male where a 9.0×6.5 cm (3.5×2.5 in) sized pleural mass was found after the patient presented with a haemoglobin (Hb) level of 3.2 in blood smear at a routine check-up. The tumour was removed and studied. Demonstrating histopathological and immunohistochemical features of schwannoma, its uniqueness and rarity after successful management may contribute to the medical literature as a histopathologic diagnostic standard and a therapeutic option for future cases of pleural schwannoma.

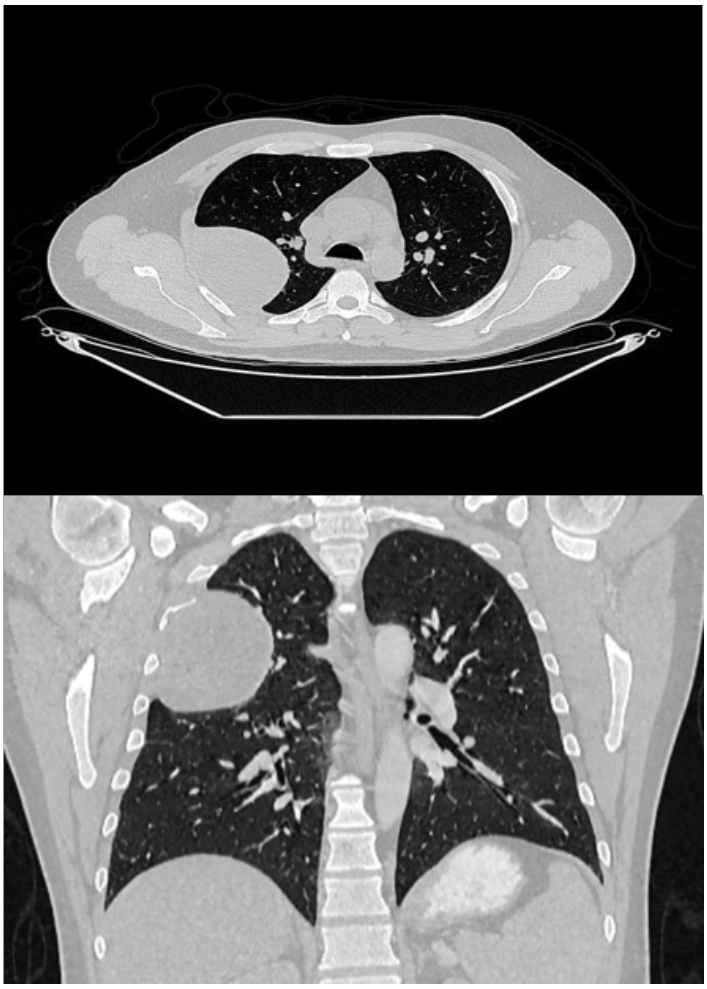
CASE REPORT

A previously healthy 51-year-old male, with no relevant medical, family, and psychosocial history, presented at the emergency room asymptomatic due to a 3.8 g/dL Hb laboratory finding in their routine check-up. They had been a smoker for 20 years, with a Global Tobacco Index score of 5 packs/year and no history of asbestos exposure, thoracic radiation, or recent trauma. During discussions with the patient, a history of haemorrhoidal disease was identified, consisting in chronic anal bleeding. The patient achieved haemodynamic stabilisation after the Hb results, and a blood pack transfusion was performed. After a series of transfusion protocols over several days, a 10 g/dL haemoglobin level was achieved.

During the routinary haemorrhoidectomy pre-operation exams, anterior-posterior and lateral chest X-rays showed an unexpected 9.0×6.5 cm (3.5×2.5 in) round-like, radiopaque mass in the right chest wall, between the middle and the superior lobe, which needed further study. The authors decided that a thoracoabdominal CT scan was needed in order to evaluate the extension. The study showed a round, encapsulated 10.0×6.5 cm (4.0×2.5 in) and hypodense pleural mass in the right posterosuperior hemithorax, which was full of liquid content, with probable infiltration to the third rib, in intimate contact with the parietal pleura (Figure 1).

A haemorrhoidectomy was performed without any complications. While the patient was recovering from the procedure, the unknown pleural mass was being held by the thoracic surgery and the medical oncology units for evaluation. Based on imaging characteristics and frequent epidemiological pleural tumours, multiple different diagnoses were considered, including a variety of benign and malignant neoplasms. After another transfusion protocol, which continued elevating the patients' Hb levels up to 12 mg/dL, the patient was offered a right thoracic exploration using minimally invasive techniques, which they accepted in the following days.

Figure 1: Axial and coronal IV contrast, enhanced high resolution chest CT scan.



MANAGEMENT AND OUTCOME

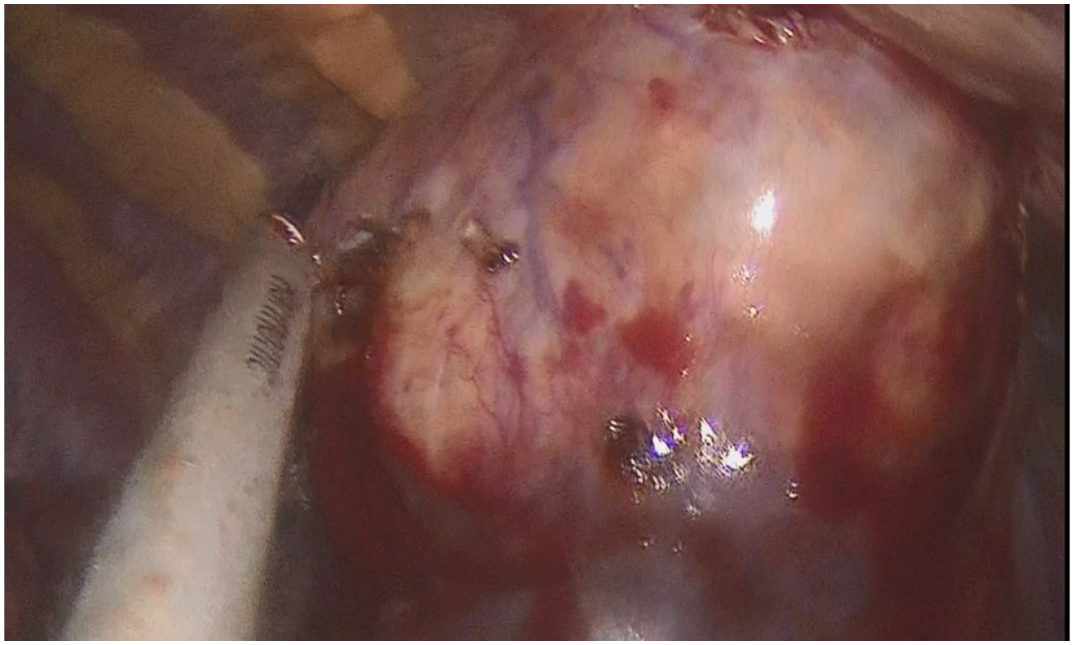
In the minimally invasive right thoracic exploration, a 10 cm pleural tumour was observed in the right apex, which was adhered to the upper lobe and to the thoracic wall (Figure 2). Dissection of the lung parenchyma tumour was initiated, and it started to present diffuse bleeding, so a conversion to a right anterior thoracotomy was performed as a result of the lack of visibility. Due to the adherence of the tumour to the pulmonary parenchyma, a non-anatomical segmentectomy of the right lobe was performed.

A specimen was sent for an intraoperative study, discarding a solitary fibrous tumour and a synovial sarcoma, while reporting a solitary pleural fibroma. After the intraoperative pathology reported a lack of malignancy information, the lung parenchyma was confronted and an endopleural tube was placed before closing.

After the surgery, the patient stayed in the intensive care unit for 2 nights, with the intention to keep close monitoring. They presented a satisfactory evolution and control chest X-rays were taken 72 hours after the procedure, which showed a complete lung re-expansion. The patient was discharged from the intensive care unit and was transferred to the internal medicine ward.

The final pathology report arrived a couple of days later and stated the macroscopic gross findings: it was fresh and partially open; it weighed 118 g and measured 10.0×7.5×6.5

Figure 2: Schwannoma during the minimally invasive surgery before converting it to an open thoracotomy



cm; it was ovoid, reddish, and smooth; when it was cut, it was a cystic solid, greyish–white and haemorrhagic, with a soft consistency. The immunophenotype was compatible with schwannoma, with a low cellular replication (Ki-67: <1%) and was negative for malignant neoplasia. The microscopic appearance of the haematoxylin and eosin-stained resected tumour images can be seen in Figure 3.

The patient stayed in hospital for a week, where their endopleural tube secretions, Hb, and haematocrit levels being closely monitored. After a day without endopleural secretions, the endopleural tube was removed. The day after that, the patient was discharged from the hospital after 21 days with no significant medications or further treatment adherence needed. They did not present any lack of tolerability after the surgical treatment. In the follow-up consultations, the patient had a full and successful recovery, a conclusion that was determined by assessing and comparing daily life activity limitations before and after the procedure, which had no significant change. There were no adverse or unanticipated events related to the treatment.

DISCUSSION

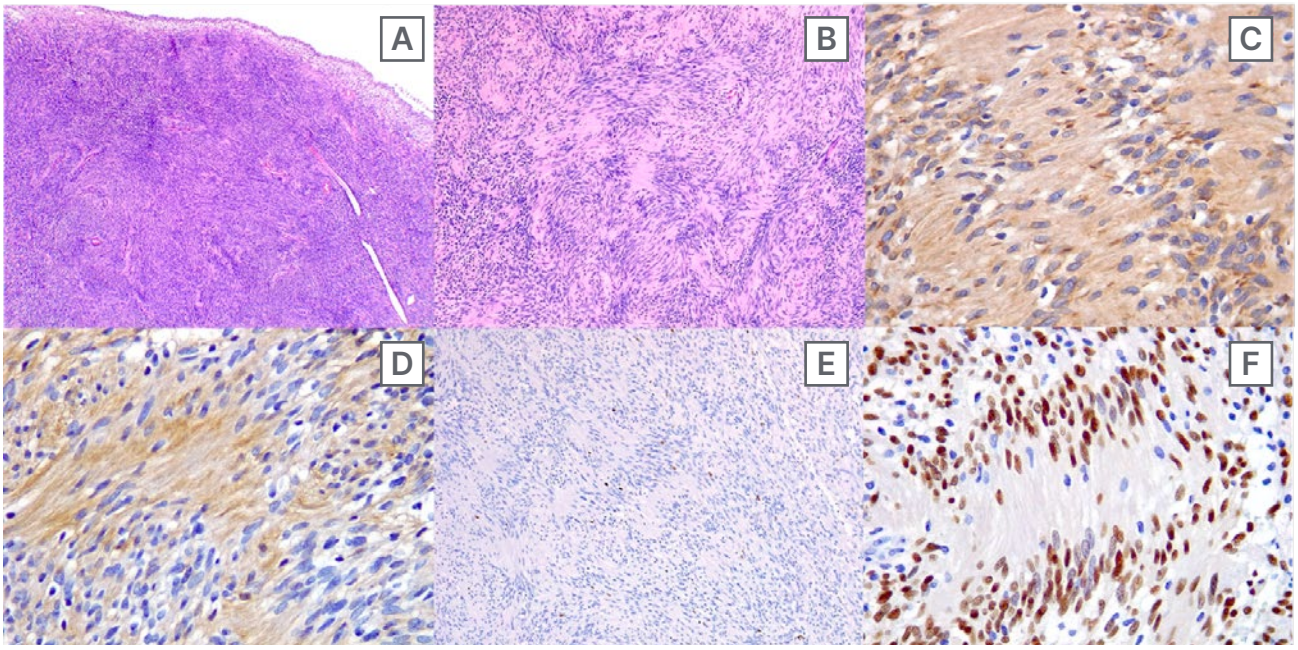
Schwannomas are benign, well encapsulated, slow growing, nerve intersecting fascicle tumours, which are composed exclusively of Schwann cells.[3] They often present as a single tumour and are most commonly found in patients between 20–50 years old. They are found incidentally, since they do not present with any specific symptomatology.[4]

Around 90% of the schwannomas are sporadic, although they occur in specific syndromes like neurofibromatosis Type 2, schwannomatosis, and Carney complex.[4,5] Some genetic studies have suggested that chromosome 22 plays an essential role in schwannoma development.

Schwannomas have a predilection for persons between the ages of 50–60. In addition, males are more commonly affected than females.[6] Generally, these tumours are located in the head, neck, and flexor surfaces of the extremities. They are not often located in the mediastinum and retroperitoneum.

Pleural schwannomas are extremely rare neoplasms of the thoracic cavity,[5] and less frequently in the pleura, with around 20 cases

Figure 3: Microscopic appearance of haematoxylin and eosin stained resected tumour.



A and **B**) Variable orientated cells, which in places appears to be arranged in intersecting fascicles. Cells show a mild degree of variation in nuclear hyperchromasia, mild nuclear pleomorphism, and mild anisonucleosis. **C**) Bcl-2. **D**) Neural cell adhesion molecule. **E**) Ki-67. **F**) SOX-10.

reported in the medical literature. Schwannomas grow slowly and, since they are generally asymptomatic, other differential diagnoses cannot be considered; however, larger tumours may compromise adjacent structures and cause cough, dyspnoea, and chest pain.[7,8] Therefore, the vast majority of pleural schwannomas are discovered incidentally during investigations for other complaints.[9]

Unfortunately, plain radiographs are not specific enough, which is why MRI or CT scans can be used as diagnostic tools as well, to clarify the differential diagnosis between solitary pleural lesions, such as lipomas, liposarcomas, haemangiomas, elastofibromas, single metastatic lesions, mesotheliomas, fibrous tumours, and other neurogenic tumours.[2,6]

Histologic differential diagnosis includes spindle cell tumours, such as neurofibroma, leiomyoma, leiomyosarcoma, and calcifying aponeurotic fibroma. Antoni A and B areas are found microscopically in most cases of pleural schwannoma. Antoni A shows areas of hyper-cellularity with Verocay bodies. Antoni B represents areas of myxoid hypocellularity exhibiting degenerating changes such as cystic formation, calcification, haemorrhage, xanthomatous infiltration, and hyalinisation.[9]

The preferred treatment consists of surgical therapy, consisting in local resection of the tumor.[10] Stereotactic radiosurgery is useful if the growing tumour is near vital blood vessels or nerves.[11] In all schwannoma cases, an intraoperative frozen section should be carried out for histopathological examination and immunohistochemical staining in order to reach an accurate diagnosis.[12] Prognosis is excellent and recurrence after resection is uncommon.

Schwannomas are rare; however, the authors have specifically discussed pleural schwannomas, which they say is an extremely rare disease, where there is not much literature available.

As seen above, the medical multidisciplinary team had all the necessary resources in order to provide an excellent diagnosis and treatment, which is not always the case when reporting a rare disease or case. Sharing the histopathologic features of schwannoma is not common and usually the available case reports lack images.

The patient was able to recover fully and had no significant or severe complications associated with medical care.

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Thyroid Papillary Carcinoma and Hyperthyroidism: A Case Study

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Abstract

Background: Concurrent thyroid cancer and hyperthyroidism is a rare finding. The frequency of this association is very variable. A rare case of papillary thyroid cancer associated with hyperthyroidism is described here.

Case: A 49-year-old male presented to the authors' outpatient clinic with complaints of a painless left-sided anterior neck swelling that had persisted for the past 8 months. He also reported weight loss for the same duration. The anterolateral swelling was non-tender, asymmetrical, mobile, and rubbery.

Investigations: Biochemical analysis confirmed hyperthyroidism. Ultrasound examination of the neck showed a well-defined, solid, and cystic lesion in the left lobe and isthmus of thyroid gland. The solid portion had few specks of calcification. A radioactive thyroid scan showed increased tracer uptake in the left lobe. Papillary carcinoma of thyroid origin was discovered after fine-needle aspiration of the left anterior cervical lymph node. After preparation, a total thyroidectomy was done. Examination of histopathology confirmed papillary thyroid carcinoma.
Treatment: Following radioactive thyroid ablation, the patient was started on suppressive doses of thyroxine daily.

Conclusion: Although thyroid cancer with hyperthyroidism is a rare finding, it should not be disregarded. To avoid missing this unusual yet uncommon discovery, a detailed history and physical examination should be performed, as well as all required investigations.

Key Points

1. Papillary thyroid cancer coexisting with hyperthyroidism is a rare concurrent finding. Thyroid carcinoma and hyperthyroidism are thought to be related conditions and therefore pose significant diagnostic, therapeutic, and prognostic challenges.

2. Concurrent thyroid cancer and hyperthyroidism can present as persistent, painless, left-sided anterior neck swelling with reported weight loss over a period of multiple months.

3. Detailed patient history alongside physical examinations is required to identify unusual findings such as thyroid cancer with hyperthyroidism. All thyroid nodules should be assessed with a high degree of suspicion for malignancy.

Thyroid cancer is the most common malignant endocrine tumour in the world, but it only accounts for 1% of all cancers.[1] The most common form of thyroid cancer is papillary thyroid cancer (PTC).[2] High-dose external radiation exposure is the most significant risk factor of PTC. Radiation causes genetic lesions that lead to neoplastic transformation.[3] The majority of radiation-induced PTC cases have *RET*/PTC fusions, which are established genetic rearrangements.[4]

Thyroid hormone development is excessive in patients with hyperthyroidism. Graves' disease, toxic multinodular goitre, thyroiditis, and exogenous thyroid intake are all common causes of hyperthyroidism.

The coexistence of thyroid cancer and hyperthyroidism is uncommon. A review of literature reports the weighted average of prevalence of malignancy to be 3.1% amongst solitary hyperfunctioning nodules.[5] Furthermore, thyroid carcinoma and hyperthyroidism are thought to be related conditions, and, therefore, pose significant diagnostic, therapeutic, and prognostic challenges.[5]

Unfortunately, due to a lack of population-based data, determining the incidence of thyroid carcinoma in Pakistan is difficult.[6]

A rare case of PTC and concurrent hyperthyroidism is reported here.

CASE DESCRIPTION

A 49-year-old male with a swelling on the left side of his neck presented to the authors' outpatient clinic. The swelling was painless and had been gradually increasing in size over 8 months. The patient also reported a significant weight loss of 5–6 kg over the same duration. There were no associated complaints of dyspnoea, dysphagia, hoarseness, heat or cold intolerance, palpitations, changes in urinary or bowel habits, or a past medical history of similar complaints. He was a non-smoker, who denied ever having been exposed to radiation in the head and neck area during his childhood or adolescence. The patient also denied having any family history of thyroid dysfunction or cancer.

The physical examination showed a middle-aged man who was afebrile, had a resting pulse rate of 96 beats per minute, a respiratory rate of 28 breaths per minute, and a blood pressure of 128/70 mmHg. On ophthalmological examination, there was no exophthalmos or lid lag on eye movement. There were no fine tremors and no voice hoarseness.

No thyroid nodule was palpable on neck examination. However, there was a palpable left anterolateral cervical lymph node. This node was asymmetrical, rubbery, mobile, non-tender, and not attached to any overlying or underlying tissue.

Complete blood count was normal. Thyroid function test revealed a thyroid-stimulating hormone (TSH) of 0.010 mIU/L (normal range: 0.4–4.0 mIU/L) and a free T4 of 2.6 ng/dL (normal range: 0.7–1.8 ng/dL). Ultrasound examination of the neck showed a well-defined, cystic, and

solid lesion in the left lobe and isthmus of the thyroid gland, measuring 21×11×16 mm. The solid portion measured 9×6 mm, with few specks of calcifications. Sub-centimetre lymph nodes were noted in Levels I, II, IV, and V of the neck bilaterally. The largest lymph node was seen on the left side, which measured 9 mm.

An ultrasound examination of the neck showed a well-defined cystic and solid lesion in the left lobe and isthmus of the thyroid gland (Figure 1).

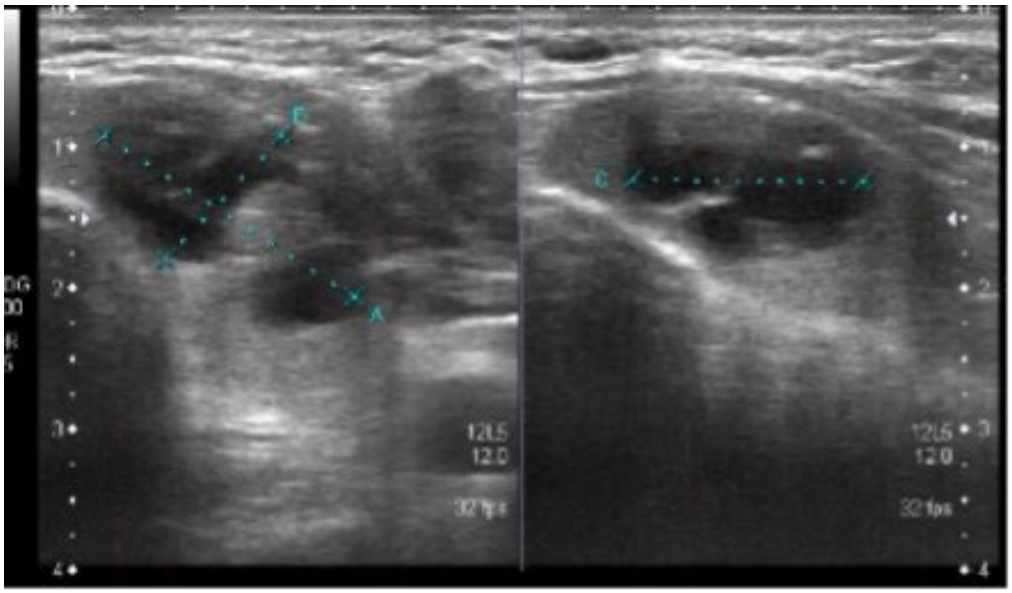
A radioactive scan was requested to determine thyroid functioning because the thyroid function tests were consistent with hyperthyroidism. These findings were consistent with the presence of a functional nodule. Increased tracer uptake was seen in the left lobe during the scan. The patient was subsequently started on carbimazole and propranolol. The hot nodule was not biopsied because of the very low risk of malignancy. Fine-needle aspiration of the left anterior cervical lymph node was performed to evaluate for sinister pathologies like tuberculosis, lymphoma, or metastasis. The histopathological report revealed metastatic papillary carcinoma of thyroid origin.

Complete thyroidectomy with radical neck dissection was planned. Propranolol 40 mg three times daily and carbimazole 30 mg/day were instituted to prevent a potential thyroid storm during surgery. The patient underwent the surgery without any complications. The presence of multicentric oval nuclei with grooving on histopathological examination confirmed PTC. The specimen sent included the thyroid gland (right lobe, left lobe, and isthmus); Level II, III, and IV lymph nodes on the right; Level II, III, IV, and V on the left; and Level VI of the neck. Bifocal PTC was identified with tumour size of 2.0×1.7×1.0 cm in isthmus and 0.5×0.4×0.3 cm in the left lobe. All lymph nodes were identified as being negative for the disease, except one lymph node in the left Level III measuring 0.1 cm, with no extra nodal extension. Pathological tumour-node-metastases was reported as pT1b N1b.

A haematoxylin and eosin stain of thyroid tissue showed classical PTC, with the cuboidal epithelium exhibiting nuclear clearing, crowding, and intranuclear groove (Figure 2). Calcification is seen at the lower-left corner.

One lymph node in left cervical Level III was involved by the tumour. The size of the nodal metastasis was 0.1 cm with no extra nodal extension. All of the other lymph nodes were negative for metastasis.

Figure 1: Ultrasound of thyroid.



Post-operative thyroid function test revealed a TSH of 29.4 mIU/mL, thyroglobulin of 0.04 ng/mL (normal range: 20–25 ng/mL), and anti-thyroglobulin antibody of 0.26 IU/ml (normal range: less than 20 IU/mL). The patient received a post-operative dose of radioactive iodine (RAI) 150 mCi. Post-ablative thyroid scan findings were suggestive of functioning residual thyroid tissue in the neck with bilateral cervical lymphadenopathy. To hold TSH below 0.1 mIU/mL, the patient was started on a suppressive dose of thyroxine.

DISCUSSION

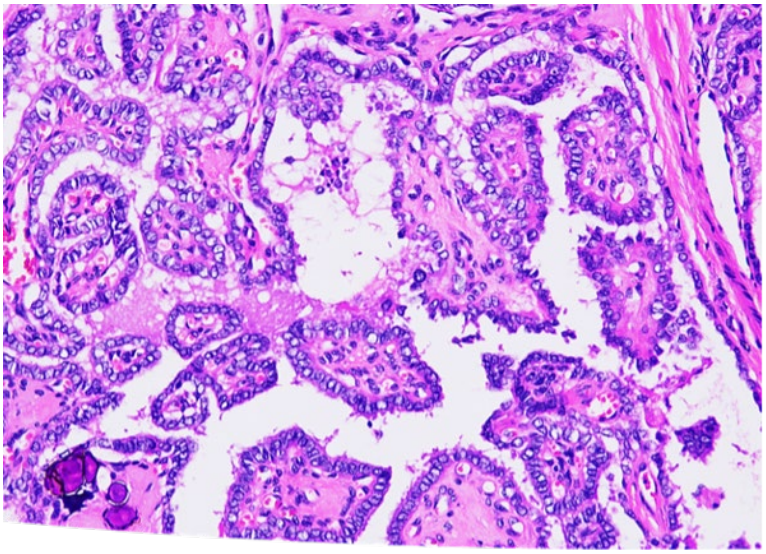
In certain cases, a hyperfunctioning thyroid nodule is thought to rule out thyroid cancer.[7] Thyroid cancer and hyperthyroidism may occur as a result of a fortuitous malignancy in the thyroid gland of a patient with clinical hyperthyroidism, or as a rare case of thyroid cancer presenting with hyperthyroidism.[8]

In patients with hyperthyroidism, the possibility of thyroid malignancy is rare, but should not be disregarded.[9] Several studies have reported cases where thyroid malignancy and hyperthyroidism occur together.[10-12] Diagnosis relies on histopathological and clinical correlation.

The exact cause of thyroid cancer with coexistent hyperthyroidism is unclear. Thyroid carcinoma can cause hyperthyroidism due to somatic mutations in TSH receptor genes. These mutations increase thyroid levels by activating the cyclic adenosine monophosphate cascade, which causes hormone secretion.[9] The combination of mutated TSH receptors and TSH stimulating further growth have been linked to the development of malignancy, but this has not yet been confirmed.[13,14]

Thyroid cancer caused by an autonomous thyroid nodule needs careful consideration and evaluation. Some factors, however, can aid in determining whether hyperthyroidism is caused by primary hyperfunctioning thyroid carcinoma. These include if there is no improvement in thyrotoxicosis after RAI treatment; if ultrasound findings show hypoechoic stable nodules with microcalcifications; or if there is rapid tumour growth.[15] In the authors' case, the patient did not receive RAI for thyrotoxicosis to monitor any positive or negative treatment outcomes. However, the ultrasonographic findings of a solid lesion with few specks of calcifications were suggestive of underlying thyroid malignancy. Family history of thyroid cancer, a prior history of head and neck irradiation, nodules having microcalcifications, irregular margins and taller-than-wide shape, genetic mutations, tumour size greater than 4 cm, fixation to adjacent structures, and signs of tumour invasion have all been identified as additional risk factors for malignancy.[16]

Figure 2: Haematoxylin and eosin stain of thyroid tissue.



Studies point out an increased incidence of follicular thyroid carcinoma (FTC) with concomitant hyperthyroidism. Mirfakhraee et al.[5] reported that out of 77 patients, 28 had thyroid carcinoma in a solitary hyperfunctioning nodule. The FTC subtype accounted for the majority of hyperfunctioning thyroid carcinomas. Similarly, Qiu et al.[17] found that the FTC subtype was prevalent in 60.5% of functional metastatic thyroid carcinomas, with five cases being hyperfunctioning. Patients with metastatic hyperfunctioning FTC have a poor prognosis compared with patients with PTC. As a result, patients with hyperfunctioning thyroid carcinoma tend to have a high prevalence of FTC, with an especially high prevalence among patients with metastatic disease. However, in this study, the hyperfunctioning thyroid carcinoma is of a papillary subtype with a mild clinical picture of hyperthyroidism.

Two studies, however, reported PTC with hyperthyroidism and extensive disease metastasis. The authors attributed the high level of free thyroid hormones to bone metastasis.[18] This explains a relatively innocuous clinical presentation (cervical lymph node involvement with no widespread metastasis) in this case, as the concentration of free thyroxine was within the higher range of the normal level.

The mainstay treatment of thyroid carcinoma with concomitant hyperthyroidism is surgery. This method not only confirms the condition after a pathological examination, but it also removes the cancer and resolves the use of anti-thyroid drugs as a hyperthyroidism treatment, as these are often implemented to prevent a potential thyroid storm. Other options for treatment include RAI fractionation or minimally invasive local ablation.[19] In patients with primary hyperfunctioning thyroid carcinoma, RAI is primarily used as a treatment alternative after surgery.[20]

CONCLUSION

Thyroid carcinoma and hyperthyroidism coexisting is an uncommon occurrence. Each thyroid nodule should be assessed with a high index of suspicion for malignancy. To prevent ignoring this unusual but important association, thorough medical history and physical examinations should be undertaken, as well as all other necessary investigations.

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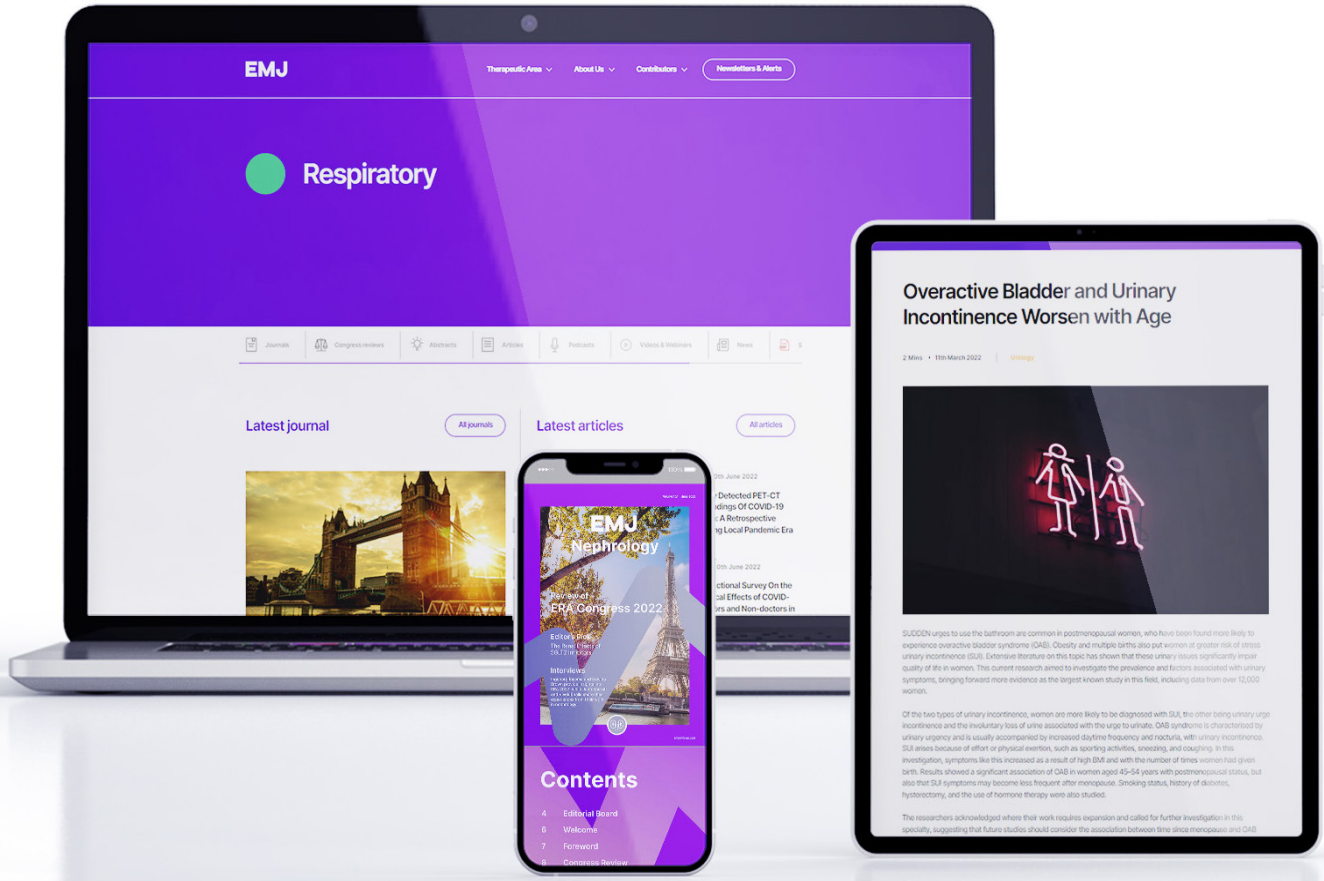

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