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ESMO Congress 2021

EDITOR'S PICK

More than FOLFOX and FOLFIRI: The Management of Metastatic Colorectal Cancer in the Era of Precision Oncology

ABSTRACT REVIEWS

Sharing the latest research findings and knowledge from leading experts in oncology from the European Society for Medical Oncology (ESMO) Congress 2021

Contents

"Shared in this issue is an engaging review of the event, alongside an exciting in-house feature covering the latest advances and future of clinical trials in the field of oncology."

Spencer Gore, CEO

+ ARTICLES

Editorial Board

VIEW IN FULL ←

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EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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EMJ Oncology 9.1

Welcome

Dear Readers,

I am delighted to welcome you to the latest issue of *EMJ Oncology*, which brings the latest updates and advancements in the field. This issue offers peer-reviewed articles, and an independent review of the European Society for Medical Oncology (ESMO) Congress 2021 for those that could not attend. This eJournal also includes a selection of abstract reviews from ESMO 2021, written by the presenters themselves to provide you with the latest updates in oncology through high-quality content.

Covering topics including hepatic metastases, the role of Aurora A in radioresistance, and the management of lower limb soft tissue sarcomas, this issue is packed with compelling peer-reviewed articles. This year's *EMJ Oncology* Editor's Pick is an engaging review entitled 'More than FOLFOX and FOLFIRI: The Management of Metastatic Colorectal Cancer in the Era of Precision Oncology', by Jácome and Johnson.

Once again, we attended the esteemed ESMO Congress 2021 which was packed full of interactivity and late-breaking research in oncological science. Shared in this issue is an engaging review of the event, alongside an exciting in-house feature covering the latest advances and future of clinical trials in the field of oncology. Despite its virtual format, the ESMO Congress successfully brought together experts in the field from over 143 countries for an enhanced virtual experience.

With almost 2,000 abstracts being presented at the ESMO 2021 congress, we certainly were not at a shortfall of exciting sessions to attend. Our selected abstract summaries covered topics including colorectal cancer screening during the pandemic, the effect of the COVID-19 vaccine in patients undergoing cancer treatment, and the BONSAI trial for renal cell carcinoma.

All that remains for me now is to thank the Editorial Board, authors, interviewees, and Editorial team for continuing to make the publication of these journals possible. I hope that *EMJ Oncology 9.1* continues to inspire budding developments in the field, and that this issue is enjoyed by all of our valued readers.

Spencer Gore

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

Dear Colleagues,

Welcome to the newest edition of *EMJ Oncology.*

In this interesting edition, a variety of important papers examine methods of supporting patients throughout their treatments and cancer journey whatever their diagnosis might be.

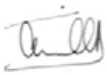
The European Society for Medical Oncology (ESMO) Congress is held annually in different locations around Europe. This year's congress was held in Paris, but due to the current climate was an enhanced virtual experience designed to reach clinicians, researchers, patient advocates and healthcare industry representatives from around the world. This issue of *EMJ Oncology* will offer readers a summary of some of the fascinating content presented at the ESMO 2021 Congress which brought together some of the worlds leading experts in oncology.

The papers included in this edition examine a wide variety of topics from the discipline of oncology. One article involves an examination of a minimally invasive surgical approach to hepatic metastases of colorectal cancer and another a discussion of potential methods to mitigate limb amputation in sarcoma patients with neurovascular involvement. Alongside this, the journal includes a paper describing efforts made to reduce the risk of ovarian failure in a case of radiation to treat cervical cancer.

Finally, biology of cancer is the basis of the two last papers, an analysis of with the role of Aurora kinase in radio resistance and precision oncology in the management of metastatic colorectal cancer, an emerging but promising field.

As always, I hope you will enjoy these articles which hold real-world clinical implications in supporting the treatment of patients and in evolving the field of cancer biology.

Kind regards,



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Congress Review

Review of the European Society for Medical Oncology (ESMO) Congress 2021: An Enhanced Virtual Experience

Location: Paris, France

Date: 16th–21st September 2021

Citation: EMJ Oncol. 2021;9[1]:11-23. Congress Review.

AN INTERNATIONAL COLLECTIVE of oncology clinicians and researchers came together to share the most recent updates in patient care and research at the European Society for Medical Oncology (ESMO) Congress 2021. Considering the current climate, ESMO 2021 was designed as an enhanced virtual experience, allowing more than 23,000 to attend from their homes, with an audience of 300 in-person in Paris, France. The mixed virtual format allowed the advancements, networking opportunities, and collective understanding of oncological care to be communicated to audience members around the world whilst maintaining the traditional congress atmosphere. ESMO President, Solange Peters, described this year's congress as "the place where oncology experts come together, as a community."

The opening session was chaired by Peters who used her time to introduce the launch of ESMO's new initiative the International Cancer Foundation (ICF). By 2040 cancer incidence could rise to almost 30 million cases, with the largest increase seen in low- and middle-income countries. The ICF aims to bring cancer care across borders, spreading effective diagnosis, treatment, cure, and follow-up care. The ICF is the embodiment of what cancer care means to ESMO, supporting doctors everywhere and expanding the organisations reach to regions where optimal cancer care might currently seem unimaginable. Peters explained that the ICF would focus on prevention, patient resources and the provision of new fellowships, all supported by the full weight of the ESMO communities' expertise in oncology and cancer care.

The ESMO 2021 Congress featured 1,989 abstracts as well as 68 that were classed as late breaking abstracts. Several of these abstract authors provided summaries of their research that are included in this issue of *EMJ Oncology*.

"The mixed virtual format allowed the advancements, networking opportunities, and collective understanding of oncological care to be communicated to audience members around the world whilst maintaining the traditional congress atmosphere."

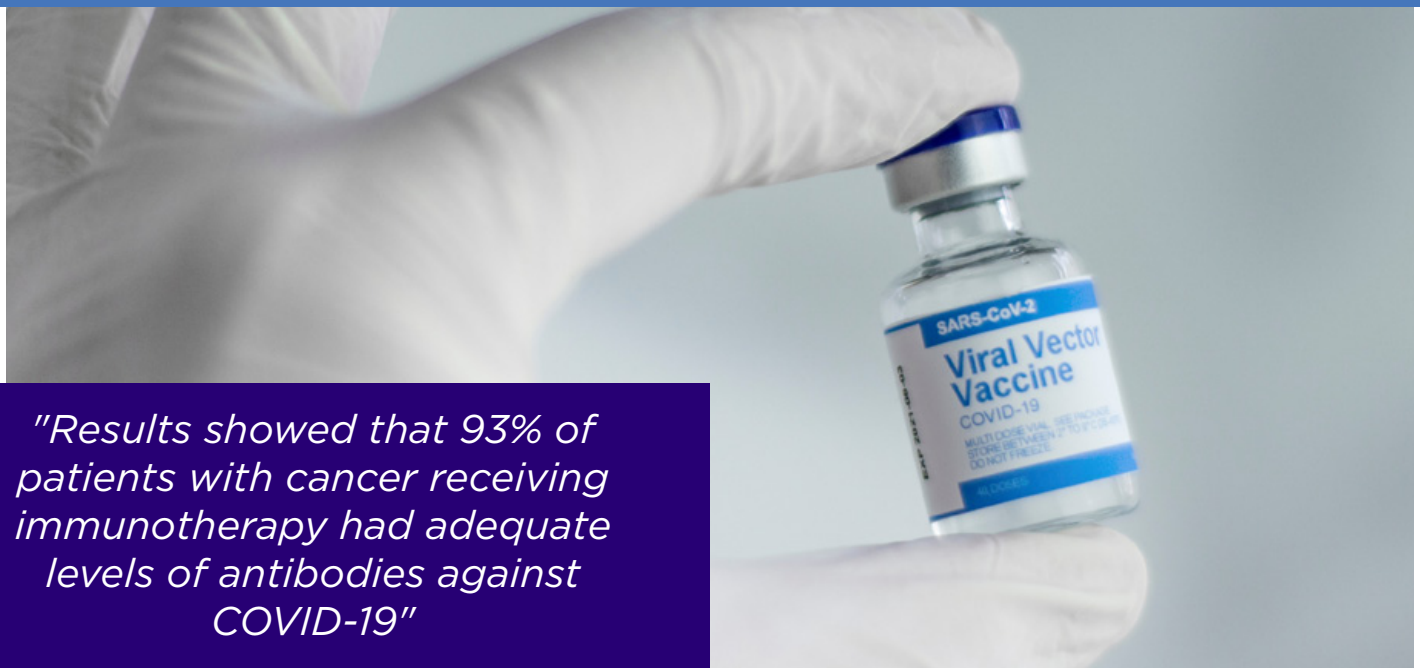
The featured abstracts range from an analysis of the efficacy of COVID-19 vaccines in patients with cancer to repurposing cancer drugs to prolong survival in prostate cancer patients to a more holistic analysis of the frequent exclusion of children from their parent's cancer journey.

The five-day congress featured more than 450 speakers, with almost 200 hours of content and 17 special sessions. Pasi Jänne, Scientific Co-chair, ESMO Congress 2021, gave an overview of some of the standout highlights that were showcased over the long weekend. Presidential symposia, presented on Saturday, included a session communicating updates in metastatic breast carcinoma as well as the outcome of adjuvant studies in melanoma. This was followed on Monday by a presidential symposium that spotlighted the rare malignancy pheochromocytoma and paragangliomas. A novel type of session introduced at ESMO 2021 were the controversy sessions. These explored wide ranging topics from molecular profiling in patients with colorectal cancer to the validity of patient derived cancer models in clinical decision making. These were topics that currently provide some degree of controversy in how to best manage patients and the sessions were interactive, allowing the audience both at home and in-person to hear differing points of view and express their own opinions.

The research and achievements of a wide range of clinicians and researchers were highlighted over the course of the congress. However, a particular mention must be given to the winners of the four ESMO awards. These were awarded on behalf of the ESMO community, and the winners were determined by the ESMO Nominating Committee and ESMO Council. The ESMO Award was presented to Lisa Licitra, Interim Director of Medical Oncology, Head and Neck Cancer Department, Instituto Nazionale Tumori, Milan, Italy. The ESMO Award for Translational Research is presented to candidates who are internationally recognised for their outstanding achievements. This year's commendation was awarded to George Coukos, Ludwig Institute for Cancer Research, Lausanne University Hospital, Lausanne, Switzerland. Rebecca Dent, Department of Medical Oncology, National Cancer Centre, Singapore, won the ESMO Women for Oncology Award and Alex A. Adjei, Mayo Clinic, Rochester, Minnesota, USA won the ESMO Lifetime Achievement Award for his work in drug development, focusing on evaluating mechanisms of drug action and synergistic drug combinations.

The ESMO Congress 2021 demonstrated the first steps towards moving back to in-person, traditional medical congresses in the wake of the last 18 months. EMJ looks forward to hopefully welcoming you all in-person next year at the 2022 ESMO Congress in Paris. However, until then, read on for the latest in key scientific insights from ESMO Congress 2021.

ESMO 2021 REVIEWED →



"Results showed that 93% of patients with cancer receiving immunotherapy had adequate levels of antibodies against COVID-19"

COVID Vaccines Successfully Protect Patients with Cancer

UNTIL recently, there was a lack of research as to whether COVID-19 vaccines were effective in patients with cancer. However, new research presented at this year's ESMO Congress revealed how patients with cancer have a suitable response to the vaccine and studies suggest that a third booster vaccine could further improve immunisation against COVID-19.

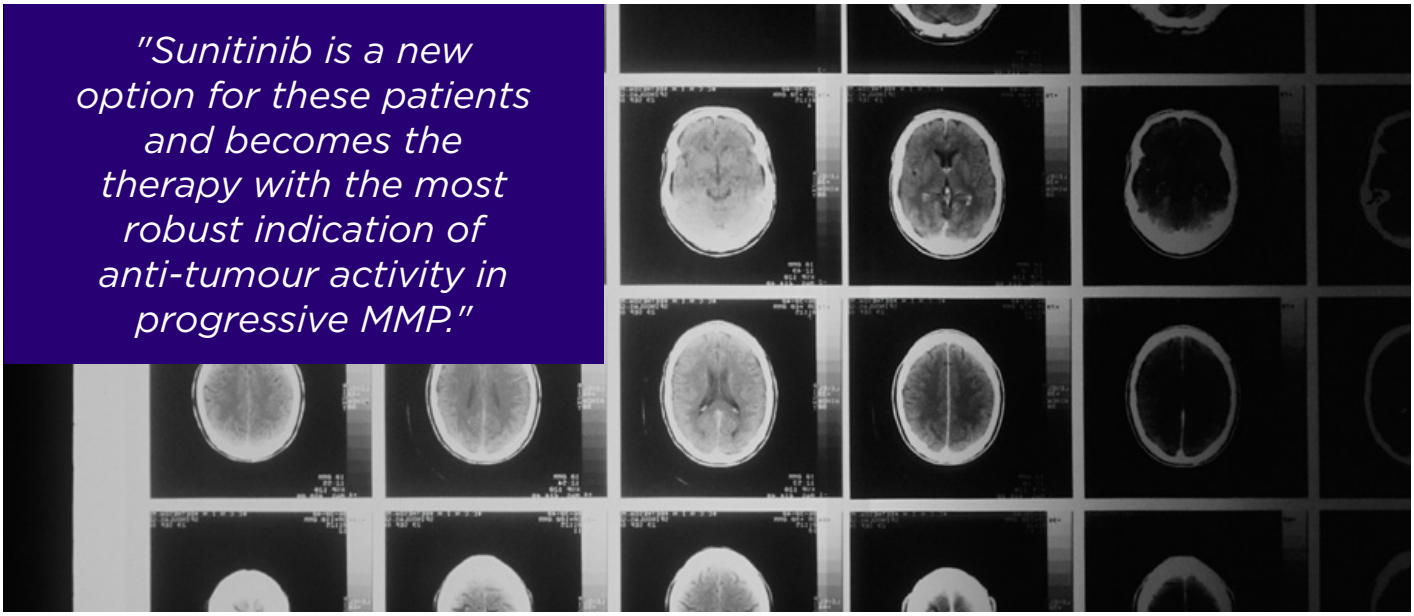
One notable study, namely VOICE, explored whether different oncological treatments affected vaccination against COVID-19. The study recruited almost 800 patients from numerous hospitals from the Netherlands. The patients were split into four groups: patients with cancer treated with immunotherapy, patients with cancer treated with chemotherapy, patients with cancer treated with a combination of chemo- and immunotherapy, and, finally, individuals without cancer.

The antibody levels of the individuals were measured after 28 days after the second dose of the Moderna (Mrna-1273) vaccine. Results showed that 93% of patients with cancer receiving immunotherapy had adequate levels of antibodies against COVID-19. Similarly, 84% of patients receiving chemotherapy and 89% of patients receiving chemo-immunotherapy had adequate levels of antibodies. To summarise, patients are sufficiently protected regardless of their oncological treatment. Comparing these results to individuals without cancer shows that antibody levels are almost just as high after two doses.

Fascinatingly, results from another study showed that patients with cancer who had two doses of AstraZeneca's COVID-19 vaccine or tozinameran and had previously contracted COVID-19 had higher levels of antibodies against COVID-19, including against the deadlier Delta variant. These results highlight the importance of patients having two doses against COVID-19 and even suggest that a booster shot could increase efficacy for more patients.

The president of ESMO, Solange Peters, concluded: "Since the very start of the pandemic outbreak, we at ESMO have made it a top priority to secure extra care for our patients: first by educating oncology colleagues throughout these unprecedented events, then by pushing for the prioritisation of COVID-19 vaccination for patients with cancer." The promising results from these studies presented at the ESMO congress prove that the COVID-19 vaccination is just as safe for patients with cancer as it is for healthy individuals. ■

"Sunitinib is a new option for these patients and becomes the therapy with the most robust indication of anti-tumour activity in progressive MMP."



Tyrosine Kinase Inhibitor as Practice Changing New Medication for Rare Neuroendocrine Tumours

PROGRESSION-FREE SURVIVAL (PFS) in malignant pheochromocytoma and paraganglioma (MPP) is prolonged by more than 5 months by sunitinib, a recent randomised trial has found. These break through results from the FIRSTMAPPP trial were presented at the ESMO Congress 2021, which was held in Paris and virtually from the 16th–21st of September.

MPP is a very rare form of neuroendocrine tumour. Annual incidence is less than 1 per million. FIRSTMAPP enrolled 78 patients with progressive MPP over an 8-year period from 15 centres across Europe. Patients were randomly allocated to sunitinib or placebo.

The primary endpoint for the study was PFS at 12 months. This was achieved by 35.9% of the sunitinib group (n=14) compared with 18.9% in the placebo group. The median PFS was 8.9 months versus 3.6 months in the sunitinib and placebo groups, respectively.

"None of the treatment options we currently have for advanced MPP are supported by randomised clinical trial evidence. This disease is commonly treated using combined chemotherapy with cyclophosphamide, vincristine and dacarbazine, all quite old agents and all very toxic. Sunitinib will be much better tolerated," commented Juan Valle, Consultant Medical Oncologist, University of Manchester and the Christie NHS Foundation Trust, Manchester, UK.

Throughout the trial, severe adverse events occurred in 54% of patients in the sunitinib group compared with 49% in the placebo group. The most frequent adverse events were asthaenia/fatigue (18% versus 3%) and hypertension (10% versus 6%). There was 1 death in both arms of the study.

"The study demonstrates that sunitinib 37.5 mg per day was tolerable," explained Eric Baudin, Chair, Neuro-Endocrine Tumours, Gustave Roussy – Cancer Campus, Villejuif, France. "In particular, we know that two-thirds of patients with MPP have hypertension due to high levels of hormones, yet hypertension induced by the drug was manageable."

Baudin further highlighted the value of the research: "This trial provides the highest level of evidence ever reached in this very rare cancer. The results are practice changing. Sunitinib is a new option for these patients and becomes the therapy with the most robust indication of anti-tumour activity in progressive MPP." ■

CDK 4/6 Inhibitors Show Prolonged Survival for Metastatic Breast Cancer

"To put these results into perspective, in my 45 years as an oncologist there have been tens of thousands of clinical trials for breast cancer and while a PFS benefit has been shown many, many times, we have rarely observed an improvement in overall survival"

BREAKING research has found that the administration of a CDK 4/6 inhibitor alongside first-line hormonal treatment in postmenopausal woman with hormone receptor positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer improves survival rates by 1 year. This evidence comes from the MONALEESA-2 trial, and was presented on 19th September at the ESMO Congress 2021.

The randomised trial, which is the first to bring a statistically significant survival outcome in this patient demographic, involved 668 patients who had not previously received endocrine therapy, chemotherapy, or a CDK 4/6 inhibitor. The trial focused on progression free survival. Individuals were administered a combination of either ribociclib (a CDK 4/6 inhibitor) plus letrozole, and aromatase inhibitor, or a placebo plus letrozole. The trial measured overall survival after 400 deaths, and saw the active treatment plus letrozole with a median rate of 63.9 months, and the placebo group with a median overall survival of 51.4 months. "To put these results into perspective, in my 45 years as an oncologist there have been tens of thousands of clinical trials for breast cancer and while a progression free survival benefit has been shown many, many times, we have rarely observed an improvement in overall survival," explained Gabriel Hortobagyi, Professor of Medicine, Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, USA.

"It is important to note that these data are related to endocrine-sensitive patients who had not previously received endocrine therapy for metastatic disease. The clinical implication is that now we have a clear demonstration that the combination of endocrine therapy plus the CDK 4/6 inhibitor ribociclib prolongs both progression free survival and overall survival," noted Giuseppe Curigliano, Clinical Director, Division of Early Drug Development for Innovative Therapy, European Institute of Oncology, Milan, Italy. He went on to highlight that further research could present the opportunity to detect biological features to identify individuals that would benefit from this treatment the most; research with this focus currently ongoing, carried out by Hortobagyi and colleagues.

Hortobagyi concluded the study by highlighting that the results obtained from this trial can be extrapolated to patients with hormone receptor positive, HER2-negative metastatic breast cancer from around the world, providing further benefit to the study. "While this is the only CDK 4/6 inhibitor to demonstrate an overall survival benefit in this patient population so far, we are still waiting for results of the palbociclib and abemaciclib trials. And of course, there are other emerging treatments such as other kinase inhibitors so there is more research to come in this field," he added, hinting at the future research that we can expect to see in this area of oncology. ■

Could Drug Repurposing Prolong Survival in Prostate Cancer Patients?

EMERGING research has suggested that a unique combination of existing drugs is able to improve survival rates in patients with hormone/castration-sensitive prostate cancer. Presented at the ESMO Congress 2021, this evidence comes from the PEACE-1 and STAMPEDE studies, which both revealed that the administration of standard therapy alongside abiraterone acetate plus prednisolone (AAP) prolonged patient survival compared to standard therapy alone.

"The administration of AAP alongside docetaxel and ADT saw a 25% reduction in mortality risk compared to docetaxel and ADT, as well as 2.5 years of progression free survival in men with high-burden metastatic prostate cancer."

For patients with metastatic prostate cancer, the standard treatment for decades was androgen deprivation therapy (ADT). Recently, docetaxel, a drug used in chemotherapy and the hormonal agent abiraterone were both found to prolong survival when administered alongside ADT. The PEACE-1 trial compared the clinical benefits of using different combinations of these drugs alongside ADT, and found that a combination of three drugs both prevented cancer progression, and improved patient survival. The administration of AAP alongside docetaxel and ADT saw a 25% reduction in mortality risk compared with docetaxel and ADT, as well as 2.5 years

of progression-free survival in men with high-burden metastatic prostate cancer.

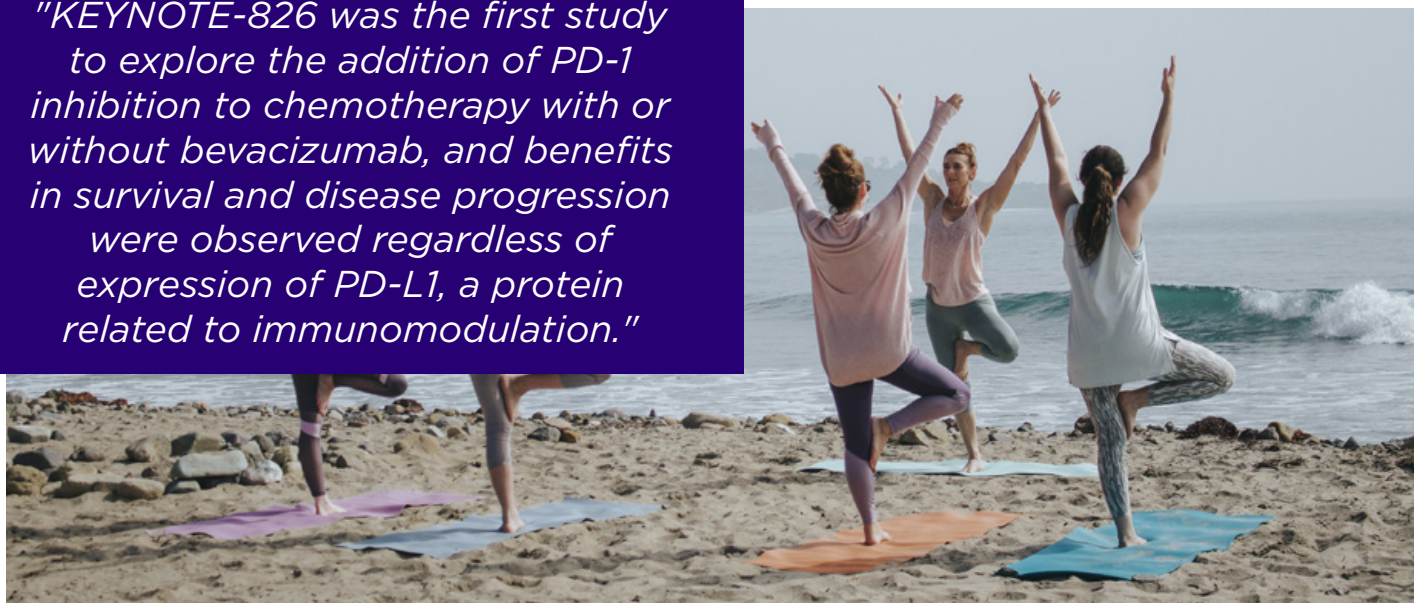
"PEACE-1 is the first trial to establish that triplet treatment should be offered to these men, especially those with the most aggressive cancers (those with multiple metastases)" stated Karim Fizazi, Medical Oncologist, Institute Gustave Roussy and Professor in Oncology, University of Paris-Saclay, France. He also noted that the side effects experienced following this treatment were mild, with few severe side effects occurring. Fizazi went on to emphasise that although systemic triplet treatment halts cancer progression, a follow-up is needed to assess survival in patients with low-burden metastatic prostate cancer.

The STAMPEDE trial, which focused on non-metastatic prostate cancer with a high-risk of spread, saw an improvement in overall survival rates following administration of standard treatment of ADT alongside AAP for 2 years. With this treatment, metastasis-free survival increased from 69% to 82%, overall survival increased from 77% to 86%, and prostate cancer-specific survival improved from 85% to 93%. Gerhardt Attard, John Black Charitable Foundation Endowed Chair in Urological Cancer Research at University College London, UK, explained: "Based on these results, all men with high-risk non-metastatic prostate cancer should be considered for 2 years of abiraterone. This will involve more hospital visits during this period to manage administration of the drug but by reducing subsequent relapse, may reduce the overall burden for both patients and health services."

Although positive results were also seen in the STAMPEDE trial, Attard also added that further trials need to be carried out to optimise the length of AAP therapy, a factor which was not studied in the trial. Maria De Santis, Chair of Interdisciplinary Urological Oncology, Department of Urology, Charité Universitätsmedizin, Berlin, Germany, explained: "With regards to the non-metastatic patients in STAMPEDE, this is a completely new patient group that has not been included in other published trials. The addition of systemic treatment with AAP for at least 2 years in this population will change our former treatment strategy, which has been only ADT plus or minus radiotherapy to the prostate for many years."

The benefits of repurposing these pre-existing drugs alongside standard therapy are clear, particularly given that drug approval is not required, allowing for quicker implementation into clinical practice. Future studies will likely focus on adjusting the combination of each therapy as well as treatment length in hope to optimise patient survival. ■

"KEYNOTE-826 was the first study to explore the addition of PD-1 inhibition to chemotherapy with or without bevacizumab, and benefits in survival and disease progression were observed regardless of expression of PD-L1, a protein related to immunomodulation."



Survival of Patients with Persistent, Recurrent, or Metastatic Cervical Cancer Could Be Prolonged by Immunotherapy

ACCORDING to a study, presented at the ESMO Congress on 18th September 2021, additional immunotherapy to standard first-line treatment prolongs survival by 8 months in patients with persistent, recurrent, or metastatic cervical cancer.

Cervical cancer is the second most common cancer in females aged 15–40 years, with roughly 340,000 deaths documented in 2020. The KEYNOTE-826 trial randomly assigned 617 females to either immunotherapy (pembrolizumab) or placebo. Additionally, the two groups also underwent chemotherapy (paclitaxel plus the doctor's choice of carboplatin or cisplatin) and, at the doctor's discretion, they could also receive bevacizumab. According to the results, the addition of pembrolizumab reduced the death risk by 33% and further lowered the disease progression or death by 35%. Anaemia was the most commonly observed side effect with 30.3% in the pembrolizumab group and 26.9% in the placebo group. Secondly, a lower concentration of white blood cells was noted at 12.4% in the pembrolizumab group compared with 9.7% in the placebo group. However, the observed side effects were manageable and expected based on previous study. Bevacizumab was administered to 63% of the participants and the authors confirmed that this drug should only be used with the pembrolizumab when safe. However, there was still a clinical benefit in the addition pembrolizumab to chemotherapy alone. Unfortunately, one of the study limitations was that it was not designed to statistically compare the outcomes as the administration of bevacizumab was not randomised.

One of the study authors, Nicoletta Colombo, Director of the Gynaecology Programme, European Institute of Oncology, Milan, Italy, said: "Previous studies showed that adding anti-angiogenesis therapy with bevacizumab to chemotherapy prolonged survival by 3.7 months over chemotherapy alone. KEYNOTE-826 was the first study to explore the addition of PD-1 [programmed cell death protein-1] inhibition to chemotherapy with or without bevacizumab, and benefits in survival and disease progression were observed regardless of expression of PD-L1 [programmed death-ligand 1], a protein related to immunomodulation. Side-effects with the new combination therapy were manageable and the observed adverse events were as expected based on previous data on the individual drugs." ■

Recurrence of Stage IIB and IIC Melanoma Could be Reduced by Adjuvant Immunotherapy

ACCORDING to the first Phase III randomised clinical trial, presented at the ESMO Congress on 18th September 2021, Stage II melanoma reoccurrence could be reduced by 35% by using adjuvant pembrolizumab. Patients with Stage IIB and IIC melanoma and those diagnosed with Stage IIIA and IIB melanoma have the similar risk rate of disease reoccurrence and death. A deep or ulcerated tumour is observed in patients with Stage IIB and IIC melanoma. Regardless of the similar risks associated, with both Stage IIB and IIC melanoma and Stage IIIA and IIB, currently only Stage IIIA and IIB standard of care is adjuvant immunotherapy.

The novel KEYNOTE-716 study, for a period of up to 1 year, randomly assigned 976 patients with complete resection of cutaneous Stage IIB or IIC melanoma and no lymph node involvement to either programmed cell death protein-1 (PD-1) inhibitor pembrolizumab or a placebo. Within a median follow up period of 14.4 months, the results showed that reoccurrence was observed patients on pembrolizumab 54 (11.1%) compared with 82 (16.8%) patients on placebo. Furthermore, the distance reoccurrence was nearly halved with pembrolizumab compared with the placebo (23 and 38 events, respectively). Additionally, this study was not just centred to adults but also adolescents and children over 12 years old.

Study author Jason J Luke, Director of the Cancer Immunotherapeutics Center, University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, USA stated that "there has been a belief that early-stage melanoma doesn't recur very fast and that these patients don't develop metastatic disease. These data clearly disprove that and show that patients with high-risk Stage II melanoma recur quickly and distantly, just the same as patients with Stage IIIA and IIIB. Treatment with pembrolizumab reduced that in a meaningful and statistically significant way, indicating that these Stage II patients should be offered adjuvant therapy." This study could be beneficial, with the potential to reducing recurrences and metastases in patients diagnosed with Stage IIB and IIC melanoma and could be used as a benchmark in associated future studies. ■

"These data clearly disprove that and show that patients with high-risk Stage II melanoma recur quickly and distantly, just the same as patients with Stage IIIA and IIIB. Treatment with pembrolizumab reduced that in a meaningful and statistically significant way, indicating that these Stage II patients should be offered adjuvant therapy."

Insufficient Follow-Up Care for Cancer Survivors

RECENT evidence has emerged from the ESMO 2021 Congress suggesting a disparity between standards of cancer follow-up care and current patient needs following treatment. This information was presented on 18th September 2021 and is thought to have stemmed from the significant improvements in cancer screening and treatment leading to earlier diagnosis, all of which contribute to long-term survival rates. A study presented alongside this research confirmed this discontent amongst the population of cancer patients.

Over half of patients in Europe now beat cancer and experience long-term survival rates of over 5 years following diagnosis, a statistic that should be positive for survivors. However, the residual impact of the disease coupled with side-effects of anticancer medicines sees a significant proportion of patients continuing to suffer from hampering symptoms, which, unfortunately, impedes a smooth return to normal life. Dorothy Keefe, CEO of Australia's National Cancer Agency, Cancer Australia, Sunny Hills, Australia, and Chair of the ESMO Supportive and Palliative Care Track, explained: "This is probably due to the increase in survival rates itself lagging behind the introduction of new therapies, but also to a lack of prioritisation compared to the need to develop a cure."

Both patients and survivors commonly experience cancer-related fatigue, which is described as a persistent sense of exhaustion that is not alleviated by sleep or rest and that interferes significantly with the person's usual functioning. The FiX study aimed to assess the patterns, severity, and management of cancer-related fatigue in 2,508 patients with 15 different cancer types. Forty percent of

"Despite increasing awareness of the effectiveness of mitigating measures like exercise to reduce fatigue, patients are still too often left alone to seek help for symptoms that cannot be directly addressed with medicines"

participants reported a moderate-to-severe burden from continued fatigue 4 years post-diagnosis in a follow-up survey conducted alongside the study. Over 40% of patients additionally experienced loss of physical ability, whilst over 30% reported sleeping problems, sexual problems, joint pain, and anxiety, all of which caused moderate burden.

"Despite increasing awareness of the effectiveness of mitigating measures like exercise to reduce fatigue, patients are still too often left alone to seek help for symptoms that cannot be directly addressed with medicines in the same way as something like pain, for which satisfaction with the support received was high in our study," noted study author Martina Schmidt, German Cancer Research Centre (DKFZ), Heidelberg, Germany. Schmidt went on to highlight the importance of long-term follow-up care involving additional systematic screening to identify these burdens and relieve patients of these symptoms as early as possible, as well as ensuring that individuals are well-informed of potential symptoms.

Keefe added: "This research shows that a staggeringly high number of patients still suffer from significant health issues years after being declared disease-free. Their dissatisfaction with the care available is a wake-up call that we should be paying more attention to these individuals, trying to understand the mechanisms at play in order to identify interventions that could help them to better recover." Currently, methods of managing these adverse symptoms are untested, warranting the implementation of a survivorship plan for patients. Keefe further explained: "Going forward, we need to develop these models of care in a way that minimises the burden on healthcare systems, implement them and research their impact so that we can come back in five years' time and evaluate whether they have made a difference for cancer survivors." ■

Is the Pace of Oncology Advancements Leaving Doctors and Patients Behind?

BREAKING RESEARCH has highlighted the growing difficulty experienced by both doctors and patients attempting to keep up with the rapid pace of developments within the field of oncology, particularly those brought on by cancer immunotherapy. Two studies presented at the ESMO Congress 2021 suggested that doctors who are not specialists in oncology struggled to keep up with the evolution of prognosis and had limited knowledge of available medicines and their potential side effects. Both studies emphasised the need for broader education on current standards of care.

CareAcross, a multilingual platform providing personalised education for cancer patients, conducted a survey amongst 5,589 of its members to evaluate patients' knowledge about immunotherapy. "It is essential for these individuals to be well-informed because it is a complex treatment that is too often mistaken for a miracle cure," stated Paris Kosmidis, Chief Medical Officer, CareAcross, and study author. Patients were asked several questions regarding immunotherapies mechanism of action, efficacy, side effects and cost.

Almost half of participants diagnosed with either breast, lung, prostate, or colorectal cancer answered that they were unsure or did not know how immunotherapy worked, with only 32% selecting the correct answer, "activates the immune system to kill cancer cells".

Understanding how cancer care has evolved is also essential for medical professionals outside of oncology. Conleth Murphy, Bon Secours Hospital Cork, Ireland, author of the second study conducted a survey exploring physicians' perceptions of cancer prognosis. This survey asked 301 non-oncology physicians and 46 medical and radiation oncologists to estimate patients' 5-year survival rates for 12 of the most common tumour types across all stages of disease. Their answers were then compared with the most recent survival figures from the National Cancer Registry of Ireland.

"Almost half of participants diagnosed with either breast, lung, prostate, or colorectal cancer answered that they were unsure or did not know how immunotherapy worked"

The non-oncologists were able to provide accurate estimates of all-stage survival for only 2 out of the 12 cancer types. When they were provided with specific clinical scenarios, non-specialists significantly underestimated 5-year survival and tended, overall, to be more pessimistic than oncologists. To avoid presenting patients with unduly bleak expectations, Murphy recommended that non-oncologists should always refrain from answering patients' questions with numbers.

"Amid this growing complexity, an important part of the family doctor's role in a patients' journey with cancer is reformulating information they have been given by their oncologist to give them a better understanding of their situation," stated Cyril Bonin, General Practitioner, Usson-du-Poitou, France. "More consistent communication with the oncology team about the therapy's expected benefits, possible side-effects and impact on prognosis could help us guide patients competently and provide the psychological support they need." ■

Children Often Excluded from Their Parent's Cancer Journey

IGNORANCE is not bliss for children of patients with cancer, according to new research presented at the ESMO Congress on 16th September 2021. Last year, an estimated 4.6 million individuals aged 20–54 were diagnosed with cancer. These are the ages when people are most likely to be raising children, meaning many children would have also been affected by these diagnoses.

A novel study, surveying 103 patients with cancer in Tunisia, reported that nearly 90% of patients struggled to communicate about their disease with their children, while 40% chose not to reveal the whole truth. Study author Sinen Korbi, Institute Salah Azaiez, Tunis, Tunisia, stated that this resulted from parents wanting to protect their children. However, 96% of patients saw behavioural changes such as anxiety and depression in their children, which affected academic life and even led to substance abuse in some.

Communication about cancer with children is an ongoing process. Parents should ask how their children are doing and explain their disease in an age-appropriate way. Although he was not involved with the study, clinical and child psychology expert Carlo Alfredo Clerici, University of Milan, Italy, believes that a certain amount of knowledge about their parent's disease can protect children from traumatic phenomena. However, this new study reported that many parents needed guidance on how to broach this topic.

"96% of patients saw behavioural changes such as anxiety and depression"

While this study highlights parent's struggle to communicate about their disease with their children, Clerici stated: "Future research should also aim to capture traumatic phenomena that unfold over time, and which are associated with more worrying long-term consequences than the individual symptoms of distress reported here." ■

ESMO: Reshaping the Future of Clinical Trials in Oncology

Robin Stannard
Editorial Assistant

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IN A MASTERCLASS conducted on Day 5 of the European Society for Medical Oncology (ESMO) Congress 2021, Emiliano Calvo, Director of START Madrid, Centro Integral Oncológico Clara Campal Hospital, Madrid, Spain, and Nathan Cherny, Head of the Cancer Pain and Palliative Medicine Unit, Shaare Zedek Medical Centre, Jerusalem, Israel, presented a joint session on the future landscape of clinical trial practice in oncology, discussing the practical, ethical, and logistical barriers to improving that landscape.

PHASE 0 TRIALS

Opening the session, Calvo presented a compelling and balanced case about the potential that Phase 0 (Ph0) trials hold for increasing efficiencies in drug development by enhancing the selection of elite drug candidates. Ph0 studies are carried out very early in the drug development life cycle, even before Phase 1 (Ph1) has occurred. They have limited duration, sample size, and drug dose and have no therapeutic or diagnostic intent. However, these characteristics mean that Ph0 trials have reduced regulatory requirements and have the potential to provide key information regarding the pharmacological profile of an investigational new drug (IND) and to streamline the entire drug development process by providing valuable data prior to Ph1.

The number of oncological drugs in development has rapidly increased in recent decades. However, attrition rates remain high with only 10–20% of drugs making it through the stages of clinical drug development to market. As Calvo explains: "Proportional increases in R&D [research and development] over the last decades do not necessarily lead to rising numbers of new drugs." This results in increasingly unaffordable drugs and skyrocketing prices that make the entire cancer care system less efficient. The U.S. Food and Drug Administration (FDA) has made efforts to address this issue communicating that one potential method of improving the efficiency of clinical drug development would be investment in pre-clinical studies, which enhance predictability of IND clinical trial success. Ph0 trials are a method of enhancing this predictability.

Ph0 trials can be categorised depending on what they are investigating. Microdose Ph0 trials investigate pharmacokinetics (PK) by collecting early information on how the body processes the drug. These studies typically use 1% of a pharmacologically active dose to profile the drug targets and pharmacological effect without eliciting any adverse consequences. The second

type of Ph0 trial focuses on the study of pharmacologically relevant doses, known as pharmacological endpoint studies. These studies involve treating with varied dose levels over a very short window, often 7 days. The final category refers to the study of the mechanism of action or pharmacodynamic Ph0 trials. This category of Ph0 is used as a proof of concept for drug mechanisms, measuring factors such as degree of receptor saturation, inhibitions of active enzymes, or other 'biomarkers' of drug activity. The doses are incredibly low as only tumour-related pharmacodynamic effects are measured; these studies should produce no toxicity and no therapeutic effects. Calvo emphasised that this third, mechanism of action, Ph0 trial may prove to be the most relevant in the era of precision medicine.

"If you do all these things, you won't be making the same mistakes that researchers have been making over the last 15 years"

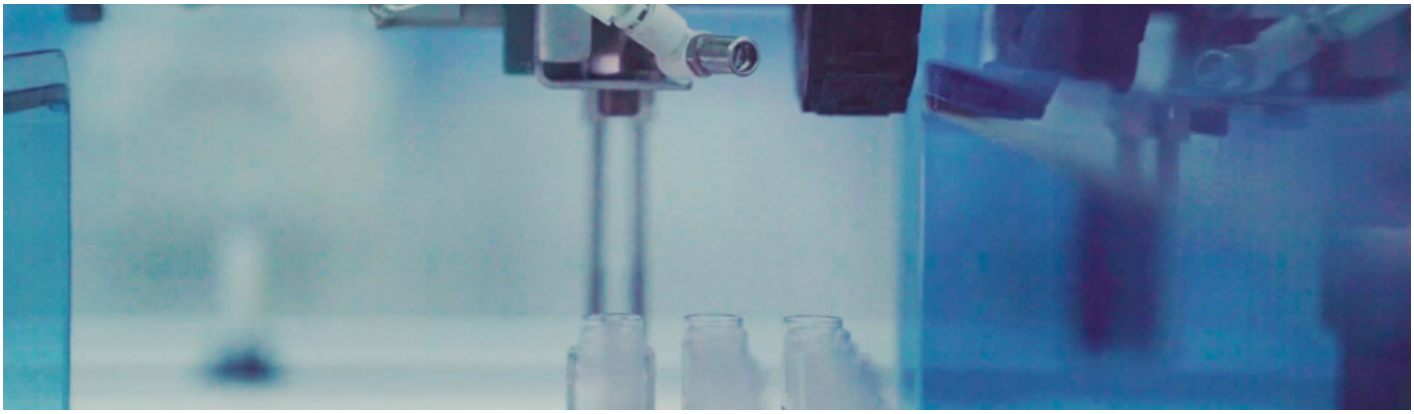
Whilst Calvo placed emphasis on the potential Ph0 trials offer to increase predictability, streamlining, and eventual efficiency and frugality in the clinical drug development process, he also offered a balanced argument of the issues that incorporating Ph0 trials into general practice may present. Technologically, Ph0 trials are challenging, as detecting drug impacts at such low doses within patients is very difficult and there are few sites with the necessary equipment for these processes. Furthermore, even though some Ph0 trials have reduced regulatory requirements compared to Ph1, this may not always be the case depending on the nature of the Ph0. However, possibly the most important challenge that Ph0 trials present is not technological but ethical. As Calvo explained, it could be argued that improved development efficiencies resulting in reduced cost and time provide large-scale practical benefits to cancer care. However, Ph0 trials are so short-term and low-dose that there is no therapeutic benefit to the individual participant, meaning that these studies are more about the drug than the patient. Calvo emphasised that as a physician with a duty of care, if there is another Ph1 trial available to the patient, this must be recommended as it is in the patient's best interest. Calvo aptly summarised the dilemma of this scenario by stating: "patients come to oncologists to fight their cancer but [the] oncologist is offering no fight at all".

Calvo ended his presentation with an important reflection of how to consider the future of Ph0 trials, which is to return to the initial question: 'Do they improve the success rate of human trials entering drug development?' He summarises that currently it is difficult to conclusively decide, but that failure of a drug early must always be better than failure later. He emphasised that improving the ethical feasibility of Ph0 trials would be necessary by considering suggestions such as amending Ph1 studies to allow participants from Ph0 trials or selecting clinically stable patients during mandatory systemic therapy vacations.

SINGLE-ARM STUDIES

Cherny, a serving member of the ESMO Designated Centre Working Group and the ESMO Magnitude of Clinical Benefit Working Group, undertook a more retrospective analysis. By taking a critical approach to practices currently harming clinical trials in oncology, he provided a convincing argument on why these practices should be left in the past and not incorporated into the future. Cherny began his presentation with a discussion on research integrity and the minimisation of bias, conceptualising the harm bias presents in three ways: direct harm through misleading outcomes; societal harm through inappropriate resource allocation; and reputational harm through loss of credibility. Establishing these directives of research integrity led him seamlessly and pertinently into his critical analysis of single-arm studies (SAS).

In a SAS all enrolled participants are treated with the experimental therapy, in contrast with a randomised controlled trial (RCT) where randomly selected groups of patients are treated with different therapies to compare medical outcomes. The FDA defines SAS as acceptable for drug approval "in settings where there is no available therapy and where major tumour regressions can be assumed to be attributed to the test drug."[1] However, in recent years SAS have been accepted as proof of efficacy in several situations such as when standard treatments



do not exist or are clearly inferior, when the disease is rare, or when patient accrual for RCTs is not perceived to be feasible.

Cherny explained that SAS are much less reliable as evidence for patient benefits and are frequently being employed despite the existence of a reasonable alternative therapy or when there is no evidence for the infeasibility of an RCT. Using evidence from a meta-analysis of clinical trial findings, Cherny demonstrated how overall response rates (ORR) in solid tumour SAS are higher than the ORR when the same medicine for the same indication is tested in a RCT. The meta-analysis evaluated the average gap in ORR between SAS and RCT, finding that SAS were on average 12.9% higher in 2005 and 8% higher in 2020.[2] Cherny described the overly optimistic findings of SAS as "an issue of generalisability and reproducibility."

"Possibly the most important challenge that Ph0 trials present is not technological but ethical"

An additional concern with SAS is that they are being used inappropriately. Rittberg et al.[3] conducted an evaluation of 31 drug approvals based on the outcomes of SAS, finding that there was an alternative drug that could have been used as a control arm available in 28 out of those 31 cases. In five cases the drugs were approved despite demonstrating inferior efficacy compared to the standard of care and in >85% the authors summarised that it would have been feasible to complete an RCT within a reasonable time frame. Cherny agreed with the authors' conclusion that this equated to bad science, with SAS generating accelerated approvals that resulted in subsequent rescindments or drugs that lingered in the market with no definitive proof of benefit.

In his concluding remarks, Cherny revisited his initial position about the value and importance of research integrity: "wasteful research is not ethical; it is not ethical to recruit patients to participate in studies that are not going to generate generalisable knowledge."

CONCLUDING COMMENTS

The arguments presented by both experts provided an interesting balance between logistical concerns including increasing efficiencies, saving money, and the availability of therapies, versus the ethics of providing optimum care, practising research integrity, and prioritising the patient over the disease. The retrospective analysis alongside a look to the future demonstrates the importance of balancing these two factors: striving to learn from mistakes, and consider improvements and innovations for the future. In the Questions and Answers at the end of the session, Cherny summarised this emerging theme: "If you do all these things, you won't be making the same mistakes that researchers have been making over the last 15 years. And the quality of the research and integrity of the research you produce is going to be of a different standard."

References

1. FDA. Clinical trial endpoints for the approval of cancer drugs and biologics. 2018. Available at: https:www.fda.gov/media/71195/download. Accessed 9 October 2021.
2. Zia MI et al. Comparison of outcomes of phase II studies and subsequent randomised control studies using identical chemotherapeutic regimens. J Clin Oncol. 2005;23(28):6982-91.
3. Rittberg R et al. Feasibility of randomized controlled trials for cancer drugs approved by the food and drug administration based on single-arm studies. JNCI Cancer Spectr. 2021;5(4):pkab061

Navigating the Current Treatment Landscape in Oesophageal Cancer with an Eye Toward the Future

This symposium took place on 18th September 2021, as part of the virtual European Society for Medical Oncology (ESMO) Congress 2021

Chairpeople: Eric Van Cutsem[1]

Speakers: Elizabeth Smyth,[2] Lucjan Wyrwicz[3]

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Disclosure: Van Cutsem has participated in advisory boards for AbbVie, Array, Astellas, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Daiichi, Halozyme, GSK, Helsinn, Incyte, Ipsen, Janssen Research, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Pierre Fabre, Roche, Seattle Genetics, Servier, Sirtex, Terumo, Taiho, TRIGR, and Zymeworks; and received research grants from Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, and Servier paid to his institution. Smyth reports personal financial interests (lecture honoraria, advisory boards, travel support) from AMAL Therapeutics, AstraZeneca, Astellas, BeiGene, Bristol Myers Squibb, Celgene, Elsevier, Everest Clinical Research, Five Prime Therapeutics, Gritstone Oncology, Merck, Novartis, Pfizer, Roche, Servier, and Zymeworks; and has held leadership roles as EORTC GI Clinical Trials Group Secretary (2018–current) and ESMO GI faculty (2017–current). Wyrwicz reports investigator fees from Bristol Myers Squibb, Merck Sharp & Dohme, and BeiGene.

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Meeting Summary

This symposium took place during the European Society for Medical Oncology (ESMO) Congress 2021. Eric Van Cutsem welcomed attendees and provided an overview of the programme, which was designed to highlight the current treatment landscape in oesphageal cancer and explore future directions in cancer care. Elizabeth Smyth discussed the epidemiology of oesphageal cancer, the use of biomarker testing in patients with advanced disease to help guide treatment choices, and the current treatment paradigms for oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC). Lucjan Wyrwicz outlined the existing therapy options and the latest data on the treatment of metastatic oesophageal cancer in first- and second-line settings. He also discussed biomarkers and how they can be used to inform therapeutic decision-making in metastatic oesophageal cancer. Van Cutsem then explained how emerging immunotherapy regimens may potentially address the unmet needs of patients with oesophageal cancer. These could include the use of programmed cell

Welcome and Programme Overview

Eric Van Cutsem

The symposium featured three talks and a live Q&A session. First, the current patient journey and standards of care in oesophageal cancer were outlined. This was followed by a discussion of the existing treatment landscape and the latest data for the treatment of metastatic oesophageal cancer in first- and second-line settings. Next, there was a presentation of biomarkers and how they inform therapeutic decision-making in metastatic oesophageal cancer. Finally, the Q&A session explored the unmet needs of patients with oesophageal cancer and how emerging immunotherapy regimens could potentially address these gaps.

The Patient Journey in Oesophageal Cancer: Standards of Care from Early-Stage to Metastatic Disease

Elizabeth Smyth

Oesophageal cancer is the sixth most common cause of cancer-related deaths worldwide.[1,2] The two main histological subtypes of oesophageal cancer are OSCC and OAC.[2] OSCC is the most common subtype of all oesophageal cancers worldwide.[2] Diagnosis of both subtypes is often at a late stage when it is unsuitable for a curative treatment approach. As a result, the 5-year survival rate for oesophageal cancer is very low (19.9%).[3] For patients with metastatic oesophageal cancer, options have previously been very limited, with just 5.2% of patients living for 5 years or more.[3]

OSCC is a tumour of the stratified squamous epithelium of the oesophagus. OSCC can occur anywhere in the oesophagus but most commonly affects the cervical, upper, and middle-thoracic oesophagus.[4] Although the incidence of OSCC is relatively stable globally, in Western countries, such as the USA, Europe, and Australia, the incidence of OSCC has fallen.[5] Although outcomes have improved for patients with oesophageal cancer overall, the prognosis for OSCC remains poor.[6,7]

OAC arises from the columnar glandular cells, which replace the squamous epithelium.[6] OAC usually occurs in the lower third of the oesophagus.[4] Tumours at the gastro-oesophageal junction (GEJ) are most commonly adenocarcinoma; squamous cancers rarely occur at the GEJ.[8] Like OSCC, the incidence of OAC also varies by region and it is the most common subtype in the Western world, including North America, Western Europe, and Australia.[2] In contrast to OSCC, the prognosis for patients with OAC has slightly improved over the past few decades, but survival is limited.[9]

Biomarker testing should be performed in patients with advanced oesophageal cancer to help guide treatment choices.[10-12] The biomarkers used to select treatment for OAC are the same as those tested in gastric cancer: human epidermal growth factor receptor 2 (HER2), mismatch repair deficiency, high levels of microsatellite instability, and PD-L1. The latter should also be tested in OSCC.

The current treatment paradigm for oesophageal cancer can be broadly divided into OSCC and OAC. Starting with OSCC,[13-17] Stage I can sometimes be treated with endoscopic resection, especially tumour 1, node 0 (T1N0). However, risk factors for recurrence may mean that these patients are not suitable for endoscopic resection and require surgical resection. Treatment for Stages II and III may or may not include surgery. This is because of the extreme sensitivity of OSCC to radiotherapy and the requirement for good cardiac and respiratory function. Those undergoing surgery should receive trimodality therapy, which refers to chemotherapy and radiotherapy followed by surgery. The chemotherapy and radiotherapy regimen is often based on the CROSS trial of weekly paclitaxel and carboplatin, although platinum and fluorouracil (5FU) might be used.[18] A pathological complete response (pCR) can be expected in approximately 50% of OSCC treated with CROSS chemoradiotherapy (CRT) and surgery. However, for patients without pCR, the new standard of care after surgery is the PD-1 inhibitor nivolumab. Nivolumab after trimodality therapy in non-pCR patients doubles disease-free survival (DFS), although overall survival (OS) data have not yet been presented. The alternative

treatment for patients with Stage II and III OSCC who do not wish to undergo surgery is definitive CRT. Given the high rates of pCR seen with CRT this is reasonable. Definitive CRT with planned salvage surgery has not been compared directly to trimodality therapy; this is being addressed in the NEEDS trial.[19]

If patients with OSCC recur locally after surgery or radiotherapy for locally advanced disease, further radiotherapy or salvage surgery may be an option. However, it is much more likely that these patients will follow a metastatic pathway. Standards of care for the first-line treatment of metastatic OSCC have changed this year, meaning that anti-PD-1 will become a standard of care for many patients, likely depending on PD-L1 status.

The recommended chemotherapy for advanced OSCC is platinum- and fluoropyrimidine-based. Pembrolizumab can be added to chemotherapy for OSCC patients in Europe with a PD-L1 combined positive score (CPS) ≥10 based on the KEYNOTE-590 results.[20] It is very likely that there will be an approval for nivolumab in combination with chemotherapy based on the CheckMate 648 trial,[21] but it remains to be seen whether that will be associated with PD-L1 status.

Finally, two approved PD-1 inhibitors are available in the second-line setting. Nivolumab can be used in a biomarker-unselected manner based on the results of the ATTRACTION-3 trial.[22] Outside Europe, pembrolizumab is available for patients expressing PD-L1 with CPS ≥10. For patients previously treated with immunotherapy, second-line chemotherapy with a taxane or irinotecan is appropriate.

Moving on to OAC, there is some divergence from OSCC, both in early and late disease. Again, very early cancers might be suitable for endoscopic resection or surgery. There are two options for Stage II and III cancers. However, it should be noted that for resectable OAC in fit patients, surgery is curative while CRT is not. Before surgery, neoadjuvant radiotherapy can be considered; again, usually based on the CROSS trial data.[18] Using CRT in OAC is not associated with the same levels of pCR seen in OSCC and is usually approximately 25%; however, this treatment does improve survival compared to surgery alone. Using data from KEYNOTE-577, it was recently established that nivolumab after surgery in patients who have not achieved pCR improves DFS.[23] The alternative treatment for patients with OAC and GEJ adenocarcinoma that is operable is 5FU, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy based on the results of the FLOT4 trial.[24] This is four cycles of chemotherapy before and after surgery. Neoadjuvant CRT and FLOT have not been formally compared and both are reasonable options for patients until results of the ESOPEC trial are available.[25] After surgery for OAC, patients are much more likely to relapse systemically, rather than locally, compared to OSCC so salvage radiotherapy is used less often.

Once patients are in the metastatic part of the pathway, many of the initial treatments for OAC are very similar to OSCC. For example, the standard first-line chemotherapy is platinum- and 5FU-based. More than 20% of patients with oesophageal and junctional adenocarcinoma are HER2-positive and these patients should have trastuzumab added to their first-line chemotherapy to improve survival.

Over the past year or so, anti-PD-1 therapies have been added to first-line chemotherapy in clinical trials. This may or may not be based on PD-L1 testing. In Europe, pembrolizumab is approved for patients with PD-L1 CPS ≥10. The approval for nivolumab is as yet unknown but may be for CPS ≥5 based on the results of the CheckMate 649 trial.[26]

In second-line OAC, treatment differs from OSCC. Paclitaxel and the anti-angiogenic antibody ramucirumab are used, if available, or irinotecan is an alternative chemotherapy. Trifluridine/tipiracil is approved in Europe for third-line treatment of OAC of the GEJ.

In summary, there are a number of steps that can be taken to improve patient management in OSCC. The first goal is to improve survival, especially in patients with advanced cancer where this has historically been poor but is now improving.[3] Second is to better understand the diagnostic and prognostic biomarkers in OSCC to inform clinical decisions.[10] Third is to develop novel combination treatment strategies that are effective and well tolerated.[27,28] The final goal is to implement effective strategies to address quality of life, given the toxicity profile of current treatments.[29]

Exploring the Current Treatment Landscape in Metastatic Oesophageal Cancer

Lucjan Wyrwicz

A number of trials have been published or are ongoing on the use of anti-PD-1 agents for the first- and second-line treatment of metastatic oesophageal cancer. Starting with first-line, pembrolizumab in combination with chemotherapy was approved in March in the USA for oesophageal cancer/GEJ that is not suitable for surgical resection or definitive chemoradiation.[30] This combination was approved in June in the European Union (EU) for oesophageal cancer/HER2- GEJ (PD-L1 CPS ≥10).[31] The combination of nivolumab with either chemotherapy or ipilimumab is under review.[32]

In the first-line setting, evidence for the use of pembrolizumab was obtained from the KEYNOTE-590 trial.[33] The trial enrolled 749 patients 1:1 to pembrolizumab versus placebo, OACh on top of 5FU plus cisplatin. The key eligibility criteria were locally advanced unresectable or metastatic OAC or OSCC or advanced/metastatic GEJ or Siewert Type 1 adenocarcinoma; Eastern Cooperative Oncology Group performance score (ECOG PS) 0–1; and treatment-naïve. The primary endpoints were OS and progression-free survival (PFS). At data cut-off (2nd July 2020), the median follow-up was 10.8 months. The median overall survival was 12.4 months (95% confidence interval [CI]: 10.5–14.0) in the pembrolizumab group compared with 9.8 months (95% CI: 8.8–10.8) in the placebo group, with a hazard ratio (HR) of 0.73 (p<0.0001) (Figure 1). The median PFS was 6.3 months (95% CI: 6.2–6.9) and 5.8 months (95% CI: 5.0–6.0) with pembrolizumab and placebo, respectively (HR: 0.65; p<0.0001) (Figure 2).

Data for nivolumab in the first-line was collected in CheckMate 648.[21] A total of 970 patients were randomly allocated 1:1:1 to nivolumab plus chemotherapy (5FU and cisplatin) or nivolumab plus ipilimumab or chemotherapy (5FU and cisplatin). The key eligibility criteria were unresectable advanced, recurrent, or metastatic OSCC; ECOG PS 0–1; no prior systemic treatment for advanced disease; and measurable disease. The primary endpoints were OS and PFS in patients with tumour cell (TC) PD-L1 ≥1%, while OS and PFS in all randomised patients were secondary endpoints. At data cut-off (January 18, 2021), the minimum follow-up was 12.9 months. In all randomised patients, OS was superior with nivolumab plus chemotherapy versus chemotherapy alone in the intention-to-treat (ITT) population (13.2 versus 10.7 months; HR: 0.74; p=0.0021). However, in all randomised patients, the prespecified significance boundary for PFS per blinded independent central review was not met. Median PFS was 5.8 versus 5.6 months with nivolumab plus chemotherapy versus chemotherapy, respectively (HR: 0.81; 95% CI: 0.64–1.04; p=0.0355). Superior OS was also observed with nivolumab plus ipilimumab versus chemotherapy in all randomised patients (12.8 versus 10.7 months; HR: 0.78; p=0.0110). PFS was not hierarchically tested in all randomised patients as the primary endpoint (PFS in TC PD-L1 ≥1%) was not met.

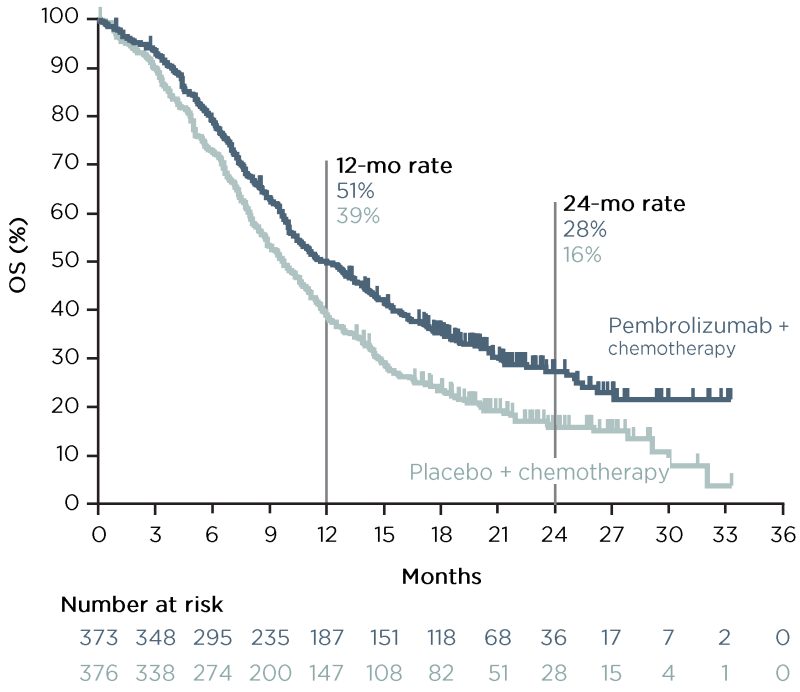
ESCORT-1st examined camrelizumab in the first-line setting.[34] The key eligibility criteria were histologically confirmed or cytologically confirmed OSCC, treatment naïve, advanced or metastatic disease, ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, and ECOG PS 0–1. A total of 596 patients were randomised 1:1 to camrelizumab or placebo, both on top of chemotherapy. The co-primary endpoints were PFS per independent review committee and OS. First-line camrelizumab plus chemotherapy led to statistically significant improvement in OS and PFS compared to placebo plus chemotherapy. The median OS in the ITT population was 15.3 versus 12.0 months with camrelizumab and placebo, respectively (HR: 0.70; p=0.001). The corresponding values for median PFS were 6.9 versus 5.6 months (HR: 0.56; p<0.001).

Ongoing Phase III trials in the first-line setting include the RATIONALE 306 trial of tislelizumab,[35] the ORIENT-15 trial of sintilimab,[36] and a clinical trial of the anti-PD-1 agent HLX10.[37]

Moving to the second-line setting, pembrolizumab was approved in July 2019 in the USA for patients with ELCC and PD-L1 CPS ≥10.[38] Nivolumab was approved in June 2020 in the USA[39] and in November 2020 in the EU for patients with OSCC.[40]

Evidence for pembrolizumab in the second-line setting was obtained in the KEYNOTE-181 trial.[41] The key eligibility criteria were confirmed OSCC or adenocarcinoma including HER2/neu-negative Siewert Type 1 GEJ adenocarcinoma; locally advanced, unresectable, or metastatic disease per RECIST v1.1; documented radiographic or clinical progression on ≥1 prior treatment; and ECOG PS 0–1. A total of 618 patients were randomly allocated 1:1 to pembrolizumab or chemotherapy. The three primary endpoints were OS in patients with PD-L1 CPS ≥10, OS in patients with OSCC, and OS in all patients. Regarding the results for all patients, there was an 11% reduction in the risk of death with pembrolizumab versus chemotherapy (median 7.1 versus 7.1 months; HR: 0.89; p=0.0560) (Figure 3). There was also an 11% increase in the risk of progression or death with pembrolizumab versus chemotherapy. The primary endpoint of OS was not met in patients with OSCC.

ATTRACTION-3 tested nivolumab in the second-line setting.[22] In this trial, the key eligibility criteria were pathologically confirmed OSCC or OAC; refractory or intolerant to fluoropyrimidine-based and platinum-based chemotherapy; one prior treatment; one measurable or non-measurable lesion per RECIST v1.1; and ECOG PS 0–1. The trial randomised 419 patients 1:1 to nivolumab or chemotherapy and the primary endpoint was OS. There was a 21% reduction in the risk of death with nivolumab versus chemotherapy (median 10.9 versus 8.5 months; HR: 0.79; p=0.0264). There was also a 7% increase in the risk of progression or death with nivolumab versus chemotherapy (median PFS 1.7 versus 3.4 months; HR: 1.07).



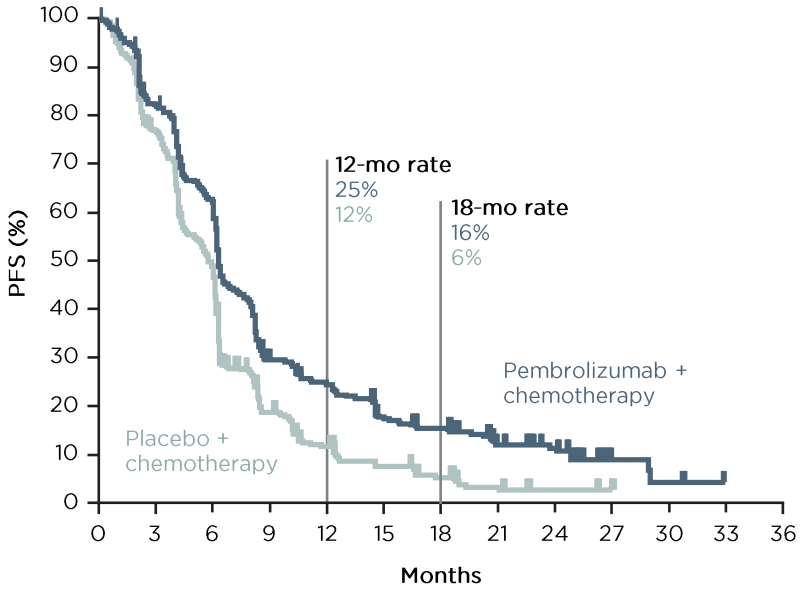
	Pembrolizumab + chemotherapy (n=373)	Placebo + chemotherapy (n=376)
OS, median (95% CI), mo	12.4 (10.5–14.0)	9.8 (8.8–10.8)
HR (95% CI)	0.73 (0.62–0.86)	
p value	<0.0001	

Figure 1: Overall survival in the KEYNOTE-590 trial.[33]

Investigator-assessed per RECIST v 1.1. Data cut-off: 2nd July 2020.

Pembrolizumab + chemotherapy led to a statistically significant improvement in OS compared to placebo + chemotherapy in the overall patient population and patients with oesophageal squamous cell carcinoma.

CI: confidence interval; HR: hazard ratio; mo: months; OS: overall survival.



	Pembrolizumab + chemotherapy (n=373)	Placebo + chemotherapy (n=376)
PFS, median (95% CI), mo	6.3 (6.2–6.9)	5.8 (5.0–6.0)
HR (95% CI)	0.65 (0.55–0.76)	
p value	<0.0001	

Figure 2: Progression-free survival in the KEYNOTE-590 trial.[33]

Investigator-assessed per RECIST v 1.1. Data cut-off: 2nd July 2020.

Pembrolizumab + chemotherapy led to a statistically significant improvement in PFS compared to placebo + chemotherapy in the overall patient population and patients with oesophageal squamous cell carcinoma.

CI: confidence interval; HR: hazard ratio; mo: months; OS: overall survival.

RATIONALE 302 examined tislelizumab in second-line treatment.[42] The inclusion criteria were advanced or metastatic OSCC, progression during or after first-line systemic treatment, and ECOG PS 0–1. A total of 512 patients were randomised 1:1 to tislelizumab or investigator-chosen chemotherapy. The primary endpoint was OS in all randomised patients. The trial demonstrated a 30% reduction in the risk of death with tislelizumab versus chemotherapy, with a median OS of 8.6 versus 6.3 months, respectively (HR: 0.70; p<0.0001).

Finally, ESCORT provided evidence for camrelizumab in second-line therapy.[43] This trial enrolled patients aged 18–75 years with histologically or cytologically confirmed OSCC who had progressed on or were intolerant to first-line standard therapy, had ECOG PS 0–1, no known CNS metastases, and no prior PD-1 or PD-L1 therapy. A total of 457 patients were randomly allocated 1:1 to camrelizumab or investigator-chosen chemotherapy (docetaxel or irinotecan). The primary endpoint was OS. There was a 29% reduction in the risk of death with camrelizumab versus chemotherapy, with a median OS of 8.3 and 6.2 months, respectively (HR: 0.71; p=0.0010).

In summary, there are sufficient data to indicate that immunotherapy has an important role in the treatment landscape of both OSCC and OAC, using combination therapy in first-line and monotherapy in second-line. It should be noted that improved understanding of biomarkers will help to stratify and select the most suitable patients for therapy and monitor their clinical

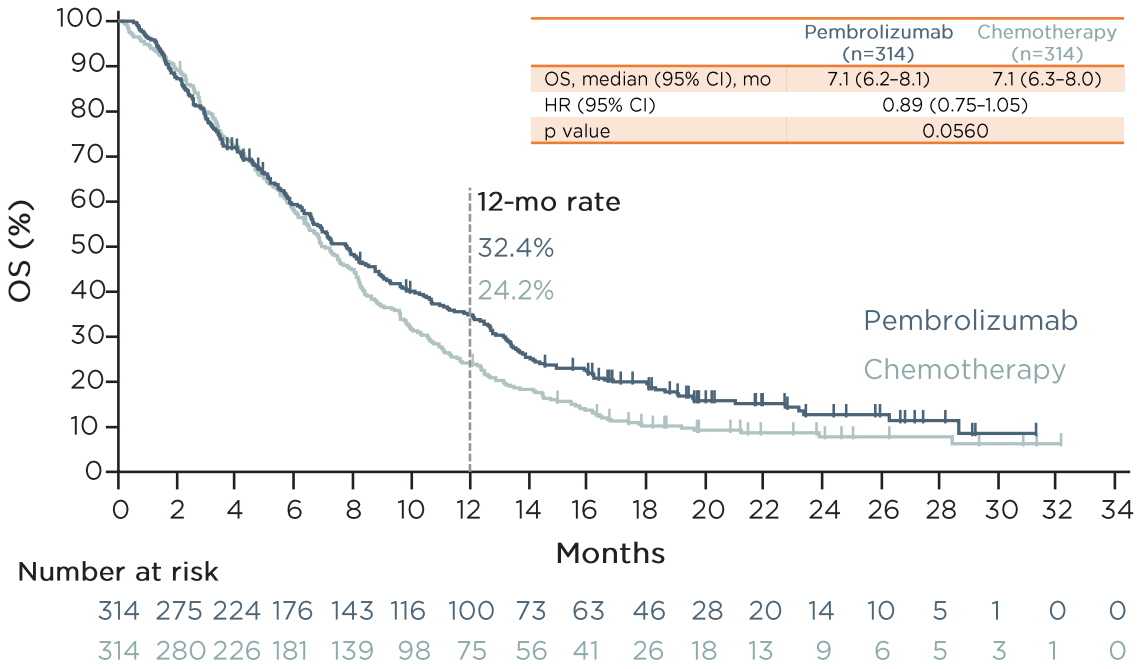


Figure 3: Overall survival in the KEYNOTE-181 trial.[41]

Data cut-off date: 15th October 2018.

In all patients, there was an 11% reduction in the risk of death and an 11% increase in the risk of progression or death with pembrolizumab versus chemotherapy.

CI: confidence interval; HR: hazard ratio; mo: months; OS: overall survival.

responses. The immune-related biomarkers currently being evaluated for immune checkpoint inhibitor therapy include tumour mutational burden,[44] microsatellite instability,[45] T-cell–inflamed gene-expression profile,[46] and tumour-infiltrating lymphocytes.[47,48] Tumour mutational burden, for example, has been associated with OS in studies of immune checkpoint inhibitors.[44]

Emerging Immunotherapy Treatment Strategies in Oesophageal Cancer

Eric Van Cutsem

There are a number of potential treatment strategies to address the unmet needs in oesophageal cancer. These include the use of anti-PD-(L)1 in earlier lines and earlier stages, and novel combination therapies involving an anti-PD-(L)1 agent.

Regarding earlier lines and earlier stages, CheckMate 648[21] in OSCC and KEYNOTE-590[33] in OSCC or OAC both showed that the addition of a PD-1 inhibitor (nivolumab and pembrolizumab, respectively) to first line-line treatment improved the outcome of patients with metastatic or advanced oesophageal cancer.

Many patients with early-stage resectable oesophageal cancer relapse after standard trimodality therapy. The challenge is therefore to move anti-PD-(L)1 agents into earlier lines in combination with trimodality therapy to increase pCR after neoadjuvant treatment, which associated with better outcome compared to non-pCR.[49] Data are emerging on how this might be achieved. In CheckMate 577, patients were treated with CROSS CRT followed by surgery then randomised to nivolumab or placebo for 1 year.[23] The trial showed that DFS was significantly longer with nivolumab compared to placebo.

A Phase II trial in OSCC of neoadjuvant tislelizumab compared with chemotherapy/CRT[50] aims to capitalise on prior data indicating that immunotherapy agents may work synergistically

with chemotherapy or CRT in the pre-operative setting. The ongoing Phase III KEYNOTE-585 study in patients with gastric/GEJ cancer is investigating the addition of pembrolizumab to standard perioperative chemotherapy.[51]

A series of trials are being conducted in patients with inoperable, locally advanced oesophageal cancer. Locoregional recurrence-free survival in patients with oesophageal cancer after definitive CRT remains frequent.[52]

On the other hand, radiotherapy and chemotherapy can exert immunomodulatory effects; therefore, combination with agents targeting the PD-1/PD-L1 axis may result in synergistic treatment responses. For example, treatment with anti-PD-1 therapy after chemotherapy and/or radiotherapy has an effect on tumour cells.[53] Trials are being designed and are ongoing examining the combination of anti-PD-(L)1 agents with CRT in patients with inoperable OSCC.[27] For example, the RATIONALE 311 trial is investigating the combination of tislelizumab and CRT in inoperable OSCC on PFS.[54] Another Phase III trial in OSCC is examining the effect of camrelizumab plus definitive CRT on PFS.[55] The KUNLUN Phase III trial is also testing the addition of an anti-PD-(L)1 agent to definitive CRT on PFS in OSCC, in this case with durvalumab.[56] Finally, the Phase III KEYNOTE-975 is evaluating the addition of pembrolizumab to definitive CRT in patients with oesophageal/GEJ cancer.[57]

Several factors should be considered regarding the use of anti-PD-(L)1 agents in earlier lines and stages of oesophageal cancer. It will be important to identify biomarkers for optimal clinical outcomes, to examine the appropriate strategy after first-line combination therapy of anti-PD-1 plus chemotherapy, and to select both the optimal anti-PD-(L)1 regimen and dose of radiation. The safety profile of treatment with CRT and anti-PD-(L)1 agents in oesophageal cancer must be determined. Despite these unanswered questions, there is a clear rationale for continuing to develop these strategies.

Turning to novel combination therapies involving an anti-PD-(L)1 agent, OACh step of the anti-tumour immunity pathway provides a potential opportunity, such as immunotherapy plus radiotherapy/chemotherapy, targeted therapy, cell therapy, or additional immunotherapy.[58,59] Ongoing studies of anti-PD-(L)1 combined with anti-T-cell Ig and ITIM domain (TIGIT) include the Phase II AdvanTIG-203 study, which is examining tislelizumab plus ociperlimab versus tislelizumab plus placebo for the second-line treatment of patients with advanced or metastatic OSCC with PD-L1 visually estimated CPS ≥10.[60] In the first-line setting, the Phase III SKYSCRAPER-08 trial is testing atezolizumab combined with tiragolumab and chemotherapy versus chemotherapy alone in patients with unresectable locally advanced or metastatic OSCC.[61]

Clinical biomarkers are also needed to identify patients who may derive the most clinical benefit from novel combination therapies with anti-PD-(L)1 agents. In addition, the optimal combination regimen and treatment sequence will need to be determined. More data are required on the safety and tolerability of novel regimens.

In summary, unmet needs in locally advanced disease may be addressed by the addition of anti-PD-(L)1 agents upfront and the use of systemic therapy over surgical approaches, while in metastatic disease unmet needs may be addressed with novel combinations and chemotherapy-free options.[62,63]

Live Q&A

Eric Van Cutsem, Elizabeth Smyth, and Lucjan Wyrwicz

The session concluded with a live Q&A session about the future directions of immunotherapy in patients with oesophageal cancer. The panellists agreed that there is evidence that immune checkpoint inhibitors are effective with a number of different chemotherapy backbones. This means that physicians have a choice of backbone therapy.

Moving on to biomarkers, Smyth recommended PD-L1 testing in patients with OSCC and using pembrolizumab plus chemotherapy in patients who express PD-L1 with CPS ≥10 in first-line. While second-line is biomarker agnostic, Van Cutsem noted that there is some evidence that pembrolizumab is more effective in high expressers of PD-L1, but negative patients do

show some response in this setting. This will become challenging in the future with checkpoint inhibitors moving first-line. Wyrwicz predicted that in 2 years the strategy will likely be similar to lung cancer where early immunotherapy is the focus for high PD-L1 expressers, while for low expressers immunotherapy is reserved for the refractory setting after chemotherapy. In addition, Smyth noted that very large cross-platform, cross-antibody validation studies are needed, as were performed in lung cancer.

Smyth highlighted claudin 18.2 as an attractive marker because it is expressed only on the tumour, thereby reducing off-target effects. The Phase II FAST study of zolbetuximab, an anti-claudin 18.2 antibody, showed positive results in terms of PFS and OS[64] and the Phase III Spotlight trial is currently recruiting.[65] More data are needed regarding co-expression of claudin 18.2 and immune checkpoint molecules like PD-1 and whether that will be impacted in future in combination therapy.

Van Cutsem point to another challenge, which is examining a strategy of PD-1 antibodies plus cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies in patients pre-treated in first-line with chemotherapy versus PD-1 antibodies. While many trials are still needed, the good news is that a lot of new data are coming through in both OSCC and OAC.

References

1. Global Cancer Observatory. Cancer Fact Sheets: Oesophageal Cancer. 2016. Available at: https://gco.iarc.fr/today/data/pdf/fact-sheets/cancers/cancer-fact-sheets-4.pdf. Last accessed: 20 July 2021.
2. Abbas G, Krasna M. Overview of esophageal cancer. Ann Cardiothorac Surg. 2017;6(2):131-6.
3. National Cancer Institute. Cancer Stat Facts: Esophageal Cancer. Available at: https://seer.cancer.gov/statfacts/html/esoph.html. Last accessed: 20 July 2021.
4. American Cancer Society. What is Cancer of the Esophagus? 2020. Available at: https://www.cancer.org/cancer/esophagus-cancer/about/what-is-cancer-of-the-esophagus.html. Last accessed: 20 July 2021.
5. Abnet CC et al. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology. 2018;154(2):360-73.
6. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013;19(34):5598-606.
7. Mimura K et al. Immunotherapy for esophageal squamous cell carcinoma: a review. Fukushima J Med Sci. 2018;64(2):46-53.
8. Greally M et al. Optimal management of gastroesophageal junction cancer. Cancer. 2019;125(12):1990-2001.
9. Coleman HG et al. The epidemiology of esophageal adenocarcinoma. Gastroenterology. 2018;154(2):390-405.
10. American Cancer Society. Tests for Esophageal Cancer. 2020. Available at: https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staging/how-diagnosed.html. Last accessed: 21 July 2021.
11. Guo W et al. Prognostic value of PD-L1 in esophageal squamous cell carcinoma: a meta-analysis. Oncotarget. 2017;9(17):13920-33.
12. Dhakras P et al. Gastrointestinal cancers: current biomarkers in esophageal and gastric adenocarcinoma. Transl Gastroenterol Hepatol. 2020;5:55.
13. American Cancer Society. Treating Esophageal Cancer by Stage. 2021. Available at: https://www.cancer.org/cancer/esophagus-cancer/treating/by-stage.html. Last accessed: 22 July 2021.
14. Borggreve AS et al. Surgical treatment of esophageal cancer in the era of multimodality management. Ann N Y Acad Sci. 2018;1434(1):192-209.
15. National Cancer Institute. Esophageal Cancer Treatment (Adult) (PDQ) Health professional version. Available at: https://www.cancer.gov/types/esophageal/hp/esophageal-treatment-pdq. Last accessed: 22 July 2021.
16. Merck Sharp & Dohme (UK) Limited. Keytruda (pembrolizumab) [summary of product characteristics]. 2021. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#gref. Last accessed: 22 July 2021.
17. Merck Sharp & Dohme Corp. Keytruda (pembrolizumab) [prescribing information]. 2021. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Last accessed: 22 July 2021.
18. Shapiro J et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
19. Karolinska University Hospital. A Study of Chemoradiotherapy Followed by Planned Surgery or by Surveillance and Surgery Only When Needed for Cancer of the Esophagus. NCT04460352. https://clinicaltrials.gov/ct2/show/NCT04460352.
20. Sun JM et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. 2021;398(10302):759-71.
21. Chau I et al. Nivolumab (NIVO) plus ipilimumab (IPI) or NIVO plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): first results of the CheckMate 648 study. J Clin Oncol. 2021;39(18 suppl):LBA4001.
22. Kato K et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(11):1506-17.
23. Kelly RJ et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384(13):1191-203.
24. Al-Batran SE et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet.

2019;393(10184):1948-57.

25. Hoeppner J et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer. 2016;16:503.
26. Janjigian YY et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40.
27. Yang H et al. The combination options and predictive biomarkers of PD-1/PD-L1 inhibitors in esophageal cancer. Front Oncol. 2020;10:300.
28. Yang YM et al. Advances in targeted therapy for esophageal cancer. Signal Transduct Target Ther. 2020;5(1):229.
29. Smyth EC et al. Oesophageal cancer. Nat Rev Dis Primers. 2017;3:17048.
30. US Food and Drug Administration (FDA). FDA approves pembrolizumab for esophageal or GEJ carcinoma. 2021. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma. Last accessed: 16 July 2021.
31. Merck. European Commission Approves Merck's KEYTRUDA® (pembrolizumab) Plus Chemotherapy for Certain Patients with Esophageal Cancer or HER2-Negative Gastroesophageal Junction (GEJ) Adenocarcinoma. 2021. Available at: https://www.merck.com/news/european-commission-approves-mercks-keytruda-pembrolizumab-plus-chemotherapy-for-certain-patients-with-esophageal-cancer-or-her2-negative-gastroesophageal-junction-gej-adenocarcinom/. Last accessed: 16 July 2021.
32. Bristol Myers Squibb. EMA Validates Bristol Myers Squibb's Applications for Opdivo (nivolumab) + Yervoy (ipilimumab) and Opdivo + Chemotherapy as First-Line Treatments for Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma. 2021. Available at: https://news.bms.com/news/corporate-financial/2021/EMA-Validates-Bristol-Myers-Squibbs-Applications-for-Opdivo-nivolumab--Yervoy-ipilimumab-and-Opdivo--Chemotherapy-as-First-Line-Treatments-for-Unresectable-Advanced-Recurrent-or-Metastatic-Esophageal-Squamous-Cell-Carcinoma/default.aspx. Last accessed: 19 August 2021.
33. Kato K et al. Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: the phase 3 KEYNOTE-590 study. Annuals of Oncol. 2020;31(suppl4):S1142-215.
34. Xu R et al. ESCORT-1st: a randomized, double-blind, placebo-controlled, phase 3 trial of camrelizumab plus chemotherapy versus chemotherapy in patients with untreated advanced or metastatic esophageal squamous cell carcinoma (ESCC). J Clin Oncol. 2021;39(15 suppl):4000.
35. BeiGene. A Study of Tislelizumab (BGB-A317) in Combination With Chemotherapy as First Line Treatment in Participants With Advanced Esophageal Squamous Cell Carcinoma. NCT03783442. https://clinicaltrials.gov/ct2/show/NCT03783442.
36. Innovent Biologics (Suzhou) Co Ltd. Sintilimab or Placebo With Chemotherapy in Esophageal Squamous Cell Carcinoma (ORIENT-15). NCT03748134. https://clinicaltrials.gov/ct2/show/NCT03748134.
37. Shanghai Henlius Biotech. A Clinical Trial Comparing HLX10 With Placebo Combined With Chemotherapy (Cisplatin + 5-fu) in the First-line Treatment of Locally Advanced/Metastatic Esophageal Squamous Cell Carcinoma (ESCC). NCT03958890. https://clinicaltrials.gov/ct2/show/NCT03958890.
38. Merck. FDA Approves New Monotherapy Indication for Merck's KEYTRUDA® (pembrolizumab). 2019. Available at: https://www.merck.com/news/fda-approves-new-monotherapy-indication-for-mercks-keytruda-pembrolizumab. Last accessed: 17 July 2021.
39. Bristol Myers Squibb. U.S. Food and Drug Administration Approves Opdivo® (nivolumab) for the Treatment of Patients with Advanced Esophageal Squamous Cell Carcinoma (ESCC) After Prior Fluoropyrimidine- and Platinum-based Chemotherapy. 2020. Available at: https://news.bms.com/news/corporate-financial/2020/US-Food-and-Drug-Administration-Approves-Opdivo-nivolumab-for-the-Treatment-of-Patients-with-Advanced-Esophageal-Squamous-Cell-Carcinoma-ESCC-After-Prior-Fluoropyrimidine--and-Platinum-based-Chemotherapy/default.aspx. Last accessed: 16 July 2021.
40. Bristol Myers Squibb. Bristol Myers Squibb Receives European Commission Approval for Opdivo (nivolumab) as Second-Line Treatment for Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma. 2020. Available at: https://news.bms.com/news/details/2020/Bristol-Myers-Squibb-Receives-European-Commission-Approval-for-Opdivo-nivolumab-as-Second-Line-Treatment-for-Unresectable-Advanced-Recurrent-or-Metastatic-Esophageal-Squamous-Cell-Carcinoma/default.aspx. Last accessed: 16 July 2021.
41. Kojima T et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. J Clin Oncol. 2020;38(35):4138-48.
42. Shen L et al. RATIONALE 302: randomized, phase 3 study of tislelizumab versus chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma. J Clin Oncol. 2021;39(15suppl):4012.
43. Huang J et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol. 2020;21(6):832-42.
44. Sanstein RM, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019;51(2):202-6.
45. Le DT et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-13.
46. Shah MA et al. Association of T-cell–inflamed gene expression profile and PD-L1 status with efficacy of pembrolizumab in patients with esophageal cancer from KEYNOTE-180. Abstract 261. SITC virtual, 11-14 November, 2020.
47. Xu J et al. Tumor-Immune Signatures Associated With Response or Resistance to Tislelizumab (Anti-PD-1) in Esophageal Squamous Cell Carcinoma (ESCC). Abstract 79. SITC virtual, 11-14 November, 2020.
48. Doi T et al. Safety and antitumor activity of the anti-programmed death-1 antibody pembrolizumab in patients with advanced esophageal carcinoma. J Clin Oncol. 2018;36(1):61-7.
49. Blum MM et al. Pathological complete response in patients with esophageal cancer after the trimodality approach: the association with baseline variables and survival-The University of Texas MD Anderson Cancer Center experience. Cancer. 2017;123(21):4106-13.
50. BeiGene. Study of Tislelizumab in Participants with Resectable Esophageal Squamous Cell Carcinoma. NCT04974047. https://clinicaltrials.gov/ct2/show/NCT04974047.
51. Bang YJ et al. KEYNOTE-585: phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. Future Oncol. 2019;15(9):943-52.

52. Versteijne E et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. Dis Esophagus. 2015;28(5):453-9.

53. Buchwald ZS et al. Radiation, immune checkpoint blockade and the abscopal effect: a critical review on timing, dose and fractionation. Front Oncol. 2018;8:612.

54. Yu R et al. RATIONALE 311: tislelizumab plus concurrent chemoradiotherapy for localized esophageal squamous cell carcinoma. Future Oncol. 2021;17(31):4081-9.

55. Jiangsu HengRui Medicine Co Ltd. Study of Camrelizumab (SHR-1210) in Combination With Concurrent Chemoradiotherapy in Locally Advanced Esophageal Cancer. NCT04426955. https://clinicaltrials.gov/ct2/show/NCT04426955.

56. AstraZeneca. Study of Durvalumab Versus Placebo in Combination With Definitive Chemoradiation Therapy in Patient With ESCC (KUNLUN). NCT04550260. https://clinicaltrials.gov/ct2/show/NCT04550260.

57. Shah MA et al. KEYNOTE-975 study design: a Phase III study of definitive chemoradiotherapy plus pembrolizumab in patients with esophageal carcinoma. Future Oncol. 2021;17(10):1143-53.

58. Gajiwala S et al. Combination immunotherapy and radiation therapy strategies for pancreatic cancer-targeting multiple steps in the cancer immunity cycle. J Gastrointest Oncol. 2018;9(6):1014-26.

59. Pan C et al. Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy. J Hematol Oncol. 2020;13(1):29.

60. Xu RH et al. AdvanTIG-203: a randomized phase 2 study comparing anti-TIGIT ociperlimab plus tislelizumab versus tislelizumab plus placebo as second-line treatment in patients with advanced or recurrent esophageal squamous cell carcinoma (ESCC) expressing programmed death-ligand 1 (PD-L1). J Clin Oncol. 2021;39(15suppl):TPS4150.

61. Hoffmann-La Roche. A Study of Atezolizumab Plus Tiragolumab in Combination With Paclitaxel and Cisplatin Compared With Paclitaxel and Cisplatin as First-Line Treatment in Participants With Unresectable Locally Advanced, Unresectable Recurrent, or Metastatic Esophageal Carcinoma (SKYSCRAPER-08). NCT04540211. https://clinicaltrials.gov/ct2/show/NCT04540211.

62. Lee S, Cohen DJ. Pharmacotherapy for metastatic esophageal cancer: where do we need to improve? Expert Opin Pharmacother. 2019;20(3):357-66.

63. Zou LQ et al. Immune checkpoint inhibitors: a new era for esophageal cancer. Expert Rev Anticancer Ther. 2019;19(8):731-8.

64. Sahin U et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. Ann Oncol. 2021;32(5):609-19.

65. Astellas Pharma Global Development IncA. Phase 3 Efficacy, Safety and Tolerability Study of Zolbetuximab (Experimental Drug) Plus mFOLFOX6 Chemotherapy Compared to Placebo Plus mFOLFOX6 as Treatment for Gastric and Gastroesophageal Junction (GEJ) Cancer (Spotlight). NCT03504397. https://clinicaltrials.gov/ct2/show/NCT03504397.

Abstract Reviews

Sharing the latest research findings and knowledge from leading experts in oncology from the European Society for Medical Oncology (ESMO) Congress 2021.

A Phase II Prospective Trial of Frontline Cabozantinib in Metastatic Collecting Ducts Renal Cell Carcinoma: the BONSAI Trial (Meeturo 2)

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Support: This trial received funding from Ipsen.

Keywords: Collecting duct carcinoma, cabozantinib, DNA sequencing, orphan disease, RNA sequencing.

Citation: EMJ Oncol. 2021;9[1]:38-39. Abstract Review No. AR1

BACKGROUND

Metastatic collecting ducts carcinoma is biologically poorly characterised and under-represented in prospective randomised trials.[1-3]

METHODS

This prospective, monocentric, Phase II trial tested cabozantinib (cabo) 60 mg in treatment naive mCDC patients. Primary endpoint was objective response rate per RECIST 1.1. Secondary endpoints were progression free survival (PFS), overall survival and safety profile. Exploratory objectives were to identify somatic mutations by targeted DNA sequencing, and to define molecular subtypes, signatures and transcript fusions genes by RNA sequencing. A central pathological review was mandatory. The study was based on a Simon's two stage optimal design.

RESULTS

From January 2018 to November 2020, 25 patients were enrolled, of whom 23 started treatment. The median age was 66 years and 19 patients were male. The most common metastatic sites were lymphnodes and bone (15 and 13 patients, respectively), followed by lung and liver (10 and 4 patients, respectively). Median follow up was 8 months. Objective response rate was 35% (1 complete response and 7 partial repsonses). Median PFS was 6 months. All patients reported at least one grade (G) 1–2 adverse event (AE). The most common were fatigue (43%), hypothyroidism (28%), stomatitis (28%), anorexia (26%), hand-foot syndrome (13%), hypertension (17%), and diarrhoea (13%). Five patients reported G3 AEs (2 thromboembolic events, 2 arterial hypertension, 1 fatigue), while no G4–5 AEs were reported. Seventeen percent of patients required dose reduction. DNA sequencing was successful in 21 (91%) patients. All tumours were microsatellite stable. No association between tumor mutational burden and response to cabo was observed. The most affected pathways were chromatin modifying enzymes (46%) and adaptive immune system (23%). Responsive patients (PFS>6 months) showed high frequency of mutations affecting deubiquitination, cell-cell communication, and TGF-n signaling. Non-responders were frequently mutated in chromatin remodeling, transcriptional regulation and Wnt signalling pathways.

CONCLUSIONS

The study met its primary endpoint showing promising efficacy and acceptable tolerability of cabo in metastatic collecting ducts carcinoma patients. Mature results according to mutational profiles and gene signatures will be presented. ■

References

1. Procopio G et al. Treatment of collecting duct carcinoma: current status and future perspectives. Anticancer Res. 2014;34(2):1027-30.
2. Gargiuli C et al. Integrative transcriptomic analysis reveals distinctive molecular traits and novel subtypes of collecting duct carcinoma. Cancers (Basel). 2021;13(12):2903.
3. Pagani F et al. Collecting ducts carcinoma: an orphan disease. Literature overview and future perspectives. Cancer Treat Rev. 2019;79:101891.

Colorectal Cancer Screening and Diagnosis During the COVID-19 Pandemic in Québec, Canada

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Keywords: Colonoscopy, colorectal cancer (CRC), COVID-19, delays, diagnosis, faecal occult blood test, surgery.

Citation: EMJ Oncol. 2021;9[1]:40. Abstract Review No. AR2.

BACKGROUND

Colorectal cancer (CRC) is the third most common cancer in Québec, Canada, and the second and third cause of cancer death in males and females, respectively.[1] Québec, a province with a population of 8.5 million, was hard-hit during the first wave of the COVID-19 pandemic (March–July 2020). A status of public health emergency was declared in Québec on 16th March 2020. All cancer screening programmes and elective procedures were, therefore, suspended on that date.

MATERIALS AND METHODS

Ministry of Health of Québec data related to cancer screening programmes and diagnosis during the periods of March 2019 to February 2020 and March 2020 to February 2021 were recently reported.[2] The 4-month period (April–July) of 2020 and 2019 were compared to study the impact of the COVID-19 pandemic on screening and diagnosis of CRC.

RESULTS

From April to July 2020, faecal occult blood tests decreased by 67.26%, colonoscopy procedures by 57.80%, and CRC surgery by 29.50% compared with the same period from 2019. The waiting list for colon endoscopy increased by 210% from April to July 2020 and by 141% from August to October 2020. With resumed activities from August to October 2020, no catching-up with the delays was seen. There were 5% fewer faecal occult blood tests, 11.4% fewer colonoscopies, and 28.0% fewer CRC surgeries compared to the same period in 2019.

CONCLUSION

The COVID-19 pandemic affected screening and lead to unprecedented delays in cancer screening, diagnosis, and treatment. Catching-up with the delays is a challenge for health authorities, and adding substantial resources is highly required. The impact of the off-loading of diagnostic and surgical activities on cancer mortality is hard to be estimated but is likely to be significant. ■

References

1. Brenner DR et al. Projected estimates of cancer in Canada in 2020. CMAJ. 2020;192(9):E199-205.
2. Ministère de la Santé et des Services sociaux. Analyse des répercussions de la pandémie de la COVID-19 sur les soins et les services en cancérologie au Québec. 2021. Available at: https://publications.msss.gouv.qc.ca/msss/fichiers/2020/20-210-378W.pdf. Last accessed: 5 October 2021.

Serologic Status and Toxic Effects of the SARS-CoV-2 BNT162b2 Vaccine in Patients Undergoing Treatment for Cancer

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BACKGROUND

The COVID-19 pandemic has been associated with inferior clinical outcomes in patients with cancer, owing to altered delivery of care and potential high-risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in distinct subpopulations.[1,2] The BNT162b2 vaccine, which is administered in 2 doses at a 21-day interval, was found to be safe and efficient in preventing COVID-19 in the general population.[3,4] However, patients with cancer under active treatment were not represented in these trials. In this study, the authors prospectively evaluated the serologic status and safety of the SARS-CoV-2 BNT162b2 vaccine in a cohort of patients with solid tumors who were receiving active anticancer treatments, compared with age-matched healthcare workers who served as vaccinated controls.

METHODS

In January 2021, mass SARS-CoV-2 vaccination of high-risk populations, including patients with cancer, was initiated in Israel. This cohort study prospectively enrolled and followed up patients with cancer and healthy participants between 15th January and 14th March 2021. The study was conducted at the Division of Oncology of Rambam Health Care Campus, the major tertiary (referral) medical centre in Haifa, Israel. Participants included 232 patients with cancer who were receiving active treatment after their first and second doses of the BNT162b2 vaccine, and 261 healthy, age-matched healthcare workers, who served as controls. Serum samples were collected after each vaccine dose and in cases of seronegativity. Questionnaires regarding sociodemographic characteristics and adverse reactions were administered at serum collection. A regulatory agencies–approved assay was used to assess IgG at all time points. Patients' electronic medical records were reviewed for documentation of COVID-19 infection and results of blood cell counts, liver enzyme levels, and imaging studies.

RESULTS

Of the 232 patients undergoing treatment for cancer, 132 were males (57%); mean (standard deviation) age was 66 (12.09) years. Cancer types included mostly gastrointestinal (27%), genitourinary (21%), lung (19%), and breast (18%) cancers. After the first dose of BNT162b2 vaccine, 29% (n=25) patients were seropositive compared with 84% (n=220) of the controls (p<0.001). After the second dose, the seropositive rate reached 86% (n=187) in the patients group. Testing rate ratios per 1,000 people days after the first dose were 12.5 (95% confidence interval

(CI): 3.4–45.7) for the patients, and 48.5 (95% CI: 37.2–63.2) for the controls. Patients undergoing chemotherapy showed reduced immunogenicity (odds ratio: 0.41; 95% CI: 0.17–0.98). No COVID-19 cases were documented throughout the study period; however, two cases in the patient cohort were noted immediately after the first dose. Reported adverse events were in concordance with previous reports comprising mostly healthy individuals. Elevation of liver enzyme levels was documented in 10.5% of patients with cancer. Newly documented axillary or cervical lymphadenopathy was noted in 5% of CT and PET scans that were performed as part of routine cancer care.

CONCLUSION

The SARS-CoV-2 BNT162b2 vaccine was found to be safe and achieved satisfactory serologic status in patients with cancer in this cohort study. A pronounced lag in antibody production was noted in patients with cancer compared with controls who do not have cancer; however, after the second dose, seroconversion occurred in most patients. Additional real-world data is required to determine the long-term efficacy of the vaccine with regard to type of anticancer treatment. ■

References

1. Desai A et al. Mortality in hospitalized patients with cancer and coronavirus disease 2019: a systematic review and meta-analysis of cohort studies. Cancer. 2021;127(9):1459-68.
2. Liang W et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
3. Polack FP et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-15.
4. Dagan N et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384(15):1412-23.

More than FOLFOX and FOLFIRI: The Management of Metastatic Colorectal Cancer in the Era of Precision Oncology

EDITOR'S PICK

My chosen article for the Editor's Pick in this issue is 'More than FOLFOX and FOLFIRI: Management of Metastatic Colorectal Cancer in the Era of Precision Oncology' by Jácome and Johnson. The paper discusses the current landscape and standard of care for metastatic colorectal cancer (mCRC), a disease known for its heterogeneity and poor prognosis. Enhancements in molecular biology in relation to oncology have allowed the identification of specific molecular subtypes and novel therapeutic targets. In the review, Jacome and Johnson describe the current and emerging predictive biomarkers in mCRC and present landmark clinical trials that have allowed for evolving and improving precision in therapeutic management of the disease. Promising findings with targeted therapies offer the possibility of a new era of precision oncology and personalised treatments sustaining hope for patients with mCRC.

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Abstract

Metastatic colorectal cancer (mCRC) is a markedly heterogeneous disease, which portends a poor prognosis, with an estimated 5-year overall survival rate of approximately 15%. The standard of care of systemic therapy remains fluoropyrimidine-based chemotherapy, with modest results, despite improvements with the combination with anti-angiogenics and anti-epidermal growth factor receptor therapy.

Significant advances in cancer therapy have been observed in the past two decades. The enhanced appreciation of molecular biology in oncology has allowed for the identification of specific molecular subtypes and novel therapeutic targets. Nevertheless, meaningful precision-based advancements in the therapeutic options for mCRC have been challenging and slow to realisation. Comprehensive molecular profiling and circulating tumour DNA highlight a heterogeneous disease at the genomic, epigenomic, and transcriptomic levels, and with a low frequency of actionable alterations.

In the present review, the authors describe the current and emerging predictive biomarkers in mCRC, as well as present landmark clinical trials that have allowed for evolving precision in the therapeutic management. The understanding of the benefit of immune checkpoint inhibitors in patients with high microsatellite instability cancer and in those with *POLE* mutations or high tumour mutational burden, the combination of BRAF with epidermal growth factor receptor inhibition in *BRAF* V600-mutated patients, the use of allele-specific KRAS G12C inhibitors, the promising findings of dual anti-HER2 therapy in *HER2*-positive mCRC, and the possibility to offer targeted therapy for patients harbouring gene fusions *NTRK/ALK/ROS1* have ushered in a new era of precision oncology for mCRC, providing personalised treatments and sustaining hope for patients affected by this challenging disease.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the USA.[1] Despite improvements in screening rates and in the overall survival (OS) of patients with localised and advanced disease over the past few decades, the 5-year OS of patients with metastatic disease is still extremely poor and estimated to be approximately 15%.[2,3]

Significant advances in cancer therapy have been observed in the past two decades. The enhanced appreciation of molecular biology in oncology has allowed for the identification of specific molecular subtypes and novel therapeutic targets. This era of precision oncology allows for the development of biomarker-guided therapeutics and has markedly transformed the landscape of cancer treatment. Precision medicine represents a paradigm shift in oncology, moving from a histology-based chemotherapy to include genome-specific targeted therapy, which has promoted ongoing discovery for novel biomarkers in all malignancies.

Nevertheless, the emergence of precision oncology has drastically improved the management of CRC. Comprehensive molecular profiling confirms a markedly heterogeneous disease at the genomic, epigenomic, and transcriptomic levels, but currently with low frequency of actionable alterations. For more than a decade, personalised therapy in CRC was restricted to the identification of *RAS* mutations, which are predictive markers of resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies. Only recently, clinical trials addressing novel genome-guided personalised therapies in specific molecular subtypes of CRC have been successfully completed, expanding the clinical relevance of precision oncology in CRC.

In this review, the authors describe the current and emerging predictive biomarkers in metastatic CRC (mCRC), as well as present landmark clinical trials that have allowed for evolving precision in the management of this heterogenous disease.

ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR MONOCLONAL ANTIBODIES IN METASTATIC COLORECTAL CANCER IN THE PAST TWO DECADES: PRECISION THAT NEEDS FURTHER REFINEMENT

For almost two decades, the clinical applicability of precision in mCRC has been limited to the use of the anti-EGFR monoclonal antibodies cetuximab and panitumumab for *RAS* wild-type disease. The knowledge accumulated over the past 20 years has demonstrated that the benefit offered by these monoclonal antibodies is restricted to a smaller subset of mCRC than initially proposed (Figure 1). Pure predictive biomarkers reflecting patient specific sensitivity to anti-EGFR monoclonal antibodies remains a developing area in mCRC. Interestingly, evidence accumulated over the past few years suggest that not only expanded *RAS* mutations such as *NRAS* and *HRAS* may confer additional resistance to cetuximab or panitumumab but also *BRAF*, *PI3KCA*, *HER2*, *MET*, *PTEN*, and *AKT1* abnormalities, as well as *NTRK/ROS1/ALK/RET* rearrangements.[4-9] Furthermore, recent studies have consistently demonstrated that patients with right-sided tumours derive lower, if any, benefit from that therapy.[10,11]

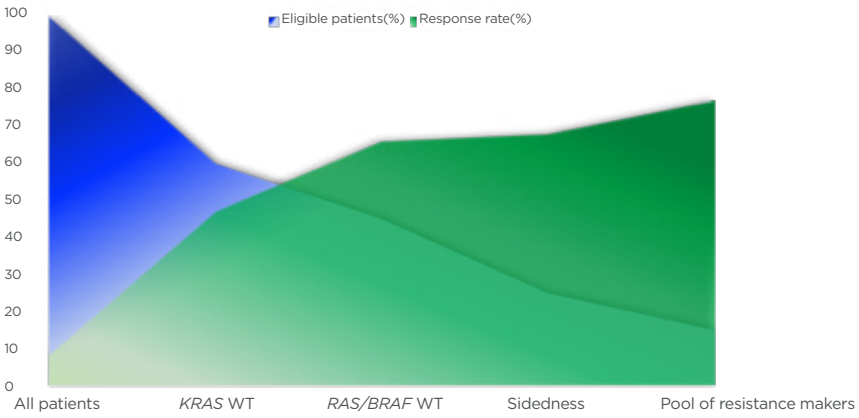

Figure 1: Negative hyper-selection of patients with metastatic colorectal cancer to anti-epidermal growth factor receptor monoclonal antibodies.

The graph shows the ascending response rate (y-axis, in green) of anti-EGFR therapy in mCRC based on patient selection by biomarkers (*RAS* and *BRAF*), sidedness, and a pool of resistance markers such as *BRAF*, *PI3KCA*, *HER2*, *MET*, *PTEN*, and *AKT1* abnormalities, as well as *NTRK/ROS1/ALK/RET* rearrangements, which lead to a descending rate of eligible patients for targeted therapy (x axis, in blue). Since there are no predictive biomarkers of sensitivity for anti-EGFR therapy, the patient selection based on predictive markers of resistance may be denominated as negative hyper-selection.

EGRF: epidermal growth factor receptor; mCRC: metastatic colorectal cancer; WT: wild-type.

Hence, the estimated rate of patients with mCRC who are actually sensitive to cetuximab or panitumumab is lower than approximately 15%.[9] The current recommendation to use anti-EGFR monoclonal antibodies in patients with left-sided tumours and *RAS/BRAF* wild-type status still is an incipient and imprecise clinical applicability of precision medicine in the systemic therapy of CRC. Therefore, the identification of refined biomarkers and novel targeted therapies are urgently needed (Figure 2; Table 1).

NOVEL THERAPEUTIC TARGETS IN COLORECTAL CANCER

MSI-H CRC

It is estimated that approximately 5% of patients with mCRC harbour high-frequency microsatellite instability (MSI-H), which might originate from two mechanisms: somatic hypermethylation of the *MLH1* gene promoter, commonly associated with *BRAF* V600E mutation; or point mutation of one of the mismatch repair genes, mainly *MLH1* and *MSH2*.[12,13] Patients with MSI-H CRC compose a subgroup with distinct molecular and clinical characteristics. Typically, they present a younger median age at diagnosis, with tumours predominantly located at the proximal colon, commonly with lymphocyte infiltration, and with a higher median number of tumour mutational burden (TMB).[13] In addition, they have lower sensitivity to chemotherapy compared with patients classified as microsatellite stable (MSS), and, more importantly, they tend to be sensitive to immunotherapeutic approaches, such as immune checkpoint inhibitors (ICIs).

Encouraging data from Phase I and II clinical trials[14-19] prompted the conception of the Phase III KEYNOTE-177 study, which compared the efficacy of standard chemotherapy (doublets plus anti-vascular endothelial growth factor or anti-EGFR) with pembrolizumab in 307 treatment-naïve patients with MSI-H mCRC.[20] One of the primary endpoints, progression-free survival, was met: 8.2 months in the chemotherapy group versus 16.5 months in the immunotherapy group (hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.45–0.80; p=0.0002). Likewise, the overall response rate (ORR) was statistically higher in the immunotherapy arm: 33.1% versus 43.8%.

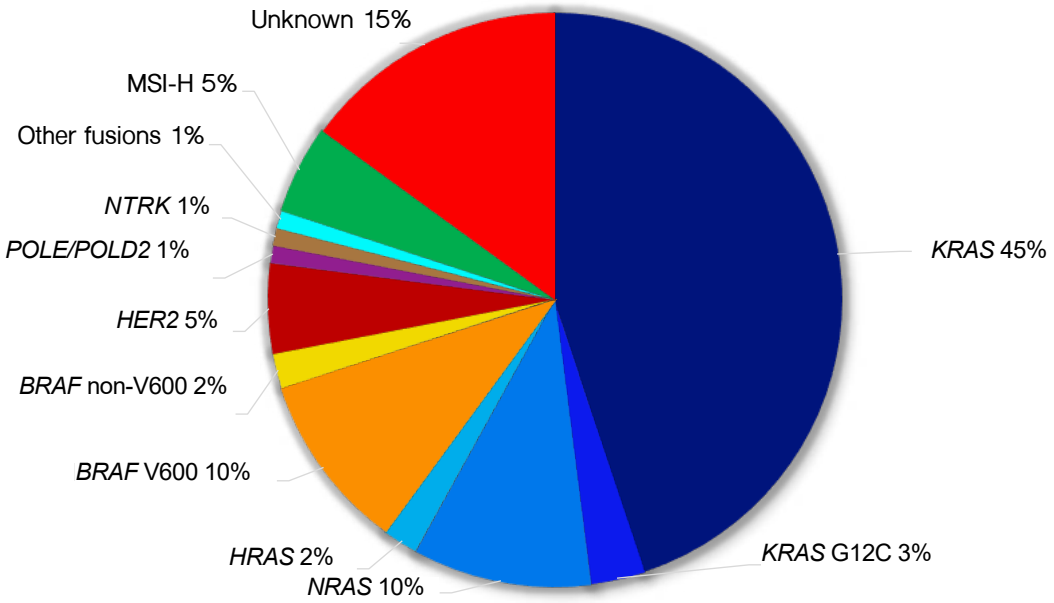

Figure 2: Molecular alterations with therapeutic implications in metastatic colorectal cancer.

MSI-H: high-frequency microsatellite instability.

Table 1: Predictive biomarkers and targeted therapies in metastatic CRC.

Biomarkers	Rates*	Predictive role to systemic therapy
KRAS non-G12C	45%	Resistance to anti-EGFR therapy
KRAS G12C	3%	Resistance to anti-EGFR therapy Poor sensitivity to sotorasib or adagrasib alone
NRAS	10%	Resistance to anti-EGFR therapy
HRAS	2%	Resistance to anti-EGFR therapy
BRAF V600E	10%	Sensitivity to encorafenib+cetuximab±binimetinib Resistance to anti-EGFR therapy
BRAF non-V600E	2%	Uncertain
HER2 amplification	5%	Sensitivity to anti-*HER2* therapies Potential resistance to anti-EGFR therapy
NTRK fusions	1%	Sensitivity to larotrectinib or entrectinib
ALK/ROS1 fusions	<1%	Sensitivity to *ALK/ROS1* inhibitors
MSI-H	5%	Sensitivity to immune checkpoint inhibitors
POLE/POLD2	1%	Potential sensitivity to immune checkpoint inhibitors

*Approximate rates.

MSI-H: high-frequency microsatellite instability, EGFR: epidermal growth factor receptor.

Interestingly, 29.4% of the patients in the pembrolizumab group presented progressive disease compared with 12.3% in the chemotherapy group, predominantly in the first 4 months of treatment. Of the patients who presented objective response to immunotherapy, an impressive rate of 83% had ongoing responses at 24 months, compared with only 35% in the chemotherapy group. Another primary endpoint, OS, did not have mature data to be analysed.

MSI-H is not the only biomarker to explain sensitivity to ICIs. Patients with MSI-H who present with low TMB seem to have a lower probability to respond to immunotherapy.[21] A high concordance rate is expected between MSI-H and TMB. Patients with abnormalities in DNA mismatch repair pathways, whether germline or somatic, tend to present higher number of nonsynonymous mutations, and thereby high TMB. In a study with 6,004 patients with mCRC, 5% were classified as MSI-H and 95% as MSS.[22] The median TMB was significantly higher in the population with MSI-H: 46.8 mutations/Mb versus 3.6 mutations/Mb. The median TMB in the overall population was 4.5 mutations/Mb. Approximately 3% of patients with MSS were classified as high TMB, defined as ≥12 mutations/Mb. Variants in the mismatch repair genes, such as *MLH1*, *MSH2*, and *MSH6*, as well as in *POLE*, were significantly more common in this population of patients with high TMB and MSS relative to those with low TMB and MSS.[22]

POLE

POLE encodes the catalytic subunit of DNA polymerase ε, which acts in the replication of the DNA strand before cell division.[23] *POLE* proofreading is an essential step in the maintenance of the integrity of the genome, which is consistent with the finding of ultra-mutated tumours in the presence of pathogenic exonuclease domain mutations, with a mean tumour mutational burden >200 mutations/Mb.[24,25] *POLE* mutation is rarely found in malignancies, being identified in approximately 5–10% of endometrial cancer,[26] 1% of CRC,[27] and less frequently in gastric and pancreatic cancers.[28]

POLE-mutated CRC portends a better prognosis. In a population of 6,517 patients with CRC, 1% (66 patients) harboured the mutation, which was associated with a reduced risk of recurrence and a superior OS in a population of patients with Stage II/III CRC.[23] Patients with *POLE*-mutated CRC were younger at diagnosis, predominantly male, with a higher frequency of right-sided tumours, and with disease diagnosed at earlier stages compared with the wild-type counterparts.[23,25,29] They also demonstrated increased CD8+ lymphocyte infiltration and expression of cytotoxic T-cell markers.[23]

This immunogenic subset of CRC has been demonstrated to be highly sensitive to the ICIs. Case reports with successful experiences in the treatment of metastatic CRC have been presented in the past few years.[31,32] Since there is a U.S. Food and Drug Administration (FDA) approval for the use of pembrolizumab for patients with metastatic disease and TMB >10 mutations/Mb,[32] the use of immunotherapy should be strongly considered in the treatment of patients with *POLE*-mutated mCRC. The probability to identify these mutations is higher in early-onset CRC compared to the late-onset.[33]

BRAF

BRAF V600E mutation is found in approximately 10% of patients with mCRC.[34-37] These patients have a poorer prognosis compared with the wild-type counterparts, demonstrating lower sensitivity to the standard chemotherapeutic drugs used in CRC, with lower ORR, and shorter progression-free survival and OS.[38-40] More commonly found in right-sided tumours, this mutation, similarly to *RAS* mutations, also denotes resistance to the anti-EGFR monoclonal antibodies.[41,42]

The success of BRAF inhibitors in the systemic therapy of *BRAF*-mutated melanoma prompted the evaluation of these drugs in mCRC. However, Phase I data addressing the efficacy of vemurafenib in patients with *BRAF*-mutated mCRC showed poor efficacy.[43] Preclinical studies demonstrated that BRAF inhibition induced adaptive feedback reactivation of mitogen-activated protein kinase signalling, often mediated by EGFR activation, suggesting that the combination of BRAF inhibitor with an anti-EGFR monoclonal antibody might overcome this

therapeutic resistance.[44-46] Subsequently, a Phase IB study confirmed the hypothesis, demonstrating that the combination of vemurafenib, irinotecan, and cetuximab yielded 35% of ORR in a population of 19 patients with *BRAF*-mutated mCRC.[47] Additionally, further work demonstrated the clinical activity of the combination of BRAF and EGFR inhibition with or without mitogen-activated protein kinase kinase (MEK) inhibition in *BRAF*-mutated mCRC.[44]

These promising findings elicited the conception of the Phase III BEACON study, a three-arm clinical trial that explored the combination of BRAF and EGFR inhibition with MEK inhibition. A total of 665 patients with *BRAF* V600E-mutated mCRC who had been submitted to at least one previous line of systemic therapy were randomised to one of three arms: the triplet-regimen composed of encorafenib plus binimetinib plus cetuximab; the doublet-regimen with encorafenib plus cetuximab; and the control arm with irinotecan-based regimens (folinic acid, fluorouracil, and irinotecan; or irinotecan) plus cetuximab.[48] The primary end points were OS and ORR in the triplet-regimen arm compared to the control arm. Updated survival results showed a median OS of 9.3 months in the triplet arm versus 5.9 months in the control arm (HR: 0.60; 95% CI: 0.47–0.75).[49] The ORR was 27%, 20%, and 2% in the triplet, doublet, and control arms, respectively. A comparison of the median OS in the doublet arm (9.3 months) with the control arm, a secondary endpoint, also favoured the BRAF inhibitor (HR: 0.61; 95% CI: 0.48–0.77). There was no statistically significant difference between the triplet and doublet arms in OS: 9.3 months in both groups (HR: 0.95; 95% CI: 0.74–1.21).[49] Grade ≥3 adverse events were found in 66%, 58%, and 64% of the patients in the triplet, doublet, and control arms, respectively. Based on BEACON data, the FDA has approved the combination of encorafenib plus cetuximab for the treatment of patients with mCRC and a *BRAF* V600E mutation with at least one prior systemic therapy.[50]

The clinical relevance of non-V600 *BRAF* mutations has not yet been fully elucidated. These mutations have been found in approximately 2% of patients with mCRC, of which the D594N (Class III) and G469A (Class II) mutations seem to be the most frequent.[51] The patients who harbour these atypical *BRAF* mutations seem to present similar prognosis compared to the wild-type counterparts. Unlike V600E, these atypical mutations are mostly identified in left-sided tumours, and younger male patients.[51] In addition, most of them are MSS and *RAS* mutations are not mutually exclusive in this context, occurring in approximately one-third of non-V600 patients.[51,52] The predictive value of these mutations for the deployment of anti-EGFR monoclonal antibodies is not yet entirely clear, and appears to differ according to the underlying *BRAF* class. Class II mutations appear to be resistant while Class III are sensitive, although with limited duration.[53-55] Furthermore, non-V600 *BRAF* mutations might be involved in the development of adaptive resistance to EGFR inhibition.[51] These distinct class-specific biochemical and functional properties highlight the importance to decipher the unique biology of atypical *BRAF* mutations in order to promote novel clinical trial design and ultimately offer effective therapeutic options for patients.

KRAS G12C

KRAS mutations are the most common activating genetic mutations in solid tumours, mainly in pancreatic cancer, non-small cell lung cancer, and CRC, where they are estimated to be found in approximately 45% of tumours.[37,56,57] Right-sided tumours present a higher percentage of *KRAS* mutations compared with their left-sided counterparts, mainly in the cecum, where approximately 70% of the tumours harbour the mutation.[56] For decades, *KRAS* mutations have not been deemed as actionable, but, together with other *RAS* mutations, they predict resistance to anti-EGFR monoclonal antibodies in CRC.[58,59]

Despite years of research focus, targeting *KRAS* has been an elusive goal in cancer therapy since the mutated protein has high affinity for guanosine triphosphate or guanosine diphosphate and has no binding pocket.[60] In addition, inhibition of the downstream effectors in the mitogen-activated protein kinase pathway (BRAF-MEK-ERK) has proven ineffective in clinical trials.[60]

The codons 12 and 13 in exon 2 are the most commonly altered in *KRAS* mutations, occurring

in approximately 30% and 10%, respectively, of the patients with mCRC.[57] The amino acid changes p.G12D, p.G12V, and p.G13D are the most frequent of these codons in CRC, found in approximately 13%, 10%, and 9% of the patients, respectively.[57] The oncoprotein KRAS p.G12C is found in 1–3% of patients with mCRC.[57,61] The substitution of glycine for cysteine at position 12 results in a predominantly guanosine triphosphate-bound KRAS protein, the active form, favouring proliferation and survival of tumour cells.[62,63]

Recently, the isoform *KRAS* G12C has demonstrated to be targetable by a covalent allele-specific inhibitor. Sotorasib (AMG510) is a small molecule that specifically and irreversibly inhibits KRAS G12C in its inactive guanosine diphosphate-bound state through an interaction with one of its pockets.[61] It was evaluated in a Phase I trial with 129 previously treated patients with advanced solid tumours harbouring the *KRAS* G12C mutation.[61] In the overall trial population, of the 42 patients with CRC, only 3 (7%) presented partial response, but 28 (67%) experienced stable disease. On the other hand, 32% of the 59 patients with non-small cell lung cancer had partial response, and 56% showed stable disease. Adagrasib (MRTX849) is another KRAS G12C inhibitor under therapeutic development and it has shown promising efficacy in preclinical studies and preliminary clinical findings.[64] Additional Phase I/II clinical trials are currently evaluating the efficacy of adagrasib in *KRAS* G12C-mutated malignancies, and an ongoing Phase III clinical trial is comparing the efficacy of adagrasib in combination with cetuximab versus chemotherapy in the second-line setting for patients with mCRC and *KRAS* G12C mutation (NCT04793958).[65]

Interestingly, patients with *KRAS* G12C-mutated mCRC seem to present poorer clinical outcomes compared with the patients with *KRAS* non-G12C mutations.[66,67] A recent single-institutional study identified 187 patients with *KRAS* G12C from an original population of 4,685 patients with mCRC.[66] When compared to a cohort of 720 patients with *KRAS* non-G12C mutations, these 187 patients had shorter OS, excluding patients who had undergone metastasectomy: 21.2 months versus 31.6 months (p=0.003). Another cohort of 839 patients with mCRC also found an inferior OS in G12C population compared with the non-G12C: 25.9 months versus 35.8 months (HR: 1.55; 95% CI: 1.08–2.24; p=0.018), which was confirmed by multivariate analysis (HR: 1.81; 95% CI: 1.20–2.70; p=0.04).[67] Correlative findings also demonstrated that this subgroup of patients with mCRC show a distinct mutational profile, with higher rates of *APC* co-mutations compared with the patients without the G12C mutation, but lower rates of *BRAF*, *ERBB4*, *NRAS*, and *TP53* co-mutations.

The reasons for the different efficacy of the KRAS G12C inhibitor according to the tissue of origin are not clear.[61] Ongoing translational studies will be crucial in the understanding of the probable intrinsic resistance of *KRAS* G12C-mutated mCRC to the KRAS G12C inhibitors as monotherapy, and for the design of clinical trials evaluating the combination of these inhibitors with other therapeutic strategies.

HER2

Comprehensive molecular characterisation of CRC and the greater availability of next-generation sequencing in tumour genomic profiling have demonstrated that *HER2* amplification is found in approximately 5–10% of patients with *RAS* wild-type mCRC.[7,8,27] This molecular abnormality is predominantly identified in patients with *RAS/BRAF* wild-type patients, who may harbour *HER2* amplification primarily or secondarily as a mechanism of resistance to anti-EGFR therapy.[58,68-70] Exploratory analyses suggest that patients with *RAS* wild-type who harbour *HER2* amplification derive lower, if any, benefit from anti-EGFR therapy.[7,8] Based on the successful experiences of anti-HER2 therapy in *HER2*-amplified breast and gastric cancers, the identification of this molecular abnormality in mCRC prompted the evaluation of anti-HER2 therapy in clinical trials.

HERACLES was the first clinical trial addressing the efficacy of anti-HER2 therapy in *HER2*-positive mCRC.[71] This proof-of-concept Phase II study was comprised of 27 treatment-refractory patients, of which 30% presented an objective response to the combination of trastuzumab plus lapatinib, and an additional 44% had stable disease. The subsequent MyPathway Phase II study showed that 32% of the 57 heavily pre-treated patients with *HER2*-positive mCRC had objective response to the

combination of trastuzumab plus pertuzumab.[72] The Phase II TAPUR basket trial evaluated the same combination of anti-HER2 therapy in 28 previously treated patients with *HER2*-positive mCRC, and 14% of the patients demonstrated objective response.[73] Impressive findings were demonstrated by the preliminary results of the Phase II MOUNTAINEER study, which evaluated the combination of tucatinib plus trastuzumab. Of the 22 evaluable previously treated patients with *HER2*-positive mCRC, 55% presented objective response.[74] Likewise, promising data have also been presented by DESTINY-CRC01 trial, which showed 45% of ORR with trastuzumab deruxtecan in 53 patients with previously treated *HER2*-positive mCRC.[75] Taken together, these initial clinical trials have demonstrated that *HER2* is a viable therapeutic target in mCRC, with encouraging efficacy data of the dual anti-HER2 therapy in treatment refractory patients. However, the FDA has not yet approved anti-HER2 therapies for mCRC in the USA. The results of the ongoing randomised clinical trial SWOG1613 evaluating the combination of trastuzumab plus pertuzumab in *RAS/BRAF* wild-type patients are eagerly awaited (NCT03365882),[76] as well as the results of the Phase II DESTINY-CRC02 trial, with more data of trastuzumab deruxtecan in mCRC (NCT04744831).[77]

NTRK, ALK, and *ROS1*

NTRK are genes that encode the tropomyosin receptor kinase (Trk) family, which is comprised of three transmembrane proteins, TrkA, TrkB, and TrkC receptors, which are encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively.[78] The signal transduction pathways activated by these receptors are associated with proliferation, differentiation, and survival in normal and neoplastic neuronal cells.[79] Gene fusions of the *NTRK* are the main molecular abnormalities with known oncogenic and transforming potential.[80] Based on a study with 408 patients with CRC, it is estimated a prevalence rate of 0.5% of this gene fusion.[81] Efficacy of larotrectinib in *NTRK* fusion-positive mCRC was demonstrated in a basket trial with 55 patients with solid malignancies, of which four had mCRC.[82] Three patients presented tumour shrinkage and one had stable disease. Entrectinib, a pan-Trk inhibitor, has also been demonstrated to be effective in this subset of patients.[83] Other gene fusions, such as those involving *ALK* and *ROS1*, are rarely found in mCRC, but, once present, they portend a poorer prognosis.[84,85] Targeted therapies, including entrectinib, have been effective in this subgroup of patients with mCRC.[86]

CONCLUSIONS

Meaningful precision-based advancements in the therapeutic options for mCRC have been challenging and slow to realisation. Comprehensive molecular profiling and circulating tumour DNA highlights a markedly heterogeneous disease at the genomic, epigenomic, and transcriptomic levels; however, to date, they only reflect a low frequency of actionable alterations. For almost two decades, clinical applicability of precision oncology in mCRC was limited to the identification of *RAS* mutations as predictive biomarkers of resistance to the use of anti-EGFR monoclonal antibodies. However, novel therapeutic targets have emerged in recent years, refining the landscape of systemic therapy of the disease. The benefit of ICIs in patients with MSI-H and in those with *POLE* mutations or high TMB, the combination of BRAF with EGFR inhibition in patients with *BRAF* V600 mutations, the advent of allele-specific KRAS G12C inhibitors, and the promising findings of dual anti-HER2 therapy in *HER2*-positive mCRC cases have ushered in a new era of precision oncology for mCRC, providing personalised treatments and sustaining hope for patients affected by this disease.

References

1. Siegel RL et al. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.
2. Noone Aet al. SEER cancer statistics, 1975–2015. 2018. Available at: https://seer.cancer.gov/archive/csr/1975_2015/. Last accessed: 26 august 2021.
3. Siegel RL et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-64
4. Morano F et al. Negative hyperselection of patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer who received panitumumab-based maintenance therapy. J Clin Oncol. 2019;37(33):3099-110.
5. Di Nicolantonio F et al. Wild-type *BRAF* is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26(35):5705-12.

6. Loupakis F et al. *KRAS* codon 61, 146 and *BRAF* mutations predict resistance to cetuximab plus irinotecan in *KRAS* codon 12 and 13 wild-type metastatic colorectal cancer. Br J Cancer. 2009;101(4):715-21.
7. Raghav K et al. Validation of *HER2* amplification as a predictive biomarker for anti–epidermal growth factor receptor antibody therapy in metastatic colorectal cancer. JCO Prec Oncol. 2019;3:1-13.
8. Martin V et al. HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in metastatic colorectal cancer patients. Br J Cancer. 2013;108(3):668-75.
9. Bardelli A, Siena S. Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. J Clin Oncol. 2010;28(7):1254-61.
10. Venook AP et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with *KRAS* wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA. 2017;317(23):2392-401.
11. Arnold D et al. Prognostic and predictive value of primary tumour side in patients with *RAS* wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol. 2017;28(8):1713-29.
12. Boland CR et al. A National Cancer Institute Workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998;58(22):5248-57.
13. Sinicrope FA. Lynch Syndrome–associated colorectal cancer. N Engl J Med. 2018;379(8):764-73.
14. Overman MJ et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol. 2018;36(8):773-79.
15. Overman MJ et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, Phase 2 study. Lancet Oncol. 2017;18(9):1182-91.
16. Overman MJ et al. Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results. J Clin Oncol. 2016;34(Suppl 15):3501.
17. Le DT et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509-20.
18. Brahmer JR et al. Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455-65.
19. Topalian SL et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.
20. Andre T et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: the Phase 3 KEYNOTE-177 Study. J clin Oncol. 2020;38(Suppl 18):LBA4.
21. Schrock AB et al. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. Ann Oncol. Jul 2019;30(7):1096-103.
22. Fabrizio DA et al. Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition. J Gastrointest Oncol. 2018;9(4):610-17.
23. Domingo E et al. Somatic *POLE* proofreading domain mutation, immune response, and prognosis in colorectal cancer: a retrospective, pooled biomarker study. Lancet Gastroenterol Hepatol. 2016;1(3):207-16.
24. Pursell ZF. Yeast DNA polymerase ε participates in leading-strand DNA replication. Science. 2007;317(5834):127-30.
25. Hu H et al. Ultra-mutated colorectal cancer patients with *POLE* driver mutations exhibit distinct clinical patterns. Cancer Med. 2021;10(1):135-42.
26. Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
27. Kandoth C et al.; Cancer Genome Atlas Research Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-7.
28. Rayner E et al. A panoply of errors: polymerase proofreading domain mutations in cancer. Nat Rev Cancer. 2016;16(2):71-81.
29. Hino H et al. Clinicopathological and mutational analyses of colorectal cancer with mutations in the *POLE* gene. Cancer Med. 2019;8(10):4587-97.
30. Gong J et al. Response to PD-1 blockade in microsatellite stable metastatic colorectal cancer harboring a *POLE* mutation. J Natl Compr Canc Netw. 2017;15(2):142-7.
31. Silberman R et al. Complete and prolonged response to immune checkpoint blockade in POLE-mutated colorectal cancer. JCO Precis Oncol. 2019;3:1-5.
32. Merck & Co., Inc. Highlights of prescribing information for Keytruda (pembrolizumab) injection. 2014. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Last accessed: 26 August 2021.
33. Ahn S-M et al. The somatic *POLE* P286R mutation defines a unique subclass of colorectal cancer featuring hypermutation, representing a potential genomic biomarker for immunotherapy. Oncotarget. 2016;7(42):68638-49.
34. Yaeger R et al. Clinical sequencing defines the genomic landscape of metastatic colorectal cancer. Cancer Cell. 2018;33(1):125-36.
35. Barras D et al. *BRAF* V600E mutant colorectal cancer subtypes based on gene expression. Clin Cancer Res. 2017;23(1):104-15.
36. Bylsma LC et al. Prevalence of *RAS* and *BRAF* mutations in metastatic colorectal cancer patients by tumor sidedness: a systematic review and meta-analysis. Cancer Med. 2020;9(3):1044-57.
37. AACR Project GENIE Consortium. AACR Project Genie: powering precision medicine through an international consortium. Cancer Discov. 2017;7(8):818-31.
38. Clarke CN, Kopetz ES. BRAF mutant colorectal cancer as a distinct subset of colorectal cancer: clinical characteristics, clinical behavior, and response to targeted therapies. J Gastrointest Oncol. 2015;6(6):660-7.
39. Tran B et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer. 2011;117(20):4623-32.
40. Loupakis F et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014;371(17):1609-18.
41. Douillard JY et al. Panitumumab-FOLFOX4 treatment and *RAS* mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023-34.
42. Pietrantonio F et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer 2015;51(5):587-94.
43. Kopetz S et al. Phase II pilot study of vemurafenib in patients with metastatic *BRAF*-mutated colorectal cancer. J Clin Oncol. 2015;33(34):4032-8.
44. Corcoran RB et al. Combined BRAF, EGFR, and MEK inhibition in patients with $BRAF^{V600E}$-mutant colorectal cancer. Cancer Discov. 2018;8(4):428-43.
45. Prahallad A et al. Unresponsiveness of colon cancer to BRAF (V600E) inhibition through feedback activation of EGFR. Nature. 2012;483(7387):100-3.

46. Mao M et al. Resistance to BRAF inhibition in BRAF-mutant colon cancer can be overcome with PI3K inhibition or demethylating agents. Clin Cancer Res. 2013;19(3):657-67.
47. Hong DS et al. Phase IB study of vemurafenib in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with *BRAF*^{V600E} mutation. Cancer Discov. 2016;6(12):1352-65.
48. Kopetz S et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. N Engl J Med. 2019;381(17):1632-43.
49. Kopetz S et al. Encorafenib plus cetuximab with or without binimetinib for *BRAF* V600E metastatic colorectal cancer: Updated survival results from a randomized, three-arm, Phase III study versus choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC). J Clin Oncol. 2020;38(Suppl 4):8.
50. Braftovi. (encorafenib). Array BioPharma Inc. Boulder. CO.2020.
51. Johnson B et al. Atypical, non-V600 BRAF mutations as a potential mechanism of resistance to EGFR Inhibition in metastatic colorectal cancer. JCO Precis Oncol. 2019;3:1-10.
52. Kotani D et al. Clinicopathological features, efficacy of anti-EGFR therapy, and survival outcomes in patients with *BRAF* non-V600 mutated metastatic colorectal cancer. J Clin Oncol. 2019;37(Suppl 4):659.
53. Fontana E, Valeri N. Class(y) dissection of *BRAF* heterogeneity: beyond non-V600. Clin Cancer Res. 2019;25(23):6896-8.
54. Wang Y et al. Activity of EGFR antibody in non-V600 *BRAF* mutant metastatic colorectal cancer. Ann Oncol. 2019;30(1):147-49.
55. Yaeger R et al. Response to anti-EGFR therapy in patients with BRAF non-V600–mutant metastatic colorectal cancer. Clin Cancer Res. 2019;25(23):7089-97.
56. Loree JM et al. Classifying colorectal cancer by tumor location rather than sidedness highlights a continuum in mutation profiles and consensus molecular subtypes. Clin Cancer Res. 2018;24(5):1062-72.
57. Vaughn CP et al. Frequency of *KRAS*, *BRAF*, and *NRAS* mutations in colorectal cancer. Genes Chromosomes Cancer. 2011;50(5):307-12.
58. Misale S et al. Emergence of *KRAS* mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature. 2012;486(7404):532-6.
59. Sorich M et al. Extended *RAS* mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol. 2015;26(1):13-21.
60. Moore AR et al. RAS-targeted therapies: is the undruggable drugged? Nat Rev Drug Discov. 2020;19(8):533-52.
61. Hong DS et al. KRAS^{G12C} Inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383(13):1207-17.
62. Ostrem JM et al. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature. 2013;503(7477):548-51.
63. Kargbo RB. Inhibitors of G12C mutant Ras proteins for the treatment of cancers. ACS Med Chem Lett; 2018;10(1):10-11.
64. Hallin J et al. The KRAS^{G12C} inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. Cancer Discov. 2020;10(1):54-71.
65. Mirati Therapeutics Inc. Phase 3 study of MRTX849 with cetuximab vs chemotherapy in patients with advanced colorectal cancer with KRAS G12C mutation (KRYSTAL-10). NCT04793958. https://clinicaltrials.gov/ct2/show/NCT04793958.
66. Henry JT et al. Comprehensive clinical and molecular characterization of KRAS^{G12C}-mutant colorectal cancer. JCO Precis Oncol. 2021;5:613-21.
67. Schirripa M et al. *KRAS* G12C metastatic colorectal cancer: specific features of a new emerging target population. Clin Colorectal Cancer. 2020;19(3):219-25.
68. Pietrantonio F et al. Heterogeneity of acquired resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer. Clin Cancer Res. 2017;23(10):2414-22.
69. Diaz Jr LA et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature. 2012;486(7404):537-40.
70. Misale S et al. Resistance to anti-EGFR therapy in colorectal cancer: from heterogeneity to convergent evolution. Cancer Discov. 2014;4(11):1269-80.
71. Sartore-Bianchi A et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, *KRAS* codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, Phase 2 trial. Lancet Oncol. 2016;17(6):738-46.
72. Meric-Bernstam F et al. Pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal *cancer* (MyPathway): an updated report from a multicentre, open-label, Phase 2a, multiple basket study. Lancet Oncol. 2019;20(4):518-30.
73. Gupta R et al. Pertuzumab plus trastuzumab (P+ T) in patients (Pts) with colorectal cancer (CRC) with *ERBB2* amplification or overexpression: results from the TAPUR Study. J Clin Oncol. 2020;38(Suppl 4):132.
74. Strickler J et al. Trastuzumab and tucatinib for the treatment of HER2 amplified metastatic colorectal cancer (mCRC): initial results from the MOUNTAINEER trial. Ann Oncol. 2019;30(Suppl 5):v200.
75. Siena S et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, Phase 2 trial. Lancet Oncol. 2021;22(6):779-89.
76. Southwest Oncology Group. S1613, trastuzumab and pertuzumab or cetuximab and irinotecan hydrochloride in treating patients with locally advanced or metastatic HER2/Neu amplified colorectal cancer that cannot be removed by surgery. NCT03365882. https://clinicaltrials.gov/ct2/show/NCT03365882.
77. Daiichi Sankyo, Inc. Trastuzumab deruxtecan in participants with HER2-overexpressing advanced or metastatic colorectal cancer (DESTINY-CRC02). NCT04744831. https://clinicaltrials.gov/ct2/show/NCT04744831.
78. Amatu A et al. *NTRK* gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open. 2016;1(2):e000023.
79. Nakagawara A. Trk receptor tyrosine kinases: a bridge between cancer and neural development. Cancer Lett. 2001;169(2):107-14.
80. Vaishnavi Aet al. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov. 2015;5(1):25-34.
81. Créancier L et al. Chromosomal rearrangements involving the NTRK1 gene in colorectal carcinoma. Cancer Lett. 2015;365(1):107-11.
82. Drilon A et al. Efficacy of larotrectinib in TRK fusion–positive cancers in adults and children. N Engl J Med. 2018;378(8):731-9.
83. Sartore-Bianchi A et al. Sensitivity to entrectinib associated with a novel LMNA-NTRK1 gene fusion in metastatic colorectal cancer. J Natl Cancer Inst. 2016;108(1):djv306.
84. Pietrantonio F et al. *ALK*, *ROS1*, and *NTRK* rearrangements in metastatic colorectal cancer. J Natl Cancer Inst. 2017;109(12):djx089.
85. Yakirevich E et al. Oncogenic ALK fusion in rare and aggressive subtype of colorectal adenocarcinoma as a potential therapeutic target. Clin Cancer Res. 2016;22(15):3831-40.
86. Amatu A et al. Novel *CAD-ALK* gene rearrangement is drugable by entrectinib in colorectal cancer. Br J Cancer. 2015;113(12):1730-4.

Perspectives on Hepatic Metastases and the Minimally Invasive Approach to Resection

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Abstract

Surgical resection is the most effective treatment approach in colorectal liver metastases. The improved survival in Stage IV colorectal cancer is associated with a better diagnosis and evaluation, proper decision-making, improved chemotherapy, and the adoption of parenchymal-sparing hepatic resections. Liver surgery was one of the last frontiers reached by minimally invasive surgery. Surgical techniques and specialised equipment evolved to overcome the technical limitations, making laparoscopic liver resections safe and feasible. The aetiology and pathophysiology of hepatic metastases are discussed along with the rationale for and efficacy of minimally invasive surgery for colorectal liver metastases. Improved imaging techniques, identification of genomic markers, advances in chemotherapy, and personalised therapy will further improve the outcome of minimally invasive surgery in the management of Stage IV colorectal cancer.

INTRODUCTION

The Natural History of Hepatic Metastases

The liver is the most common site for colorectal cancer (CRC) metastases, accounting for 80% of patients with Stage IV CRC and 40% as the only site of distant disease. Of the patients with CRC, 20–25% present with synchronous metastases and 50–60% will develop metachronous disease.[1] Liver metastases develop in the absence of lymph node involvement and, presumably, this occurs via the haematogenous route (the portal circulation) in gastrointestinal tumours from where tumour cells can embolise via the mesenteric veins.[2] However, the fact that tumour cells from outside the gastrointestinal tract also commonly spread to the liver suggests that organ preference is not purely anatomical and the 'seed and soil' hypothesis, first proposed by Paget in 1889,[3] is still tenable. The complex tumour cell interactions that occur with the endothelial lining and lymphatic cells are, in part, what determines their final organ distribution.[4] Tumour cells that invade lymphatics may also spread haematogenously via venolymphatic communications or directly via the thoracic duct.[5] Some large metastases do not demonstrate spread to local periportal lymph nodes even in the presence of extensive disease within the liver.[6]

A liver metastasis may attain an enormous size, sometimes occupying much of the liver by concentric growth with extension in all directions, and may occasionally spread to adjacent structures such as the diaphragm by penetrating the usually unyielding Glisson's capsule.[7] The right lobe of the liver is involved with metastases more frequently than the left lobe, although the reasons remain unclear as there is no gross difference of either arterial or portal blood received by each lobe. It may, however, be due to portal vein 'streaming', resulting in tumour emboli preferentially entering the right portal vein branches.[8,9] Approximately one-third of patients with colorectal liver metastases (CRLM) cancer will have disease located in one lobe;[10] whereas multiple deposits throughout the liver are more commonly seen in patients with breast, oesophageal, gastric, and pancreatic cancer and are indicative of a more widespread metastatic process.[11]

It has been estimated that that the subclinical phase of a liver metastasis (i.e., from a metastatic implantation to clinical appearance) may be 2.5–5 years.[12] This would suggest that survival rate may be improved if liver metastases are detected much earlier. A cluster of similar-sized metastases, suggestive of a common tumour embolic event clearly occurring in a segment or lobe, will leave the residual liver disease free; whereas metastases of differing sizes are probably indicative of showers of tumour emboli occurring at different times.[11,12] Small lesions within the liver are usually asymptomatic and patients with advanced disease usually present with a combination of upper abdominal discomfort, weight loss, and general malaise. Pain may be due to the unremitting rapid growth of large metastases and is occasionally referred to the right shoulder, although central necrosis and infarction may also cause pain and pyrexia transiently. Hepatomegaly is indicative of advanced disease and may occasionally be accompanied by fulminant hepatic failure if the metastases are rapidly growing. Evidence of advanced liver failure such as jaundice, ascites, and occasionally portal hypertension are late signs and indicative of an extremely poor prognosis.[7]

In patients with carcinoid, the first presentation may be of carcinoid syndrome, characterised by diarrhoea, flushing, and wheezing due to excessive secretion of serotonin and tachykinin peptides from the hepatic metastases overwhelming its metabolism. The tumour, node, metastases (TNM) staging system does not adapt to recent advances in metastatic treatment.[13-15] The survival of patients with resectable solitary metastasis (Stage IV disease) is better than patients with Stage II disease.[13,14] Tumour deposits in adjacent vessels are associated with peritoneal disease, and tumour deposit with nodal disease (N2) has worse survival.[14]

Liver Regeneration

The ability of the surgeon to remove large volumes of liver tissue safely and with expectation of survival depends on a knowledge of the anatomy of the liver[16] and on an appreciation of the extraordinary rapid regenerative capacity following major resection, which have been extensively studied.[17] Following resection as extensive as a right hepatectomy (at which half the liver mass is removed), liver size is regenerated within 3–4 weeks. This increase in size is accompanied by histological evidence of regenerative hyperplasia as early as 3 days after resection. During the period of liver regeneration liver function is depressed and the patient may require supportive measures. However, it is interesting to note that the outcome of regeneration following traumatic injury is different from liver regeneration following hepatocellular injury such as hepatitis, which follows the course of cirrhosis (alternating regeneration and fibrosis), dysplasia, and finally hepatocellular carcinoma after approximately 10–20 years. This implies that the mechanism and molecular pathways differ in the two modes of liver regeneration.[18]

TREATMENT OF COLORECTAL LIVER METASTASES

There is no advantage in delaying hepatic resection following diagnosis and patients should undergo liver resection as soon as is feasible. The old dogma that a waiting period is necessary to evaluate tumour aggressiveness is no longer tenable. The median survival of untreated CRLM following diagnosis is 6–12 months and 5-year survival is extremely rare.[19,20] For CRLM, 80% are initially non-resectable due to tumour size, location, and functional liver reserve.[1]

Other factors that may indicate a poor outlook and exclude the possibility of a cure are the presence of abnormal liver function tests, spread of tumour to extrahepatic sites, and primary tumours that are not resected.[7] Currently, patients with definitely unresectable disease may have widespread hepatic disease, non-resectable extrahepatic lesions, or multiple metastatic sites.[1]

In untreated patients, tumour burden is the major determinant of outcome and patients with solitary metastases usually live longer than those with multiple, bilobar disease.[13] New chemotherapy regimens including biologicals are bringing more patients to resection, including resectable extrahepatic disease. Resectability is the complete removal of liver metastases while leaving at least 30% of functional remnant liver. In several studies, metastases >5 cm were associated with poorer survival than smaller metastases.[8] Although larger liver metastases have usually been present for a longer time than smaller lesions, in the situation of a giant solitary metastasis the tumour biology may be such that the capacity for multiple metastases may well be limited and, therefore, the outcome may be good after resection.[1]

Although neoadjuvant chemotherapy such as folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) as a first-line treatment and then single agent irinotecan as a second-line treatment has improved tumour response, the median survival for patients with unresectable disease is poor, and there is no 5-year survival. Resection, when feasible, confers a higher chance of cure and can improve 5-year survival to 34–60%.[1,8,21-23] However, apart from the risk of chemotherapy-associated steatohepatitis (CASH), the rationale in using neoadjuvant chemotherapy for patients with resectable disease has been supported by the better prognosis obtained compared to upfront surgery, due to the lower rate of positive surgical margins and the rendered ability to identify the subgroup of patients who will develop progressive disease while on chemotherapy.[22,23]

The resectability criteria for (CRLM) are expanded in an advanced multidisciplinary team (MDT) meeting alongside the evolution of imaging and neoadjuvant and adjuvant techniques such as thermal ablation, selective internal radiation therapy, and transarterial chemoembolisation.[24-26] The management of Stage IV CRC would be optimised by bringing together all relevant specialties involved in colorectal metastatic disease management in a centralised high-volume centre. The major objective and endpoint of the advanced MDT meeting on Stage IV CRC management is resectability due to the impact on patient survival (40% >5 years).[1,24,25] The main determinants of the decision-making process are the tumour statuses of both the primary tumour and metastases, the need for emergency surgery of a complicated primary tumour, and the resectability of both tumour sites.[24,25,27] The diagnosis and decision-making for the management of resectable, borderline resectable, or unresectable CRLM is expedited in the advanced MDT. The utilisation of protocols, appropriate preparation of patients, audit, and trial recruitments are optimised. Non-adherence to MDT decisions has been shown to result in a trend towards lower survival rates.[28-30] A number of series with sufficient long-term follow-up indicate a 10-year survival after resection in 20–30% of patients.[31,32]

Unresectable unilobar disease may be treated by neoadjuvant chemotherapy followed by extended liver resection, with or without portal vein embolisation or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)[33,34] to stimulate the size of the future liver remnant. For multiple bilobar CRLM, the strategies for improved margin clearance include staged resection, which entails a first-stage local resection of metastases of the future left remnant liver followed by portal vein embolisation or ALPPS, and then a second-stage right hepatectomy 4 weeks later, after the left remnant has hypertrophied.[1,24,25]

Although high-quality contrast-enhanced CT and liver MRI are commonly used preoperatively, laparoscopic ultrasonography, usually performed with a high-resolution 7.5–10 MHz probe, allows for the direct visualisation of liver metastases in regard to segmental anatomy, local vascular involvement, and regional nodal disease. Laparoscopic ultrasonography improves the diagnostic accuracy of staging laparoscopy alone, provides additional information on resectability in 14–25% of patients, and detects occult metastases and new findings in 40–55% of cases.[25,35]

Intra-operative ultrasound via real-time imaging aids planning at the time of resection and allows for the safe removal of all viable tumours, with a

clear margin of >1 cm. It facilitates liver-sparing and microwave or radiofrequency thermal ablation techniques in patients with compromised parenchyma (CASH, prior liver resection), and avoids the 'small for size' syndrome.[25,36]

Anatomical liver resections follow anatomical planes and thus have better oncological clearance than non-anatomical liver resections. Major anatomical resections have better oncological clearance than limited segmental resections, with reduced recurrence rate and improved survival. However, segmental liver resection of localised tumours, based on Couinaud's liver segmental classification (Figure 1), would improve vascular control (less blood loss), minimise the risk of recurrence from intrahepatic spread, and reduce the amount of normal liver unnecessarily removed.[16] Clearly, for small, awkwardly located lesions (such as the apex of Segment VIII in the axilla of the right and middle hepatic veins), local resection might be preferable to formal hemihepatectomy, whereby a whole, healthy lobe may need to be sacrificed for a small deposit. For larger metastases or multiple deposits, standard anatomical resections based on Couinaud segments should ensure adequate margins unless this increases the risk of postoperative liver failure.

Fortunately, secondary liver metastases from CRCs have better biology than metastases from other gastrointestinal sites and are amenable to non-anatomical surgical resections. In addition, a parenchymal-sparing approach in CRLM is supported by evidence that more aggressive resection at primary surgery does not prevent intrahepatic recurrence.[37,38] Thus, the oncologically safe, non-anatomical, parenchymal-sparing resections are used for CRLM to achieve a complete metastasectomy. It is appropriately utilised in the modern setting of multimodal treatments and repeat resections. It may, however, result in compromising the vascularity of the adjacent residual liver tissue and may be technically more difficult with repeat resections.[1,8,24,25]

Simple wedge excision of peripheral lesions is not appropriate since it compromises the resection margin and risks the danger of leaving satellite metastases.[1,24,25] A diligent search for other metastases should be carried out using intra-operative ultrasound before attempting to 'wedge out' an apparently superficial tumour nodule.[1,24,32]

Approximately 20% of patients have liver-only recurrence, with more than one-third occurring in the opposite side of the liver[39] and hence amenable for re-resection.[1,24,25,40]

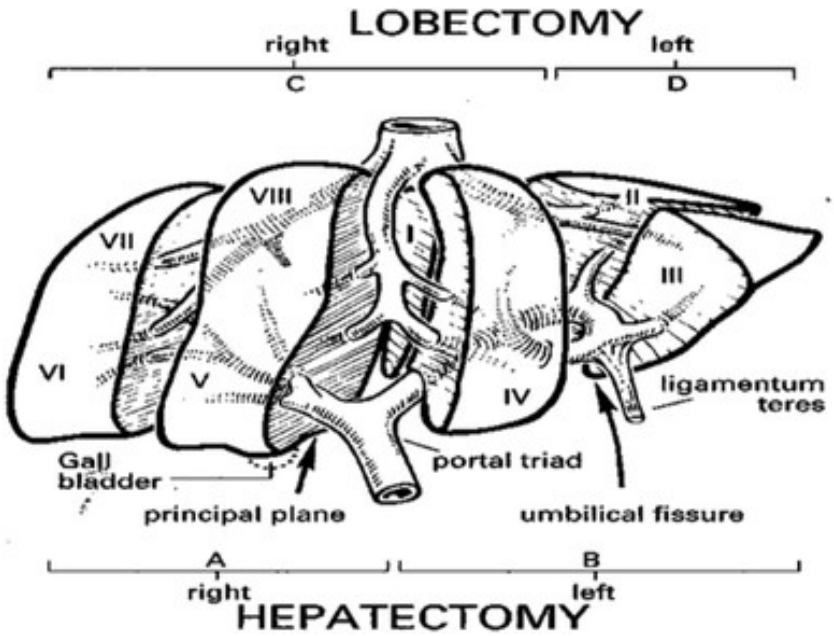

Figure 1: Couinaud's segmental anatomy of the liver (with permission: Weledji et al. Curr Surg Rep 2016;4:4).[16]

When disease recurs in the liver, it is more often at some site distant from the original resection line and most likely to have arisen in undetected micrometastases present at the time of original liver resection.[1,24]

This would corroborate the importance of peri-operative chemotherapy in surgical oncology as it increases progression-free survival.[41] Thus, ideally, a resection margin of at least 1 cm should be attempted, judged by intra-operative ultrasonography, but if not technically possible narrow margins should not be an absolute contraindication to resection.[1,24] There is controversy as to the significance of resection margin status following ablation with haemostatic devices as this will destroy the margin to some extent (1–3 mm) giving an appearance of a 'R0' margin (no tumour cells) in the patient remnant but an 'R1' margin (tumour cells present) in the pathological specimen.[1,24,25] Generally, the major determinant of success in the elderly (>80 years of age) is the volume of residual liver (since liver adaptations following resection diminishes with age), and fitness for general anaesthesia.[1,8,24,25]

Minimally Invasive Surgery

Laparoscopic surgery had been slowly introduced in surgical oncology because of the concern of inadequate margins or lymph node sampling, tumour seeding, missing small metastases, and poor pathological and oncological outcomes. The OSLO-COMET randomised controlled trial showed that in patients undergoing parenchyma-sparing liver resection for colorectal metastases, laparoscopic surgery was associated with significantly fewer postoperative complications compared to open surgery, was cost-effective, and the rate of free resection margins was the same.[42] The LapOpHuva prospective, randomised controlled trial comparing laparoscopic liver resection (LLR) with open liver resection (OLR) in patients with CRLM showed LLR presenting with a lower global morbidity (11.5% versus 23.7%), but with similar severe complications. The long-term survival outcomes were similar in both groups. LLR involved more use of the Pringle manoeuvre (15.5% versus 30.2%) and a shorter hospital stay (4 versus 6 days). There were no differences regarding surgical time, blood losses, transfusion, and mortality.[43] Thus, the study demonstrated that in selected patients with CRLM, LLR presented similar oncological outcomes to OLR, with the advantages of the short-term results associated with LLR.

The concerns of the rare air embolism are met by putting the patient in 15° Trendelenberg position and careful surgical technique, especially when dissecting the hepatic veins.[1,24,44] In the current COVID-19 pandemic, just as with surgery during the HIV/AIDS epidemic,[45] care should be taken during laparoscopy upon using disposable ports, with a vestibular flange to prevent splash-back and by deflating the abdomen prior to port withdrawal because any aerosol emanating from the port entry wound will harbour COVID-19.[46,47] In addition to the currently advised personal protective equipment for healthcare staff in the operating theatre, this simple method would further lessen the risk of occupational transmission. Patients with COVID-19 would benefit from the reduced surgical stress of minimally invasive surgery, but it would be important to know the effect of immunosuppression from major LLR on COVID-19 disease progression.[48] Larger resections, especially in patients with intrinsic liver disease, should be avoided if possible since postoperative COVID-19 infection might threaten the hypertrophic potential of the future liver remnant, placing the patient at risk of liver failure-related death or insufficient hepatic reserve to survive any COVID-19-related complication.[49]

During the 1990s, minor resections of two or fewer easily accessible Couinaud's liver segments had been the standard of care. The posterior-superior segments (VII, VIII) and inferior segments (I, IVa) were excluded as they posed a higher surgical challenge from the extensive mobilisation required to bring those segments to the operative field. Resections of lesions located on anterolateral segments (II, III, IVb, V, VI) and left lateral sectionectomy (II, III) were performed systematically by laparoscopy in hepatobiliary centres. The posterior-superior resections had been indicated as 'major operations', despite including only two segments (VII, VIII). This was corroborated by the associated higher conversion rates, higher blood loss, prolonged operative times, and narrower surgical margins.[50] Resection of lesions located on posterior-superior segments and major liver resections were shown to be feasible but remain technically demanding and reserved for experienced surgeons in high-volume hepatobiliary centres. Laparoscopy-

assisted and transthoracic port placement are useful strategies applied to difficult resections.[44,50]

In 2000, Cherqui et al.[51] published the feasibility study of LLR for both benign and malignant diseases of the liver including hepatocellular carcinoma in cirrhotic livers. Since then, nearly 10,000 minor and major LLRs as alternatives to open surgery have been reported in the literature, showing the wide acceptance and safety.[48,52] Currently, the indications for LLR do not differ from those for open surgery.[52,53] A recent meta-analytic study[54] showed LLR as having a better peri-operative outcome than OLR for recurrent liver cancer, without compromising oncological outcome. With longer overall and median survival rates following recurrent resections, the indications for surgery are increasing with R1 surgery (complete tumour resection without safe margins) being justified for patients, with a response to preoperative chemotherapy.[1,21,25,28] It makes sense that minimally invasive procedures are made available to these elderly patients who may also have CASH, prior liver resections, and other comorbidities.[28,42,44]

In addition, the majority of patients (approximately 65%) develop intrahepatic recurrence within 3 years, even with the addition of systemic chemotherapy, but approximately 20% of these patients have liver-only recurrence, which may be suitable for re-resection.[1,24,25,31] Although repeat hepatectomy is often more difficult than the initial procedure because of dense adhesions and more friable and fibrotic liver parenchyma,[55] reported mortality and morbidity rates after repeat liver resection of metastases are surprisingly similar to those reported after initial hepatectomy.[35,56] Adjunctive treatment such as laparoscopic radiofrequency or microwave ablation is acceptable for patients of high surgical risk for liver resection or with small solitary CRLM.[1,24,25] Therefore, the favourable biology of CRLM have enabled patients to live with their disease with repeat resections for recurrence.[1,24,25,31]

However, oncogenic mutations of RAS genes (*NRAS* and *NRAS*) controlling cell proliferation have been associated with worse disease-free and overall survival following CRLM resection, even with adjuvant anti-epidermal growth factor cetuximab therapy.[57] The addition of cetuximab to FOLFOX in the neoadjuvant setting results in an overall survival advantage in patients with advanced disease who have the *KRAS* exon 2 wild-type tumour genotype.[58] Thus, the rationale for neoadjuvant chemotherapy, even for resectable lesions, and the addition of biologic agents for the *KRAS* exon *2* wild-type is to destroy occult micrometastases and increase progression-free survival.[1,23,24]

After resection of the primary CRC, neoadjuvant chemotherapy with mFOLFOX6 and the vascular endothelial growth factor inhibitor bevacizumab for patients with resectable synchronous CRLM was safe and feasible with an impressive response rate of 72.9% and 90.9% of patients proceeding to liver resection;[59] however, it lacked proven benefit as adjuvant treatment.[60] Where CRLM are unresectable, chemotherapy may downsize tumours and improve biological selection for resection. This is seen as a complete radiological response, which depends on the quality and completeness of preoperative imaging, or as ‘“missing’ metastases. As a complete radiological response does not signify a complete pathological response, liver resection of curative intent would include all initial and currently known sites of disease (Figures 2 and 3).[1,24] Robotic-assisted resections are feasible as demonstrated in reported case series. The 3D view and greater range of movement can be useful for complex resections.[61] The dynamic applicability of the 3D planning to navigation during operation may also improve operative results.[62]

One Stage: Simultaneous or Staged Procedure?

The decision as to whether the operations for the primary tumour and liver metastases are performed at the same time (simultaneous) or separately (staged) is made at the advanced MDT meeting and in discussions with the patient.[1] The advantages of a one-stage (simultaneous) operation[63,64] are the decreased risk of disease dissemination (transperitoneally), no repeated postoperative immunosuppression causing increased tumour growth, and lower costs. A staged procedure would allow for the assessment of biological behaviour of metastases, avoid operating on patients who are progressing while on chemotherapy, and allow more precise selection for curative surgery.[1,24,65] Delayed hepatic resection may not impair survival but help to select those patients most likely to benefit

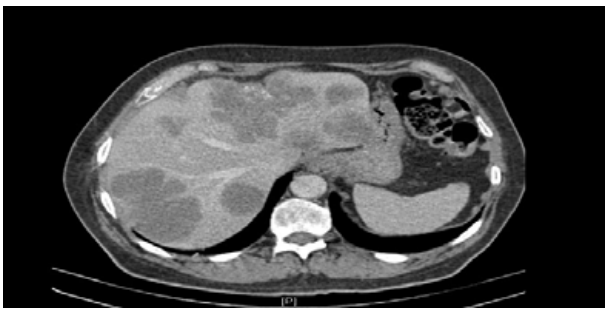

Figure 2: Pre-operative chemotherapy CT scan of colorectal liver metastases (with consent).

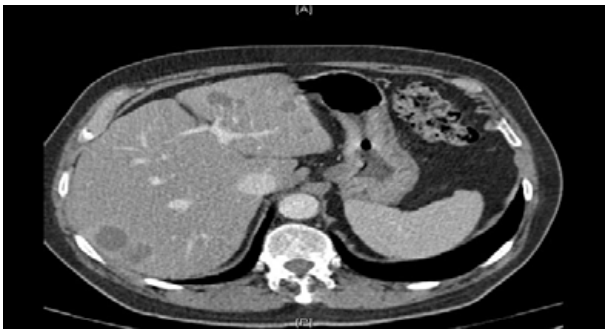

Figure 3: CT scan post-chemotherapy of colorectal liver metastases (with consent).

from hepatic resection (i.e., stable disease).[66,67]

For mid- and low-rectal primary tumours, chemoradiotherapy is often needed and, in addition to a difficult resection, a one-stage surgery is not recommended.[1,24,25] One-stage surgery is not advocated for complex colonic and upper-rectal primary tumours, for high-risk patients, or when hepatectomy is major (>3 segments). Minor liver resections (2 segments or fewer) may be safely performed at the same time as colorectal resection (open or laparoscopic) when both the primary tumour and the metastases are easily resectable. The outcomes are similar to sequential surgery in this scenario.[1,24,68]

The Four Clinical Scenarios of Stage IV Colorectal Cancer

The management of the four clinical scenarios are as follows:

- For asymptomatic CRC and resectable synchronous CRLM, chemotherapy is first, with or without radiotherapy, for rectal cancer. It is followed either by surgery in a one-stage procedure for patients with limited hepatic disease and easy to resect primary tumour, or by staged (liver-first) surgery for other patients.
- For asymptomatic CRC and non-resectable synchronous CRLM, the consensus is for optimal chemotherapy first, with the aim of making the liver metastases resectable. This is followed by hepatic surgery and then resection of the primary tumour.
- For symptomatic CRC and resectable synchronous CRLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours (but not for tumours with bleeding causing anaemia), followed by chemotherapy and then surgery for liver metastases.
- For symptomatic CRC and non-resectable synchronous CRLM, recommendations are for resection of the primary tumour for perforated or occlusive tumours, followed by chemotherapy and then surgery for liver metastases if tumour shrinkage is achieved. For tumours with bleeding causing anaemia, induction chemotherapy is recommended

to down-size both the primary tumour and livermetastases, followed by surgery at the site with the most significant tumour load, which is usually the liver (i.e., a reverse approach).[1,24,25]

Thus, although the treatment strategy depends on the clinical scenario,[69] the disease being systemic, and synchronous disease, which has been widely recognised as prognostically unfavourable in various patient cohorts, chemotherapy should come before surgery in most cases.[70,71]

CONCLUSIONS

Both the proper selection of patients who will benefit from liver resection and a high degree of experience in minimally invasive surgery are warranted in a hepatobiliary unit. Improved imaging techniques, identification of genomic markers, advances in chemotherapy, and personalised therapy will further improve the outcome of minimally invasive surgery in the management of Stage IV CRC.

References

1. Jones RP et al. Defined criteria for respectability improves rates of secondary resection after systemic therapy for liver limited metastatic colorectal cancer. Eur J Cancer. 2014;50(9):1590-601.
2. Fisher ER, Turnbull RB. The cytological demonstration and significance of tumor cells in the mesenteric venous blood in patients with colorectal carcinoma. Surg Gynecol Obstet. 1955;100(1):102-8.
3. Paget S. The distribution of secondary growths in cancer of the breast. Lancet. 1889;8(2):571-3.
4. Naito S et al. Correlation between the in vitro interaction of tumor cells with an organ environment and metastatic behavior in vivo. Invasion Metastasis. 1987;7(1):16-29.
5. Fisher B, Fisher ER. The interrelationship of haematogenous and lymphatic tumour cell dissemination. Surg Gynecol Obstet. 1966;122(4):791-8.
6. Dworkin MJ et al. Importance of hepatic artery node involvement in patients with colorectal liver metastases. J Clin Pathol. 1995;48(3):270-2.
7. Foster JH, Lundy J. Liver metastases. Curr Probl Surg. 1981;18(3):157-202.
8. Scheele J et al. Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery. 1991;110(1):13-29.
9. Holbrook RF et al. Patterns of colorectal liver metastases according to Couinaud's segments. Dis Colon Rectum. 1995;38(3):245-8.
10. Cady B, Stone MD. The role of surgical resection of liver metastases in colorectal carcinoma. Semin Oncol. 1991;18(4):399-406.
11. Pickren JW et al., "Liver metastasis: analysis of autopsy data," Weiss L, Gilbert HA (eds.), Liver Metastasis: A Monograph Series (1982) Boston: GK Hall Medical Publishers, pp.2-19.20
12. Finlay IG et al. Growth rate of hepatic metastases in colorectal carcinoma. Br J Surg. 1988;75(7):641-4.
13. Gayowski TJ et al. Experience in hepatic resection for metastatic colorectal cancer-analysis of clinical and pathological risk factors. Surgery. 1994;116(4):703-11.
14. Nagtegal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolon: a critical review. Histopathology. 2007;51(2):141-9.
15. Poston GJ et al. Urgent need for a new staging system in advanced colorectal cancer. J Clin Oncol. 2008;26(29):4828-33.
16. Weledji EP, Ngounou E. The impact of segmental anatomy on hepatic oncologic resections. Curr Surg Rep. 2016;4:4.
17. Blumgart LH et al. Observations on liver regeneration after right hepatic lobectomy. Gut. 1971;12(11):922-8.
18. Ramakrishna G et al. From cirrhosis to hepatocellular carcinoma: new molecular insight on inflammation and cellular senescence. Liver Cancer. 2013;2(3):357-63.
19. Lykoudis PM et al. Systematic review of surgical management of synchronous liver metastases. Br J Surg. 2014;101(6):605-12.
20. Manfredi S et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006;244(2):254-9.
21. August DA et al. Lymphatic spread of tumour to extrahepatic sites-implications for the follow-up and treatment of patients with colorectal cancer. Cancer. 1985;55(7):1490-4.
22. Adson MA et al. Resection of hepatic metastases from colorectal cancer. Arch Surg. 1984;119(6):647-51.
23. Finlay IG, McArdle CS. Occult hepatic metastases in colorectal carcinoma. Br J Surg. 1986;73(9):732-5.
24. Adam R et al. Managing synchronous liver metastases from colorectal cancer: multidisciplinary international consensus. Cancer Treat Res. 2015;41(9):729-41.
25. Weledji EP. Centralization of liver cancer surgery and impact on multidisciplinary teams working on stage IV colorectal cancer. Oncol Rev. 2017;11(2):331.
26. Gruber-Rouh T et al. Current strategies in interventional oncology of colorectal liver metastases. Br J Radiol. 2016;89:(1064)20151060.
27. Wanebo HJ et al. Current perspectives on repeat hepatic resection for colorectal carcinoma: a review. Surgery. 1996;119(4):361-71.
28. Goyer P et al. Single-center multidisciplinary management of patients with colorectal cancer and resectable synchronous liver metastases improves outcomes. Clin Res Hepatol Gastroenterol. 2013;37(1):47-55.
29. Viganò I et al. Colorectal cancer with synchronous resectable liver metastases: monocentric management in a hepatobiliary referral centre improves survival outcomes. Ann Surg Oncol. 2015;22:1533-9.
30. Vasudevan SP et al. Close collaboration between local and specialist multidisciplinary teams allows 'fast-tracking' of patients with colorectal liver metastases. Colorectal Dis. 2013;15(10):1253-56.
31. Lordan JT et al. A 10-year study of outcome following hepatic resection for colorectal liver metastases-the effect of evaluation in a multidisciplinary team setting. Eur J Surg Oncol. 2009;35(3):302-6.
32. Prades E et al. Is it worth reorganizing cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organization of MDTs and their impact on patient outcomes. Health Policy.

2015;119(4):464-74.

33. May BJ, Madoff DC. Portal vein embolization: rationale, technique, and current application. Semin Intervent Radiol. 2012;29(2):81-9.
34. Zhang GQ et al. Associating liver partition and portal vein ligation for stage hepatectomy (ALPPS): a new strategy to increase liver surgical resection. Int J Surg. 2014;12(5);437-41.
35. Hoch G et al. Is intraoperative ultrasound still useful for the detection of colorectal cancer liver metastases? HPB (Oxford). 2015;17(6):514-9.
36. Kingham TP et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. J Am Coll Surg. 2015;2020(4):471-9.
37. Kokudo N et al. Anatomical major resection versus non-anatomical limited resection for liver metastases from colorectal carcinoma. Am J Surg. 2001;181(2):153-9.
38. Mise Y et al. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. Ann Surg. 2016;263(1):146-52.
39. Nordlinger B et al., "Surgical resection of hepatic metastases: multicentric retrospective study by the French Association of Surgery," Nordlinger B, Jaeck D (eds.), Treatment of Hepatic Metastases of Colorectal Cancer (1992) Paris: Springer-Verlag, pp.129-61.
40. Adam R et al. Liver resection for colorectal metastases: the third hepatectomy. Ann Surg. 2003;238(6):871-83.
41. Fisher B. Biological research in the evolution of cancer surgery: a personal perspective. Cancer Res. 2008;68(24):10007-20.
42. Fretland AA et al. Laparoscopic versus open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. Ann Surg. 2018;267(2):199-207.
43. Robles-Campos R et al. Open versus minimally invasive liver surgery for colorectal liver metastases (LapOpHuva): a prospective randomized controlled trial. Surg Endosc. 2019;33(12):3926-36.
44. Schiffman SC et al. Laparoscopic versus open liver resection for metastatic colorectal cancer: a metaanalysis of 610 patients. Surgery. 2015;157(2):211-22.
45. Weledji EP et al. Gastrointestinal surgery and the acquired immune deficiency syndrome. Ann Med Surg (Lond). 2015;4(1):36-40.
46. Hanbali N et al. A safe method to evacuate pneumoperitoneum during laparoscopic surgery in suspected COVID-19 patients. Annals R Coll Surg Engl. 2020;102(5):392-3.
47. Doremalen N et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Eng J Med. 2020;382(16):1564-7.
48. Weledji EP. Cytokines and the metabolic response to surgery. J Clin Cell Immunol. 2014;5:2.
49. Tzenga D et al. Surgical decision-making and prioritization for cancer patients at the onset of the COVID-19 pandemic: a multidisciplinary approach. Surg Oncol. 2020;34:182-5.
50. Coelho FT et al. Laparoscopic liver resection: experience based guidelines. World J Gastrointest Surg. 2016;8(11):5-26.
51. Cherqui D et al. Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg. 2000;232(6):753-62.
52. Wakabayashi G et al. Recommendations for laparoscopic liver resection: a report from the second international conference held in Morioka. Ann Surg. 2015;261(4):619-29.
53. Garden OJ et al. Guidelines for resection of colorectal cancer liver metastases. Gut. 2006;55(Suppl 3):iii1-8.
54. Liang YL et al. Perioperative outcomes comparing laparoscopic with open repeat liver resection for post-hepatectomy recurrent liver cancer: a systematic review and meta-analysis. Int J Surg. 2020;79:17-28.
55. Elias D et al. Repeat hepatectomy for cancer. Br J Surg. 1993;80(12):1557-62.
56. Jones RP, Poston G. Resection of liver metastases in colorectal cancer in the era of expanding systemic therapy. Annu Rev Med. 2017;68:183-96.
57. Nortlinger B et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol. 2009;20(6):985-92.
58. Primrose J et al. A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild type patients with operable metastases from colorectal cancer: the new EPOC study. J Clin Oncol. 2013;31(15): 3504.
59. Jones RP et al. Colorectal liver metastases: a critical review of state of the art. Liver Cancer. 2016;6(1):66-71.
60. Nordlinger B et al. Should the results of the new EPOC trial change practice in the management of patients with resectable metastatic colorectal cancer confined to the liver? J Clin Oncol. 2015;33(3):241-3.
61. Montali R et al. Robotic versus laparoscopic hepatectomy: what is the best minimally invasive approach? Ann Surg. 2015;262(2):e70.
62. Hallet J et al. Systematic review of the use of pre-operative simulation and navigation for hepatectomy: current status and future perspectives. J Hepatobiliary Pancreat Sci. 2015;22(5):353-62.
63. Feng Q et al. Timing of hepatectomy for resectable synchronous colorectal liver metastases: for whom simultaneous resection is more suitable - a meta-analysis. PLos One. 2014;9(8):e104348.
64. Slesser AA et al. Outcome of simultaneous resections for patients with synchronous colorectal liver metastases. Eur J Surg Oncol. 2013;39(12):1384-93.
65. Reddy SK et al. Simultaneous resection of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol. 2002;14(12):3481-91.
66. Lambert LA et al. Interval hepatic resection of colorectal metastases improves patient selection. Arch Surg. 2000;135(4):473-9.
67. Yin Z et al. Timing of hepatectomy in resectable synchronous colorectal liver metastases (SCRLM): simultaneous or delayed? Hepatology. 2013;57(6):2346-57.
68. Tanaka K et al. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. Surgery. 2004;136(3):650-9.
69. Chow FC, Chok KS. Colorectal liver metastases: an update on multidisciplinary approach. World J Hepatol. 2019;11(2):150-72.
70. Araujo R et al. Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. Ann Surg Oncol. 2013;20(13):4312-21.
71. Lehmann K et al. Chemotherapy before liver resection of colorectal metastases: friend or foe? Ann Surg. 2012;255(2):237-47.

Balancing Risk of Thromboembolism and Bleeding in Patients with Cancer: Selecting Anticoagulant Therapy Based on Recent Clinical Trials

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Abstract

Patients with cancer may experience venous thromboembolism (VTE), leading to various medical complications or death, more often than the population without cancer. Moreover, patients with cancer usually experience both higher rates of recurrent VTE and bleeding. For the past decade, low-molecular-weight heparin (LMWH) has been considered a standard therapy for VTE related to cancer; however, daily injections of LMWH have augmented the burden of neoplastic disease and decreased adherence to therapy in some patients.

At present, direct oral anticoagulants (DOAC) such as factor Xa inhibitors (e.g., rivaroxaban, edoxaban, and apixaban) have been recommended as a new treatment modality, mostly because of their convenient use (i.e., the oral route of delivery) for the patient population with cancer. Notably, large recent randomised controlled trials that have compared DOACs with LMWH in patients with malignancies have revealed that DOACs represent a valuable alternative to LMWH for the therapy of VTE related to cancer. Despite their unique advantages, the DOACs may not be appropriate for some groups of patients with cancer due to their elevated risk of bleeding, among other factors.

This mini-review presents the main findings from some recent randomised controlled trials, comparing the use of DOACs and LMWH for the management of VTE associated with malignancy. It highlights the efficacy, safety, and various other considerations of treatment and prophylaxis of VTE depending on the individual patient context. It provides current guidance on the selection of the optimal anticoagulant for comprehensive and personalised patient care.

INTRODUCTION

Venous thromboembolism (VTE) is one of the main reasons for morbidity and mortality among patients with malignancies.[1] In addition, in this group of patients, the rates of recurrent VTE and bleeding complications are higher than in the general population. Over the past decade, low-molecular-weight heparin (LMWH) has been the standard of care for treatment of VTE related to cancer.[1] However, its injectable form

of administration has been inconvenient and thus patient compliance has been reduced and quality of life has been impaired. Furthermore, anticoagulation with vitamin K antagonists (VKA), such as warfarin, which requires frequent laboratory testing and is often complicated by bleeding or multiple drug–drug or drug–food interactions, was not a satisfactory solution for a majority of patients with cancer. Under these circumstances, direct oral anticoagulants (DOAC) have recently emerged as a desirable treatment option for patients with cancer-related VTE.[2]

DOACs include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors, such as rivaroxaban, apixaban, and edoxaban.[3] From a practical point of view, the oral route of delivery for DOACs, minor pharmacologic interactions, and no requirement for continuous laboratory parameter monitoring represent definite advantages.[3] Regardless of particular anticoagulant selection, anticoagulation therapy has usually been more complicated among patients with cancer, who are characterised by higher rates of VTE and bleeding episodes than patients without malignancies. Since the comprehensive care for patients with cancer requires an individualised approach, physicians have to take into consideration different factors, such as prevention of recurrent VTE, bleeding episodes, interactions with anti-cancer therapies, administration, frequency of laboratory test monitoring, comorbidities, and patient preferences.[3] In addition to initial anticoagulation for VTE in the patient with malignancy, primary prevention (e.g., before the first VTE event) and extended anticoagulation therapy (e.g., over the initial period of 6 months or 1 year) are valid considerations, especially among high-risk patients in whom risk stratification and prediction scores should be simultaneously assessed.[4] It should be underscored that in spite of the unquestionable advantages of DOACs, these medications can be inappropriate for some groups of patients because of their elevated risk of major bleeding, potential exacerbation of some medical conditions, extremes of body mass (overweight or underweight), and other factors (e.g., relating to tumour type, location, stage, and therapy).[2]

This article outlines recent clinical guidelines on various aspects of cancer-related VTE. Furthermore, this mini-review presents the main findings from recent large randomised clinical trials (RCT) comparing the use of DOACs and LMWH for the management of VTE associated with malignancy. It highlights the efficacy, safety, and various other considerations of treatment and prophylaxis of cancer-related VTE, depending on the individual patient's clinical context. It discusses some important topics relevant to the selection of anticoagulants for personalised management of patients with malignancies and associated VTE.

CHALLENGES OF ANTICOAGULATION IN PATIENTS WITH MALIGNANCY-ASSOCIATED THROMBOSIS

VTE is a common medical complication in the population of patients with cancer, occurring in approximately 20% of these patients.[4] Furthermore, different anti-cancer therapies (e.g., cytotoxic chemotherapy [CHT], radiation therapy, hormonal therapy [HT], targeted therapy, immune therapy, and surgery) can additionally augment VTE risk.[4] Typically, patients with cancer-related VTE have more hospital admissions, higher rates of metastases, and worse overall survival (OS) rates than patients with cancer without VTE.[5] Unfortunately, VTE is one of the main causes of mortality in patients with cancer, and thus, its prevention and treatment are of utmost importance.[6]

This problem is very challenging, since the pro-thrombophilic factors of malignant tumours can be extremely difficult to manage in many of these patients, despite the most intensive treatment efforts with modern anticoagulants.[7] It should be highlighted that the complications of anticoagulation are quite serious in patients with cancer, who usually experience more episodes of recurrent VTE compared to patients without cancer, and have elevated rates of major bleeding compared to patients without cancer receiving anticoagulants.[8] These adverse effects can be due to an anticoagulant's interactions with different anti-cancer agents, impaired oral intake, thrombocytopenia, or abnormal hepatic metabolism that influences the serum levels of anticoagulants.[9]

LMWH FOR TREATMENT OF CANCER-ASSOCIATED VTE: PERSPECTIVES FROM THE CLOT AND CATCH TRIALS

For over a decade, consensus guidelines have recommended LMWH as the standard of care for initial treatment of cancer-associated VTE, according to the data from leading RCTs, CLOT and CATCH, which compared LMWH to VKAs.[10,11] Subsequently, a meta-analysis of large RCTs has shown that LMWH decreased the recurrence of VTE compared to VKAs.[12] However, LMWH might increase the risk of major bleeding, aggravating in this way the disease burden in patients with cancer-associated VTE.[12] Notably, the CLOT and CATCH RCTs, comparing LMWH to VKA (warfarin) for cancer-related VTE, have revealed different results.[10,11] The earlier CLOT trial had shown a significant decrease in VTE recurrence rate with dalteparin (LMWH) versus warfarin treatment.[10] In contrast, the later CATCH trial did not reveal the superiority of tinzaparin (LMWH) over warfarin.[11]

However, a detailed assessment of the cancer burden and pre-existing risk of VTE may help elucidate the exact difference between these two RCTs. It should be noted that there were higher proportions of patients with metastatic cancer, ongoing anti-cancer therapies, and mortality rates in the CLOT trial compared to the CATCH trial.[10,11] This suggests that the patient populations of these two RCTs were different. In particular in the CATCH trial, the patient population was less likely to develop recurrent VTE than the CLOT study patients, and this could have reduced the power of the trial to identify a significant difference in the adverse event rates (e.g., the reported rate of VTE episodes in the CATCH trial was lower than anticipated).[10,11]

A PARADIGM SHIFT OF ANTICOAGULATION STRATEGIES FOR CANCER-ASSOCIATED VTE: THE EMERGENCE OF DOACS

The emergence of DOACs has offered novel strategies for the therapy and prophylaxis of VTE among patients with cancer.[3] In particular, the results of several Phase III trials have shown the non-inferiority of DOACs to warfarin for prevention of VTE recurrence, as well as lower rates of bleeding in the general population.[13] At present, DOACs have replaced warfarin as the standard of care for treatment of VTE in the majority of patients without cancer.[13] Notably, the main RCTs on DOACs (as standard therapy for VTE in the population without cancer) have included only a small number of patients with cancer.[13] A meta-analysis of the patient population with cancer (from six of these Phase III clinical trials) has revealed significantly lower VTE recurrence rates in the DOAC arm than in the VKA arm, with a similar risk of major bleeding complications.[13]

Recent RCTs, including SELECT-D, Hokusai VTE Cancer, ADAM VTE, Caravaggio, CASSINI, and AVERT trials, comparing direct factor Xa inhibitors and LMWH for therapy or prevention of cancer-associated VTE, have focused on various aspects of the efficacy and safety of DOACs and LMWH in various clinical contexts (Table 1).[14-21] Unlike the pivotal trials comparing DOACs to VKAs in the general population, the SELECT-D, Hokusai VTE Cancer, ADAM VTE, Caravaggio trials had strict inclusion criteria for patients with active cancer (Table 1).[14-17] The results of these four studies suggest that DOACs are non-inferior to LMWH for preventing VTE recurrence in patients with cancer, and these reports have been convergent with a recent meta-analysis.[22] However, based on the SELECT-D and Hokusai VTE Cancer trials, as well as the recent meta-analysis, the observed increased rates of bleeding events have included numerous gastrointestinal (GI) bleeds in the DOAC arms (e.g., such bleeding episodes occurred mostly in patients with oesophageal and gastric cancers).[22,23] Notably, a safety analysis of the first half of the patient population enrolled into the SELECT-D trial has revealed a non-significant difference in major bleeding, especially upper GI bleeding, between the rivaroxaban and dalteparin arms among patients with cancers of the oesophagus or gastroesophageal junction. However, it should be noted that the patients with these GI tract cancers were subsequently excluded for the SELECT-D trial (Table 1).[14] Similarly, a subgroup analysis of the Hokusai VTE Cancer trial has shown that in patients with GI cancers there was a higher risk of major bleeding events originating from the GI tract in the edoxaban arm than in the dalteparin arm (Table 1).[15,23]

Table 1: Comparison between direct oral anticoagulants and low-molecular-weight heparin (or placebo) for the management of cancer-associated thrombosis: the main findings from recent randomised clinical trials.

Clinical trial	Trial design and sample size	Trial out-comes*	Exclusion criteria (cancer types and other factors)	Main results of RCT† and implications for clinical practice
SELECT-D; Young et al.,[14] 2018	RCT, open-label; rivaroxaban versus dalteparin in treatment of patients with malignancy-associated VTE; N=406	Recurrent VTE: 4% versus 11%; major bleeding: 6% versus 4%; CRNMB: 13% versus 4%	Oesophageal or gastroesophageal cancer; Basal cell skin cancer, squamous cell skin cancer; prior VTE, high bleeding risk	Rivaroxaban revealed significantly lower rate of recurrent VTE; major bleeding rates were not significantly different; CRNMB rates were significantly greater in the rivaroxaban arm
Hokusai VTE Cancer; Raskob et al.,[15] 2018	RCT, open-label; edoxaban versus dalteparin in treatment of patients with malignancy-associated VTE; N=1050	Composite of recurrent VTE or major bleeding; recurrent VTE: 6.5% versus 8.8%; major bleeding: 5.6% versus 3.2%; CRNMB: 12.3% versus 8.2%	Basal cell skin cancer, squamous cell skin cancer	Edoxaban was non-inferior to LMWH in combined outcome of VTE recurrence or major bleeding; major bleeding occurred more often in the edoxaban arm; CRNMB rates were not significantly different
ADAM VTE; McBane et al.,[16] 2020	RCT, open-label; apixaban versus dalteparin in treatment of patients with malignancy-associated VTE	Recurrent VTE: 3.4% versus 14.1%; major bleeding: 0.0% versus 2.1%; CRNMB: 6.2% versus 4.2%.		Significant reduction in recurrent VTE with apixaban; no significant difference in bleeding rates
Caravaggio; Agnelli et al.,[17] 2020	RCT, open-label; apixaban versus dalteparin in treatment of patients with malignancy-associated VTE; N=1170	Recurrent VTE: 5.6% versus 7.9%; major bleeding: 3.8% versus 4.0%; CRNMB: 9.0% versus 6.0%	Primary brain tumour, intracerebral metastasis, acute leukaemia, Basal cell skin cancer, squamous cell skin cancer; high bleeding risk	Apixaban was non-inferior to dalteparin for treatment of cancer-associated VTE, without increased risk of major bleeding; patients with GI cancer were not excluded; GI bleeding occurred in 1.9% of patients in apixaban versus 1.7% in the dalteparin arm
CASSINI; Khorana et al.,[18,20] 2017	RCT, open-label; rivaroxaban versus placebo for preventing VTE in high-risk ambulatory patients with various cancers, starting systemic CHT (KS≥2)	VTE occurrence: 2.60% versus 6.41%; major bleeding: 1.98% versus 0.99%; CRNMB: 2.72% versus 1.98%	Occult VTE diagnosed via venous duplex ultrasound	Rivaroxaban significantly reduced the rate of VTE; no difference in the rates of major bleeding
AVERT; Kimpton et al.,[19] 2018; Carrier et al.,[21] 2019	RCT, open-label; apixaban versus placebo for preventing VTE in high-risk ambulatory patients with active cancers using CHT	VTE occurrence: 4.2% versus 10.2%; Major bleeding: 3.5% versus 1.8%; CRNMB: 7.3% versus 5.5%		Apixaban significantly reduced the rate of VTE; Major bleeding was greater in ITT analysis; No difference in CRNMB rates

*Treating VTE: DOACs versus LMWH arm; preventing VTE: DOACs versus placebo arm.

†DOACs versus LMWH, or DOACs versus placebo arm.

CHT: chemotherapy; CRNMB: clinically relevant non-major bleeding; DOAC: direct oral anticoagulants; DVT: deep venous thrombosis; GI: gastrointestinal; ITT: intention-to-treat; KS: Khorana score; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; RCT: randomised clinical trial; VTE: venous thromboembolism.

The appropriateness of DOAC use (e.g., rivaroxaban or edoxaban) among patients with GI cancers remains questionable. At this point, the findings from the ADAM VTE trial, indicating possible superiority of apixaban without increased bleeding complications, have revealed that the results of a given study, exploring a particular DOAC such as apixaban, should not be generalised for the entire class of DOACs (Table 1).[16] Notably in the Caravaggio trial, which compared the efficacy and safety of apixaban and dalteparin in patients with cancer-related VTE, approximately 30% of participants were diagnosed with GI cancers (Table 1).[17] In addition, patients with a pulmonary embolism (PE) made up over half of the participants in the apixaban and dalteparin arms.[17] Approximately 20% of the participants were patients with incidental deep vein thrombosis or PE detected during diagnostic work-up, usually conducted for reasons unrelated to the suspected VTE.[17] In contrast to prior studies with other DOACs, in the Caravaggio study the occurrence of major bleeding (e.g., systemic or GI) was almost identical in the apixaban and dalteparin arms.[17] However, the clinical advantage of apixaban therapy, conducted for >6 months, should be evaluated in the future trials. Overall, apixaban and rivaroxaban represent a very convenient and safe treatment option for cancer-related VTE, which can be used from the beginning of anticoagulation therapy, particularly in patients with deep vein thrombosis and incidental PE.[17]

THE PREVENTIVE ROLE OF DOAC IN PATIENTS WITH CANCER AND ELEVATED RISK OF VTE

Two main RCTs, which explored the preventive role of DOACs in patients with cancer and elevated risk of VTE, include CASSINI and AVERT (Table 1).[18-21] It should be underscored that the Khorana risk score (KS) was >2 in the participants of both of these trials.

The CASSINI trial examined the safety and efficacy of rivaroxaban in the prevention of cancer-related VTE.[18,20] Contrary to the AVERT study, in which patients were not tested for VTE at the study screening period, participants in the CASSINI trial underwent venous duplex ultrasound screening for VTE in both legs prior to entering the trial, and then every two months during the entire trial period.[18,20] Notably, patients in whom an occult VTE was diagnosed were excluded from the CASSINI study (Table 1).[18,20]

In the AVERT trial, patients with an active malignancy receiving CHT (with a KS of ≥2) were randomised to apixaban or placebo for 6 months. In the intention-to-treat analysis, the apixaban group had a decreased incidence of VTE compared to the placebo group (4.2% versus 10.2%, respectively).[19,21] However, the apixaban group had an increased incidence of major bleeding (3.5% versus 1.8%) and clinically relevant non-major bleeding (7.3% versus 5.5%) compared to the placebo group.[19,21] There was no difference in OS between these two groups in the AVERT trial (Table 1).[19,21]

Moreover, it should be underscored that the CASSINI study had a greater proportion of participants with pancreatic cancer than the AVERT trial (32% versus 13%, respectively).[18-21] In addition, in the CASSINI trial, the intention-to-treat analysis found no significant reduction in VTE events after 6 months in the rivaroxaban arm compared to the placebo, and no increased risk of major bleeding.[18,20] However, in the on-treatment analysis, rivaroxaban significantly reduced VTE compared to placebo (2.6% versus 6.4%, respectively).[18,20] These findings suggest that in the AVERT and CASSINI studies the application of the KS (e.g., KS of ≥2), resulted in more precise evaluation of low-dose DOAC versus LMWH therapy in comparison to the unselected population, assessed in the prior LMWH trials.[24] In fact, the AVERT study had slightly more patients with KS scores of ≥4 than the CASSINI trial (8.9% versus 6.6%, respectively).[19,21]

It should be highlighted that each of these trials excluded certain sub-populations of patients with cancer (e.g., who had Eastern Cooperative Oncology Group [ECOG] performance status of 3 or 4, cerebral metastases, and thrombocytopenia of $<50x10^9$ /L). Notably, a recent retrospective study has shown no increase in bleeding rates among patients with primary brain tumours or brain metastases in those receiving DOACs compared with those receiving LMWH.[25]

AN INDIVIDUALISED SELECTION OF ANTICOAGULANTS IN CANCER-ASSOCIATED VTE: A LOOK FROM THE PATIENT'S PERSPECTIVE

According to the International Society for Thrombosis and Haemostasis (ISTH), DOACs have been recommended for patients with cancer-related VTE, a low risk of bleeding complications, and low probability of pharmacologic interactions with current medications.[26] Similarly, the National Comprehensive Cancer Network (NCCN) has recommend the use of particular DOACs as follows: rivaroxaban as a monotherapy, apixaban for patients who have contraindications to LMWH (or decline therapy with LMWH), and edoxaban following initial heparin therapy.[27] It should be highlighted that DOACs have some important advantages, such as convenient oral route of delivery, established dosing, no requirement for laboratory monitoring, and few interactions with anti-cancer therapies or other medications.[28] As a consequence, DOACs are usually more acceptable to many patients (e.g., those who require a prolonged anticoagulation), which has a positive impact on their adherence to therapy and quality of life .[27,28]

Nevertheless, DOACs are not the perfect solution for every patient with cancer-associated VTE (Table 2).[4,9,14,15,29-32] Unquestionably, the oral route of administration is a big positive of DOACs, while the subcutaneous injections of LMWH usually cause more inconvenience. However, somewhat unexpectedly, an analysis of patient interview records (including from the SELECT-D trial), has shown that many patients found injections acceptable as a component of comprehensive anti-cancer management.[33] Moreover, it has been reported that the patient's preference for oral administration over injection was rather mild. On the other hand, the minor interference with anti-cancer treatment, low VTE recurrence rate, and low risk of major bleeding were the most appreciated features of LMWH, according to several interviewed patients.[34] This report was consisted with a previous international survey, including over 500 physicians and 800 patients, which showed that clinicians often over-estimate their patients' perceived burden of daily LMWH injections.[35] Since numerous patients with cancer who are treated for VTE appreciate the effectiveness, safety, and comfort of such a treatment, physicians should discuss individual preferences with regard to anticoagulant choice with their patients.[36]

BIOAVAILABILITY AND PHARMACOLOGIC INTERACTIONS OF DOAC

While multiple pharmacologic interactions with VKAs have been known, there is a scarcity of information about interactions between DOACs and anti-cancer agents. It should be noted that rivaroxaban, edoxaban, and apixaban, factor Xa inhibitors, are metabolised via the cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2J2 pathways;[7] in contrast, another DOAC, dabigatran (a direct thrombin inhibitor), is metabolised by P-glycoprotein pathways.[37] In general, DOACs have fewer drug interactions compared to VKAs. However, interactions have been encountered with some commonly used anti-cancer agents (e.g., CHT, targeted therapy with tyrosine kinase inhibitors, and HT); e.g., certain anti-neoplastic medications (CHT: doxorubicin or vinblastine; HT: enzalutamide and dexamethasone) that induce P-glycoprotein or CYP3A4 can cause a decrease in DOAC blood levels.[37] Some other anti-cancer agents (e.g., tyrosine kinase inhibitors: imatinib, dasatinib, lapatinib, nilotinib, or sunitinib; HT: tamoxifen) inhibiting P-glycoprotein or CYP3A4 can cause an increase in DOAC blood levels.[37] Unfortunately, it still remains unclear which interactions are clinically relevant. For this reason, physicians need to be vigilant and regularly communicate with pharmacists to determine whether certain interactions with DOACs could be potentially harmful to individual patients. Moreover, GI problems in patients with cancers can potentially alter drug delivery and absorption of DOACs.[37]

An ability to reverse anticoagulation is important, especially for older and more frail patients who may experience the most serious consequences of bleeding. Reversal agents for DOACs include idarucizumab (a Fab antibody fragment rapidly reversing the effects of dabigatran)[38] and andexanet alfa (a recombinant modified human FXa protein that binds factor Xa inhibitors and thus reduces anti-Xa activity).[39] However, these agents are not readily available and very expensive.

Table 2: Clinical considerations for selection of anticoagulation therapy in patients with cancer-associated thrombosis.

Decision for individualised choice of anti-coagulation therapy	DOAC[4,9,14,15]	LMWH[4,9,14,15,31]	VKA[4,9,29-32]
Yes	No evidence of GI cancer; low risk of major bleeding; ease of therapy is for the patient a 'top' priority; absence of strong pharmacologic interactions	GI adverse effects of CHT; nausea/vomiting, impaired oral intake; poor GI absorption (feeding tubes, s/p gastric or bowel resections); pharmacologic interactions with DOACs or VKAs; motivated patient willing to use injections for extended period of time; known increased bleeding risk; recurrent cancer-associated VTE while on anticoagulants	Any situation in which close anticoagulant monitoring is necessary (e.g., history of multiple prior systemic bleeds), poor GI absorption, or impaired metabolism; advanced renal failure; extremes of body weight (<50 kg or >150 kg)
No	Presence of active GI cancer; history of GI bleeding; extremes of body weight (<50 kg or >150 kg); renal failure	Strong aversion to injectable therapy; perceived 'needle fatigue'; renal failure; extremes of body weight (<50 kg or >150 kg)	Difficult access to a laboratory monitoring INR

Yes: Patient is considered as a potentially good candidate for specific anticoagulation therapy; No: Patient is considered as a potentially poor candidate for specific anticoagulation therapy.

CHT: chemotherapy; DOAC: direct oral anticoagulant; GI: gastrointestinal; INR: international normalised ratio; LMWH: low-molecular-weight heparin; s/p: status post; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Furthermore, impaired renal function related to advanced age or toxic effects of CHT can limit the use of anticoagulants such as DOACs and LMWH. In particular, dabigatran is not recommended for patients with reduced creatinine clearance, and apixaban and rivaroxaban should be used with great caution.[29] LMWH is mostly excreted renally, and thus also should be used with extreme caution in patients with renal insufficiency.[9] It should be underscored that among several patients with malignancy-associated VTE, the degree of renal insufficiency has been related to the risk of major bleeding, which can further aggravate the clinical outcomes.[30] In such patients, a VKA (warfarin) may be the best option, since this is the only anticoagulant that can be precisely monitored (Table 2).[4,9,29-32]

CONSIDERATIONS IN TREATMENT OF CANCER-ASSOCIATED VTE AMONG PATIENTS WITH A HIGH BLEEDING RISK

In order to provide comprehensive support for specific clinical scenarios and address some challenges in the management of anticoagulation among patients with cancer at high bleeding risk (e.g., GI tract and haematological cancers), some clinical scenarios are described below. It should be highlighted that some issues specific to patients with cancer, which often contribute to bleeding, include the extent, location, and histologic features of the cancer, requirements for invasive diagnostic or treatment procedures, and the development of thrombocytopenia from CHT or from the underlying malignancy.[37] Other comorbidities, such as kidney impairment and coagulopathy due to hepatic dysfunction, disseminated intravascular coagulopathy, or sepsis, can further predispose to bleeding.

Because of potentially serious bleeding complications, all patients require an individualised assessment of their bleeding versus thrombosis risk prior to possible anticoagulation (e.g., any bleeding sources should be promptly identified and managed).[37]

Among patients with cancer who experience minor bleeding episodes, anticoagulation can be applied if close monitoring has been provided. However, in the case of contraindications to anticoagulation, or when the risk of bleeding outweighs the benefit of treatment, the anticoagulants should be discontinued. In such situations, the VTE progression needs to be evaluated and, if necessary, inferior vena caval filter may be inserted.[40] Furthermore, in cases of serious cancer- or CHT-induced thrombocytopenia, platelet transfusions can be applied to allow anticoagulation (e.g., therapeutic anticoagulation with LMWH can be given if the platelet (PLT) count can be maintained >50x10^9 /L. For PLT counts 20–50x10^9 /L, a half-dose LMWH can be given, and for PLT count <20x10^9 /L, a therapeutic dose of the anticoagulant should be stopped.[40]

In patients with intracranial malignancies, the management of VTE has been particularly difficult because of the danger of intracranial haemorrhage (ICH).[41] According to a recent systematic literature review concerning the survival of patients with haematologic malignancies and ICH, a median OS for such patients was in a range of approximately 3–6 weeks, while a median OS for the sub-population of patients who experienced ICH within 10 days of haematologic carcinoma diagnosis was only five days. Notably, the worse outcomes were correlated with ICH cases that appeared early, displayed multi-focal or intra-parenchymal bleeding, and had thrombocytopenia (resistant to transfusion), leukocytosis, or low scores on Glasgow Coma Scale (upon admission). Overall, the prognosis of patients with haematologic malignancies and ICH is poor.[41] Some new light on this topic has been shed by a study that compared the rates of ICH in patients with brain tumours who were treated with DOACs versus LMWH.[25] Based on this study, DOACs were related to a lower incidence of ICH in patients with primary brain tumours.[25] However, physicians need to be cautious of various risk factors for ICH to make the most reasonable therapeutic decisions, in agreement with the patient's preferences.[25,41]

Similarly, a retroperitoneal hematoma (RPH) is a dangerous complication, encountered in some patients with cancer (e.g., with GI tract and haematological cancers, or undergoing abdominal surgery). A retrospective analysis of the risk factors (including anticoagulation therapy), clinical features, treatments, and outcomes of RPH has revealed that almost 60% of patients have improved with medical management, while the remaining patients required surgical interventions (e.g., laparoscopy or laparotomy) or interventional radiology procedures.[42] These findings reinforce the necessity of close monitoring and early interventions among patients in whom RPH has been suspected.

It should be highlighted that in the management of patients with cancer at high risk for bleeding and recurrent VTE, in the individual decisions for anticoagulation precise patient selection is crucial.[40] In particular, DOACs are not indicated if a patient has GI tract cancer, a history of GI bleeding, body mass <50 kg or >150 kg, or renal failure.[40] Under these circumstances, LMWH can be an alternative to DOACs, especially in patients with decreased oral intake or reduced GI absorption (e.g., due to vomiting, feeding tubes, status post-stomach or bowel resections).[40]

NEW AND SUSTAINED RECOMMENDATIONS FROM THE ASCO CLINICAL PRACTICE GUIDELINE UPDATE

According to the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update, the standard recommendations about prophylaxis and therapy of VTE in patients with cancer have been provided.[40] There are the following changes, compared to previous recommendations: physicians may offer thromboprophylaxis with DOACs (apixaban or rivaroxaban) or LMWH to selected high-risk outpatients with malignancies; rivaroxaban and edoxaban were added to VTE therapy options; patients with brain metastases have been addressed for possible VTE treatment; and long-term post-operative LMWH administration has been expanded.[40]

Recommendations that will be continued are as follows: most inpatients with cancer and an acute medical illness require thromboprophylaxis during hospitalisation; thromboprophylaxis is not routinely recommended for every outpatient with malignancy; patients scheduled for major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7–10 days; and assessment of VTE risk should be performed periodically among patients with malignancies, and oncology teams should provide patient education, focused on the signs and symptoms of VTE.[40]

Further trials are necessary to precisely explain how to manage individual patients from the heterogeneous cancer-related-VTE population in a more personalised manner, focused on achieving the subtle equilibrium between anti-thrombotic actions and bleeding risk.

CONCLUSION

Although one-fifth of patients with cancer experience an episode of VTE during the natural course of their malignancy, the risk of VTE differs among those patients. It should be emphasised that for VTE prevention, DOACs can provide a suitable option, especially among patients with low bleeding potential and high VTE risk.

With regard to VTE treatment, two main approaches have been recommended, including DOACs and LMWH. However, the precise identification of individual patients as candidates to one of these therapies is of utmost importance. For this reason, both the clotting and the bleeding risk assessment need to be performed (e.g., with an application of risk stratification tools and prediction scores, such as KS). It should be highlighted that many factors related to cancer itself (e.g., its type and stage); its therapy (e.g., concurrent CHT); and the patient's clinical context (e.g., medical comorbidities), functional status, and preferences are crucial for making well-balanced decisions in this area.

Therefore, clinical oncology practitioners, in tandem with their well-informed patients, need to be able to reasonably select from the anticoagulant 'menu': DOACs, LMWH, or VKA, depending on the particular patient's scenario.

References

1. Lyman GH et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Oncol Pract. 2015;11(3):e442-4.
2. Ay C et al. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. Ann Oncol. 2019;30(6):897-907.
3. Al-Samkari H, Connors JM. The role of direct oral anticoagulants in treatment of can-cer-associated thrombosis. Cancers (Basel). 2018;10(8):271.
4. Khorana AA, Francis CW. Risk prediction of cancer-associated thrombosis: appraising the first decade and developing the future. Thromb Res. 2018;164 (Suppl 1):S70-6.
5. Watson HG et al. Guideline on aspects of cancer-related venous thrombosis. Br J Haematol. 2015;170(5):640-8.
6. Khorana AA et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007;5(3):632-4.
7. Al-Samkari H, Connors JM. Dual anticoagulation with fondaparinux and dabigatran for treatment of cancer-associated hypercoagulability. Am J Hematol. 2018;93(6):E156-8.
8. Prandoni P et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484-8.
9. Patel HK, Khorana AA. Anticoagulation in cancer patients: a summary of pitfalls to avoid. Curr Oncol Rep. 2019;21(2):18.
10. 10. Lee AYY et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146-53.
11. Lee AYY et al. Tinzaparin vs warfarin for treatment of acute venous thromboembo-lism in patients with active cancer: a randomized clinical trial. JAMA. 2015;314(7):677-86.
12. Sobieraj DM et al. Anticoagulation for the treatment of cancer-associated throm-bosis: a systematic review and network meta-analysis of randomized trials. Clin Appl Thromb Hemost. 2018;24(Suppl 9):182-7S.
13. van Es N et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968-75.
14. Young AM et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36(20):2017-23.
15. Raskob GE et al. Edoxaban for the treatment of cancer-associated venous thrombo-embolism. N Engl J Med. 2018;378(7):615-24.
16. McBane RD et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost. 2020;18(2):411-21.
17. Agnelli G et al. Apixaban for the treatment of venous thromboembolism associated

with cancer. N Engl J Med. 2020;382(17):1599-607.

18. Khorana AA et al. Rivaroxaban for preventing venous thromboembolism in high-risk ambulatory patients with cancer: rationale and design of the CASSINI trial. Rationale and design of the CASSINI trial. Thromb Haemost. 2017;117(11):2135-45.
19. Kimpton M et al. Apixaban for the prevention of venous thromboembolism in high-risk ambulatory cancer patients receiving chemotherapy: rational and design of the AVERT trial. Thromb Res. 2018;164(Suppl 1):S124-9.
20. Khorana AA et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory pa-tients with cancer. N Engl J Med. 2019;380(8):720-8.
21. Carrier M et al. Apixaban to prevent venous thromboembolism in patients with can-cer. N Engl J Med. 2019;380(8):711-9.
22. Li A et al. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. Thromb Res. 2019;173:158-63.
23. Kraaijpoel N et al. Clinical impact of bleeding in cancer-associated venous throm-boembolism: results from the Hokusai VTE Cancer Study. Thromb Haemost. 2018;118(8):1439-49.
24. Agnelli G. Direct oral anticoagulants for thromboprophylaxis in ambulatory pa-tients with cancer. N Engl J Med. 2019;380(8):781-3.
25. Carney BJ et al. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. J Thromb Haemost. 2019;17(1):72-6.
26. Khorana AA et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2018;16(9):1891-4.
27. Soff GA. Use of direct oral anticoagulants for treating venous thromboembolism in patients with cancer. J Natl Compr Cancer Netw. 2018;16(5S):670-3.
28. Riess H et al. Direct oral anticoagulants for the treatment of venous thromboembo-lism in cancer patients: potential for drug-drug interactions. Crit Rev Oncol Hematol. 2018;132:169-79.
29. Weber J et al. The efficacy and safety of direct oral anticoagulants in patients with chronic renal insufficiency: a review of the literature. Eur J Haematol. 2019;102(4):312-8.
30. Kooiman J et al. Impact of chronic kidney disease on the risk of clinical outcomes in patients with cancer-associated venous thromboembolism during anticoagulant treat-ment. J Thromb Haemost. 2013;11(11):1968-76.
31. Schulman S et al. Recurrent venous thromboembolism in anticoagulated patients with cancer: management and short-term prognosis. J Thromb Haemost. 2015;13(6):1010-8.
32. Marshall AL et al. Recurrence of venous thromboembolism in patients with cancer treated with Warfarin. Clin Appl Thromb Hemost. 2015;21(7):632-8.
33. Hutchinson A et al. Oral anticoagulation is preferable to injected, but only if it is safe and effective: an interview study of patient and carer experience of oral and in-jected anticoagulant therapy for cancer-associated thrombosis in the select-d trial. Pal-liat Med. 2019;33(5):510-7.
34. Noble S et al. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica. 2015;100(11):1486-92.
35. Cimminiello C, Anderson FA Jr. Physician and patient perceptions of the route of administration of venous thromboembolism prophylaxis: results from an international survey. Thromb Res. 2012;129(2):139-45.
36. Farge D et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol. 2016;17(10):e452-66.
37. Lee AYY, Peterson EA. Treatment of cancer-associated thrombosis. Blood. 2013;122(14):2310-17.
38. Pollack CV Jr et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373(6):511-20.
39. Connolly SJ et al. Andexanet Alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016;375(12):1131-41.
40. Key NS et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2020;38(5):496-520.
41. Raghavan A et al. Outcomes and clinical characteristics of intracranial hemorrhage in patients with hematologic malignancies: a systematic literature review. World Neu-rosurg. 2020;144:e15-24.
42. Sahu KK et al. Clinical spectrum, risk factors, management and outcome of patients with retroperitoneal hematoma: a retrospective analysis of 3-year experience. Expert Rev Hematol, 2020;13(5):545-55.

Evaluation of Treatment Outcome and Acute Toxicity in Patients Undergoing Adjuvant Therapy in Ductal Carcinoma Pancreas: A Prospective Observational Study

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Abstract

Ductal adenocarcinoma of the pancreas is one of the commonly diagnosed cancers and is a leading cause of cancer mortality in the population. The prognosis of patients even after undergoing a complete resection is generally poor, with a median survival of 13–20 months and a 3-year survival of 30%. Therefore, adjuvant therapies including adjuvant chemoradiation and adjuvant chemotherapy are given in an effort to improve survival. In the authors' centre, all patients undergoing resection are given adjuvant chemoradiation followed by adjuvant chemotherapy. This study was conducted to evaluate the acute toxicity and treatment outcome (patterns of failure, overall and disease-free survival) of patients undergoing adjuvant therapy in resected carcinoma pancreas. Adjuvant chemoradiation was well tolerated by most patients with resected carcinoma pancreas and all patients completed chemoradiation. Adjuvant chemotherapy was associated with high haematological toxicity, similar to previously published literature. However, treatment interruptions were higher and only 77% patients completed adjuvant chemotherapy. The adjuvant gemcitabine, given on Days 1, 8, and 15, for a 4-weekly schedule was poorly tolerated by the authors' patient population and there were only fewer interruptions in patients who were switched to the 3-weekly schedule. Inclusion of a greater number of patients and longer follow-up of this study is required to clearly assess the patterns of failure and survival outcomes.

INTRODUCTION

Pancreatic cancer is the eleventh most commonly diagnosed cancer worldwide and is the seventh leading cause of cancer-related death.[1] It can arise from both exocrine (95%) and endocrine portion (5%) of the pancreatic gland.[2] The most common histology is ductal adenocarcinoma of the pancreas, which accounts for around 80% of all pancreatic cancers,[3] while 65% of the cases arise in the pancreatic head, 15% in the body or tail, and 20% involve the gland diffusely.[4]

Known risk factors for development of carcinoma of the pancreas include family history, advancing age, smoking, alcoholism, obesity, diabetes mellitus (DM), and chronic calcific pancreatitis (CCP). However, age is the major determinant of pancreatic cancer. Most patients are diagnosed at >50 years of age, with peak incidence in the seventh and eighth decades of life.[5]

In terms of preventable risk factors, tobacco smoking is the most important and most studied risk factor. Individuals who smoke have a 2–3-fold higher risk of developing pancreatic cancer than people who do not smoke. A dose–risk relationship has been noted as having a favourable effect of smoking cessation.[6]

DM is both a risk factor for disease and a consequence of early-stage pancreatic cancer. Long-term DM approximately doubles the risk of pancreatic cancer.[7] However, DM can also be caused by pancreatic cancer (Type 3c DM) and, accordingly, new-onset DM can be the first clue to the diagnosis of pancreatic cancer in elderly patients.[8]

Of the patients with pancreatic cancer, 10% have a family history of the disease.[9]

The primary curative option for carcinoma of the pancreas is surgical resection but only 15–20% of patients present with a potentially resectable disease at the time of diagnosis. Local unresectability is often due to major vascular invasion. Based on the extent of vascular invasion, they are broadly classified as operable, borderline operable, or unresectable disease.

The prognosis of patients with carcinoma of the pancreas is generally poor, even for those undergoing a complete (R0) resection. Long-term survival of patients undergoing resection of localised pancreatic carcinoma is only 20%, with a median survival of 13–20 months.[10] Recent data suggest that the survival of patients who undergo resection of their pancreatic cancer may be improving, with a 3-year survival rate around 30%[11] and 5-year survival around 10%.[12] In an effort to reduce recurrence rates and improve the survival of patients who have undergone resection, adjuvant therapies including chemotherapy and chemoradiation therapy have been explored.

Although adjuvant chemotherapy has been associated with an improvement in overall survival (OS), the benefits of radiotherapy remain controversial due to the conflicting results from various randomised controlled trials across the world. Adjuvant chemotherapy alone is the standard of care in Europe, based on ESPAC-1, CONKO-001, and EORTC trials. On the other hand, the American approach more often includes chemoradiotherapy in addition to adjuvant chemotherapy, based on the survival benefit from chemoradiotherapy in the GITSG study.

Apart from the ESPAC-1 trial, with its many flaws associated with the study design, no other Phase III studies have evaluated the relative benefits of chemoradiotherapy over chemotherapy alone. Hence, the standard adjuvant therapy (chemoradiation followed by chemotherapy, or chemotherapy alone) is unanswered. Data from the retrospective series and some Phase II studies suggest that patients at high-risk of recurrence may benefit from adjuvant radiation in addition to chemotherapy. The European Society for Medical Oncology (ESMO) guidelines do not recommend the use of adjuvant chemoradiation outside the context of a clinical trial.[13] However, the current National Comprehensive Cancer Network (NCCN) guidelines recommend chemotherapy alone, induction chemotherapy followed by chemoradiation +/- subsequent chemotherapy, or to enrol patients in a clinical trial (all of which are Category 1 recommendations).[14]

In the authors' centre, all patients who underwent curative resection of exocrine pancreatic cancer were treated with adjuvant chemoradiation: 45 Gy in 25 fractions of 3D conformal radiotherapy or intensity modulated radiotherapy 5 days per week, with concurrent chemotherapy 825 mg/m^2 of capecitabine taken orally twice daily on all days of radiation, followed by adjuvant chemotherapy with gemcitabine 1,000 mg/m^2 intravenously given on Days 1, 8, and 15 every 4 weeks (Q4 weekly) for 4 cycles. Patients who could not tolerate a Q4 weekly regimen were changed to Days 1 and 8 Q3 weekly schedule.

This study was conducted to evaluate the compliance, acute toxicity, and treatment outcome of patients with resected ductal adenocarcinoma of the pancreas, who were undergoing adjuvant therapy in the authors' centre.

METHODS

Fifteen patients with ductal adenocarcinoma of the pancreas who were registered at the authors' centre and had received adjuvant treatment after surgery (chemoradiation: 45 Gy in 25 fractions with concurrent capecitabine, followed by adjuvant chemotherapy with gemcitabine given intravenously [1,000 mg/m^2 on Days 1, 8, and 15 Q4 weekly for 4 cycles, or on Days 1 and 8 Q3 weekly for those not tolerating the Q4 weekly regimen) from January 2016 to June 2017 were prospectively observed for acute toxicity, relapse pattern, and survival outcomes.

Inclusion Criteria of the Study

- Histologically proven pancreatic ductal adenocarcinoma after a complete resection
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0–2
- Adequate haematological, hepatic, and renal function

Exclusion Criteria of the Study

- Periampullary carcinomas not arising from the pancreatic ductal epithelium
- Metastatic or locally advanced carcinoma in the pancreas and borderline resectable tumours that received neoadjuvant treatment prior to resection
- Incomplete resection

Treatment Protocol

- Adjuvant therapy after resection was started as soon as possible, usually 4–6 weeks after surgery.
- Routine CT simulation was completed for radiation planning and then target volumes and organs at risk were contoured according to the Radiation Therapy Oncology Group's (RTOG) contouring guidelines.
- Radiation therapy was given using a 3D conformal radiotherapy or intensity modulated radiotherapy technique, delivering 45 Gy in 25 fractions (1.8 Gy per fraction), along with 825mg/m^2 of capecitabine taken orally twice daily for 5 days per week, until completion of radiation therapy.
- This was followed by 4 cycles of adjuvant chemotherapy with gemcitabine given by injection of 1, 000 mg/m^2 on Days 1, 8, and 15 Q4 weekly (as per RTOG 9704 protocol), or on Days 1 and 8 Q3 weekly for 6 cycles in those not tolerating Q4 weekly schedule.

Outcome Measurement

Acute toxicity was evaluated weekly during chemoradiation using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, and for 3 weeks after completion of chemoradiation and then during each cycle of adjuvant chemotherapy.

Relapse-free time was calculated from the date of registration to the date of death or first relapse. OS time was calculated from the date of diagnosis to the date of death or last follow-up. Disease-free survival (DFS) and OS were calculated using the Kaplan–Meier method.

The statistical significance of prognostic factors was assessed using the log-rank test (univariate analysis) and the Cox-proportional hazards regression model (multivariate analysis).

RESULTS

Fifteen eligible patients with ductal adenocarcinoma of the pancreas who were registered at the authors' centre and had received adjuvant chemoradiation and chemotherapy treatment after surgical resection, from January 2016 to June 2017, were included in the study. The sample size was small, as patients with ductal adenocarcinoma of the pancreas were the only patients included in the study. In the authors' study, periampullary carcinomas were excluded as they have an entirely different natural history and are associated with a better prognosis compared to pancreatic ductal adenocarcinomas.

Patient Characteristics

The median age of the study population was 63 years (range: 45–75 years) and the majority (53.3%) of them were between 61 years and 70 years, which is similar to the reported literature.[5] The majority (60%) of patients were females. In this study population, 26.7% of patients were smokers. The proportion of carcinoma of the pancreas cases attributable to tobacco smoking has been estimated to be 15–30% in various study populations.[15] Only 26.7% had history of alcoholism. None of the patients in study population were obese, although obesity is described as a risk factor for the development of

carcinoma of the pancreas.[16] Of all the patients in this study, 46.7% had a history of Type 2 DM and, among them, nearly half had a recent onset DM. This is similar to the reported literature that shows a high (40%) prevalence of DM in patients with pancreatic cancer. According to the literature, 50% of people with pancreatic ductal adenocarcinoma have a history of recent onset DM.[8] In the authors' study, it is more or less the same, with 42.8% of patients having DM. In the authors' study 26.7% of patients had history of CCP. However, only one patient (6.7%) had a family history of carcinoma of the pancreas, while the proportion of patients with a positive family history is 10%, according to the available published literature.[9]

Tumour Characteristics

Similar to the known pattern of tumour origin, with 60–70% arising from the pancreatic head and less than 15% from body or tail, the authors also observed that 80% of their patients had tumours confined to head and 20% had tumours arising from body or tail of pancreas. The majority of patients were Stage II (40% were Stage IIA [T3N0] and 40% were Stage IIB [T1–3N1]). Only 13.3% were Stage III (T4, any N).

However, 40% of patients had inadequate nodal sampling, which is defined as less than 15 nodes removed during surgery, as per the detailed pathology report. Forty percent of tumours were positive for perineural invasion, which was less than the published literatures, showing a high incidence of perineural invasion of around 70–100% in pancreatic ductal adenocarcinoma.[17] Only 53.3% of patients had preoperative carbohydrate antigen (CA) 19-9 level values available as the majority of patients (66.6%) had surgery at another centre and reported to the authors' hospital for adjuvant treatment. The normal range of CA 19-9 is 0–37 U/mL. Two patients (13.3%) had preoperative values of more than 500 U/mL and 20% had values between 100–500 U/mL. Post-operative CA 19-9 values were available for all patients and the majority (73.3%) had values below 50 U/mL.

Treatment Characteristics

However, only three patients (23%) completed all 12 doses of adjuvant chemotherapy without any interruptions. The rest (77%) had interruptions in form of a delay, skipped cycles, or dose reduction. Of these, 46.0% of patients had a delay in chemotherapy, 69.0% of patients had at least one chemotherapy doses skipped, and 61.6% of patients required dose reduction. Haematological toxicity accounted for delay in 66% of cases, for skipping chemotherapy in 69% of case and a dose reduction in 75% of cases.

The chemotherapy schedule was changed from an injection of gemcitabine on Days 1, 8, and 15 Q4 weekly to Days 1 and 8 Q3 weekly due to poor tolerance in 4 patients (31%).

Chemotherapy regimen was changed from an injection of gemcitabine to an injection of 5-flurouracil plus an injection of calcium leucovorin in one patient (7.7%), due to repeated Grade 3 liver function test alteration.

Chemotherapy was stopped in two patients due to poor general condition and one patient developed systemic metastasis before the completion of adjuvant chemotherapy. In total, only 77% completed adjuvant chemotherapy (54% completed with interruption and 23% without any interruptions). This, however, was hugely different from the RTOG 9704 trial,[81] where 90% of patients completed chemotherapy in the gemcitabine arm. This might be due the inclusion of patients with good performance and nutritional status in the trial setting, which was not possible in the authors' scenario. Their patients came from low socio-economic status and the majority (80%) had a BMI less than 25, which is hugely different from a western population. However, in the GERCOR Phase II study, only 73.3% patients completed adjuvant chemotherapy, similar to the authors' study.[18]

Acute Toxicity

Table 1 shows toxicity during chemoradiation, and Table 2 shows toxicity during adjuvant chemotherapy. After a median follow-up of 12.5 months, three patients had a recurrence (20.0%). The median and mean times to relapse were 2 and 2.5 months, respectively. One patient had a local recurrence (33.3%), and two patients had a systemic recurrence (66.6%).

This is similar to the pattern of recurrence observed in the RTOG 9704 trial, where the incidence in loco-regional relapse was 30% and systemic relapse was 70%. Relapse was identified by an asymptomatic marker rise (CA 19-9) alone

in the patient with local recurrence and he was salvaged successfully and is alive and disease-free. In one patient with systemic relapse, the marker rise preceded the development of symptoms and radiological evidence of relapse. Hence, CA 19-9 monitoring should be a part of surveillance during follow-up after adjuvant treatment. Median OS and DFS were 15 and 14 months, respectively. OS and DFS at 18 months were 65.5% and 71.6%, respectively (Figure 1). The presence of CCP was associated with a significant difference in OS in both univariate and multivariate analysis.

Table 1: Toxicity during chemoradiation.

	Frequency	Percentage (%)
ECOG PS		
1	12	80.0
2	3	20.0
3	0	0.0
4	0	0.0
Weight loss		
Grade 1	2	13.0
Grade 2	0	0.0
Grade 3	0	0.0
Weight loss		
Grade 1	15	100.0
Grade 2	4	26.6
Grade 3	1	6.7
Nausea		
Grade 1	15	100.0
Grade 2	7	46.6
Vomiting		
Grade 1	6	40.0
Grade 2	2	13.3
Grade 3	1	6.7
Grade 4	0	0.0
Diarrhoea		
Grade 1	2	13.3
Grade 2	0	0.0
Grade 3	0	0.0
Grade 4	0	0.0
Abdominal pain		
Grade 1	7	46.6
Grade 2	1	6.7

Table 1 contined.

	Frequency	Percentage (%)
Grade 3	0	0.0
Anaemia		
Grade 1	1	13.3
Grade 2	0	0.0
Grade 3	0	0.0
Grade 4	0	0.0
Neutropenia		
Grade 1	2	13.3
Grade 2	0	0.0
Grade 3	0	0.0
Grade 4	0	0.0
Thrombocytopenia		
Grade 1	1	6.7
Grade 2	1	6.7
Grade 3	0	0.0
Grade 4	0	0.0
Hypoalbuminaemia		
Grade 1	2	13.3
Grade 2	1	6.7
Grade 3	0	0.0
Grade 4	0	0.0

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 2: Toxicity during adjuvant chemotherapy.

	Frequency	Percentage (%)
ECOG PS		
1	8	75
2	5	38
3	2	13.3
4	0	0.0
Weight loss		
Grade 1	13	100
Grade 2	7	53.8
Grade 3	2	15.3

Table 2 continued.

	Frequency	Percentage (%)
Nausea		
Grade 1	13	100.0
Grade 2	6	46.2
Grade 3	1	7.7
Vomiting		
Grade 1	4	30.1
Grade 2	2	15.3
Grade 3	1	7.7
Grade 4	0	0.0
Abdominal pain		
Grade 1	2	15.3
Grade 2	1	7.7
Grade 3	1	7.7
Anaemia		
Grade 1	4	30.1
Grade 2	3	23.1
Grade 3	3	23.1
Grade 4	0	0.0
Neutropenia		
Grade 1	3	23.1
Grade 2	2	15.3
Grade 3	6	46.2
Grade 4	2	15.3
Thrombocytopenia		
Grade 1	6	46.2
Grade 2	1	7.7
Grade 3	0	0.0
Grade 4	1	7.7
Worsened bilirubin		
Grade 1	1	7.7
Grade 2	1	7.7
Grade 3	0	0.0
Grade 4	0	0.0
Worsened SGOT/SGPT		
Grade 1	2	15.3
Grade 2	2	15.3

ECOG PS: Eastern Cooperative Oncology Group performance status; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase.

Table 2 continued.

	Frequency	Percentage (%)
Grade 3	2	15.3
Grade 4	0	0
Hypoalbuminaemia		
Grade 1	5	38.5
Grade 2	4	30.1
Grade 3	1	7.7
Grade 4	1	7.7

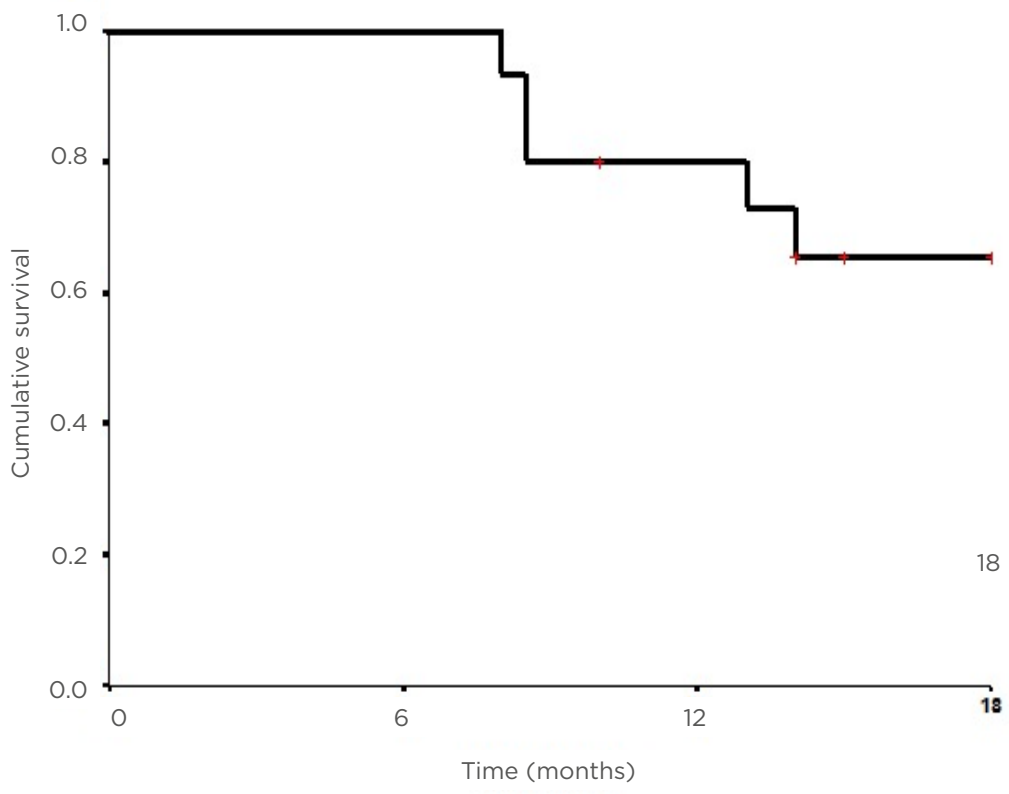

Figure 1: Kaplan–Meier curve showing the overall survival for the study population.

DISCUSSION

The data demonstrates that locally advanced pancreatic adenocarcinoma treated with adjuvant chemoradiation was well tolerated by most patients (with only one reported Grade 3 toxicity, being nausea, vomiting, fatigue, and no haematological toxicity more than Grade 2). All patients completed chemoradiation (with interruption in only 13.3). OS at 12 months was 80% and at 18 months was 65.5%. The median OS was 15 months. In the RTOG 9704 trial, the OS at 12 months and 18 months were 70% and 55%, respectively. The relatively high OS in this study compared to the RTOG trial might be due to the smaller sample size of the study.

Compared with chemoradiation, adjuvant chemotherapy was associated with a high incidence of haematological toxicity (Grade 3 or higher neutropoenia in 61.5% of cases and Grade 4 neutropoenia alone in 15.3% of cases) similar to the RTOG 9704 trial (the followed protocol in this study). However, treatment interruptions were higher compared to the RTOG trial and only 77% completed adjuvant chemotherapy with interruptions in 54%. The main cause of interruption was haematological toxicity.

The chemotherapy schedule was changed from an injection of gemcitabine on Days 1, 8, and 15 Q4 weekly to Days 1 and 8 Q3 weekly due to poor tolerance in 4 patients (31%). There were fewer interruptions in patients who were changed to the 3-weekly schedule.

CONCLUSION

Adjuvant chemoradiation was well tolerated by the majority of patients. Adjuvant chemotherapy was associated with a high incidence of haematological toxicity.

The ongoing RTOG 0848 trial is evaluating the approach of deferring chemoradiation until the completion of adjuvant chemotherapy as an option to decrease the added bone marrow toxicity of radiation that could lead on to chemotherapy interruptions due to haematological toxicities. However, until the results of this trial are available, no such recommendations can be made as if now.

This warrants the need for similar studies with inclusion of greater number of patients and longer follow-up period.

References

1. Ferlay J et al. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 Lyon. France: International Agency for Research on Cancer. 2010. GLOBOCAN 2008.
2. Cowgill SM, Muscarella P. The genetics of pancreatic cancer. Am J Surg. 2003;186(3):279-86.
3. Wilentz RE, Hruban RH. Pathology of cancer of the pancreas. Surg Oncol Clin N Am. 1998;7(1):43-65.
4. Esposito I et al. Pathology of pancreatic ductal adenocarcinoma: facts, challenges and future developments. World J Gastroenterol. 2014;20(38):13833-41.
5. Bosetti C et al. Pancreatic cancer: overview of descriptive epidemiology. Mol Carcinog. 2012;51(1):3-13.
6. Bosetti C et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol. 2011;23(7):1880-8.
7. Bosetti C et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. Ann Oncol. 2014;25(10):2065-72.
8. Chari ST et al. Pancreatic cancer–associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology. 2008;134(1):95-101.
9. Turati F et al. Family history of cancer and the risk of cancer: a network of case–control studies. Ann Oncol. 2013;24(10):2651-6.
10. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg. 1993;165(1):68-73.
11. Lillemoe KD. Current management of pancreatic carcinoma. Ann Surg. 1995;221(2):133-48.
12. Wagner M et al. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg. 2004;91(5):586-94.
13. Ducreux M et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56-68.
14. Tempero MA et al. Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15(8):1028-61.
15. Parkin DM. 2. Tobacco-attributable cancer burden in the UK in 2010. Br J Cancer. 2011;105(Suppl 2):S6-13.
16. Genkinger JM et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol. 2015;26(11):2257-66.
17. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006;20(2):197-209.
18. Van Laethem JL et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR Phase II study. J Clin Oncol. 2010;28(29):4450-6.

Emerging Role of Aurora A in Radioresistance: A Comprehensive Review

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Abstract

Radiotherapy is one of the most conventional modes of treatment in several cancers. Failure of radiotherapy followed by acquisition of radioresistance is one of the emerging challenges faced by clinical experts. Unusual expression and functional implications of several molecules are observed to facilitate radioresistance. Aurora A, a member of the Aurora kinase (serine/threonine kinase) family, is one such molecule that shows significantly altered expression as well as non-canonical functional crosstalk with other associated factors (cell cycle regulators, signaling molecules, stemness markers, etc.) to favour the adaptations for the acquirement of radioresistance. These mechanisms include progression of cell cycle, stimulatory activation of factors by phosphorylation for enhancing the chance of cellular survivability, and prevention of apoptosis. This review article summarises how Aurora A is responsible for radioresistance in cancer and why this kinase should be considered a negative biomarker of radiosensitivity. This review discloses a wider opportunity in the field of research to find the mechanistic key regulatory pathway of Aurora A, which can be a potential target for enhancing the efficiency of treatment. Further investigations are required to explore the potential of Aurora A inhibitors as reliable radiosensitisers.

INTRODUCTION

Radioresistance is known to create complications in the treatment of cancer.[1] Radiation-induced altered adaptive responses by tumour cells or tissues are considered to be primary reasons behind the failure of radiotherapy.[2] Acquirement of radioresistance followed by treatment failure and locoregional recurrence is a multifaceted process. Emerging data have suggested various molecular biomarkers necessitate radioresistance in cancer.[3,4] It is well established that the level of radioresistance alters in different phases of the cell cycle. Several researchers have experimentally proven that most cells are resistant in the G0 phase, early G1 phase, and late S phase of the cell cycle. In contrast, most cells are radiosensitive in the late G1 phase, G2 phase, and throughout the M phase of the cell cycle.[5] In the S phase, radiation resistance is thought to be due to an increased amount of DNA synthesis and repair enzymes, as well as a rise in the intracellular levels of glutathione (a free radical scavenger). In response to ionising radiation, the G1 phase of

the cell cycle is generally blocked to allow time for the recognition and repair of DNA damage prior to the initiation of DNA synthesis. Cells show the most sensitivity towards radiation during the G2/M phase of the cell cycle because of the lack of time for adequate repair before chromosome segregation. The key participating genes and their products halting cell cycle progression, which increase or are post-translationally altered following DNA damage, are p53, p21, growth arrest and DNA damage-inducible protein 45, and the retinoblastoma protein. Overall, there is a damage-responsive G1 block, halting the cell cycle at G2/M until DNA damage can be repaired. Thus, those cells having the ability to repair the damaged DNA may improve cell survival and impart additional resistance towards radiation.[6,7] It is widely reported that the essential mechanism by which ionising radiation exerts its therapeutic effect is by induction of DNA damages, such as double-strand breaks, single-strand breaks, and oxidation of DNA bases. These damages may be removed by homologous recombination, non-homologous end joining, single-strand break repair, and base excision repair.[8] Now, it is of importance to note why and how these participating genes get altered following DNA damage. Aurora A is found to interact with most of these regulators of cell cycle checkpoints to override their effect and continue cell cycle progression, and thereby contributes to radioresistance.

Three families of human Aurora kinases, Aurora kinase A, B, and C, share a common C-terminal catalytic domain in their proteins.[9] These three kinases are known to participate in mitotic progression of cells; however, little is known about Aurora kinase C.[9] During mitosis, centrosome maturation and separation followed by the assembly and stability of spindle is controlled by Aurora Kinase A.[10] Aurora kinase B is a member of the chromosomal passenger complex along with other members (survivin, borealin, and INCENP).[11] This kinase allows proper segregation of chromosomes and completes the cytokinesis process.[11] Evidence suggests that the zone of Aurora kinase B localisation is at the K-fibres, which are the specialised microtubules near kinetochores;[11] however, this localisation varies in different phases of the cell cycle, and is at the chromosomes in prophase, the centromere in prometaphase and metaphase, and the central mitotic spindle in anaphase.[12] Although Aurora kinase A and B are found in most of the somatic cells, Aurora kinase C is distributed in a limited manner to germline cells (sperm and oocyte) undergoing meiosis.[13] Aurora C primarily acts as a regulator of chromosome segregation in a lesser-known mechanism. The cell cycle specific distributions of these kinases are summarised in Figure 1.

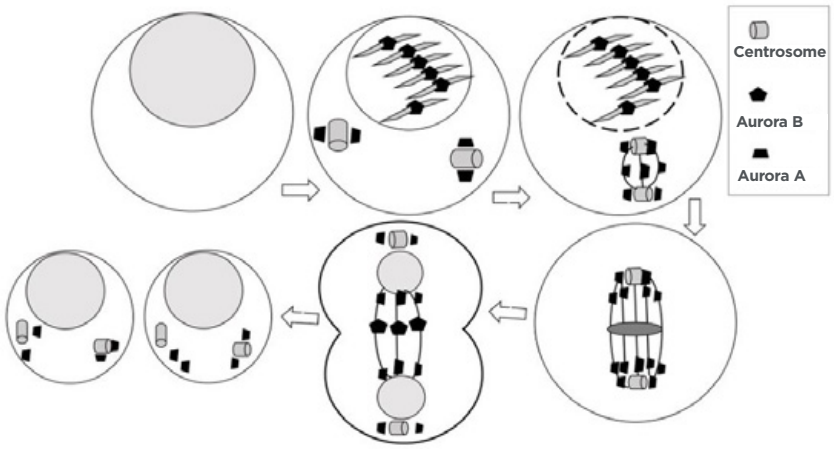

Figure 1: Cell cycle phase-specific distribution of Aurora kinases.

Aurora A localises to the centrosome from G1/S phase, with the progression of cell cycle it localises in spindle poles until telophase. Aurora B localises to the kinetochore followed by midbody of the central spindle during mitosis. The progression of cell division is shown using arrow signs from left showing normal cell, cover by onell in early prophase, cell in late prophase, cell in metaphase, cell in anaphase, and cells after division.

Apart from the canonical activities regulated by Aurora A, its overexpression also correlates with acquired radioresistance in several cancers. This review highlights some of the mechanisms performed by Aurora A in imparting radioresistance in cancer.

AURORA A

Salient Structural Features

Aurora A (or STK15/BTAK) is a well-known cell cycle regulatory kinase. Being a mitotic kinase, it is a member of the serine/threonine protein kinase family, which plays an important role in proper entry of cells in mitosis, formation of a bipolar spindle, control of centrosome maturation, and appropriate chromosomal segregation during mitosis.[8] If the activity of Aurora A is suppressed by RNA interference, it results in delayed mitotic entry of cells,[14] whereas centrosome amplification, cytokinesis inhibition, and aneuploidy are some well-verified after-effects of its overexpression.[15] Before looking into the functional mechanism of Aurora A, it is essential to understand the different protein domains of this kinase. The Aurora A gene has its chromosomal location at 20q13.2, which is often found to be significantly amplified in several human epithelial tumours.[16] The molecular weight of the mammalian Aurora A protein is 46 kDa and the protein is 402–403 amino acids long. The common structural configuration of all Aurora kinases includes an N-terminal domain (39–139 amino acids), a kinase domain (250–300 amino acids), and a C-terminal domain (15–20 amino acids).[17] The kinase domain of Aurora A is mainly composed of a β-stranded N-terminal lobe and α-helical C-terminal lobe that are linked together by a hinge region in order to acquire the active conformation.[18] The ATP-binding domain of Aurora A consists of three specific sequence variants (leucine 215, threonine 217, and arginine 220), of which the threonine 217 locus particularly distinguishes Aurora A from Aurora B kinase domains.[19] These particularities of the Aurora A domain are useful for the design of specific Aurora A inhibitors. Some non-catalytic domains present in Aurora A trigger its degradation. These include the D-boxes, KEN motifs, and the DAD/A boxes. Mutation of the C-terminal D-box sequence is essential for the stability of Aurora A, and degradation of Aurora A depends on D-Box instead of KEN-box motifs (residues 6–9). Aurora A degradation is also mediated by the anaphase promoting complex or cyclosome, which occurs at an atypical degradation sequence present in Aurora A named the DAD/A box.[20,21] Aurora A possesses a short α-helix called the B-helix, located just prior and perpendicular to the C-helix. The structure of Aurora A is depicted in Figure 2.

The C-terminal region of the kinase domain consists of seven α-helices and a two-stranded β-sheet, and contains the catalytic aspartic acid of the HRD motif (sequence histidine, arginine, and aspartate at positions 254–256) and the mobile activation loop, whose position and conformation determine whether a kinase is active or inactive.[22,23] The Aurora A activation loop (the most crucial part required for functional activation of the protein) spans 274–299 amino acid residues, beginning with an aspartate, phenylalanine, and glycine sequence motif and ending with an alanine, proline, and glutamate motif (sequence proline, proline, and glutamate in Aurora A). Aurora A becomes active by its autophosphorylation (discussed in detail later) and trans-phosphorylation at threonine 287 and threonine 288 residues by targeting protein for Xenopus kinesin-like protein 2,[24] p21 activated kinase,[25] protein kinase A,[26] or atypical protein kinase C.[27]

Localisation

Being a centrosomal protein, Aurora A resides next to the centrosome late in the G1 phase and early in the S phase. The N-terminal domain of Aurora A participates in the localisation of the kinase to the centrosome during interphase. With the progression of the cell cycle, Aurora A concentrations increase and an association of the kinase with the mitotic poles and the adjacent spindle microtubules is observed. Such association lasts until telophase. Re-localisation of Aurora A to the mid-zone of the spindle occurs immediately before mitotic exit.[28]

AURORA A ACTIVATION

Transcriptional

The cell cycle-induced transcription of Aurora proteins is made possible by the presence of the cell cycle-dependent element and cell cycle gene homology region in *Aurora A* promoters.

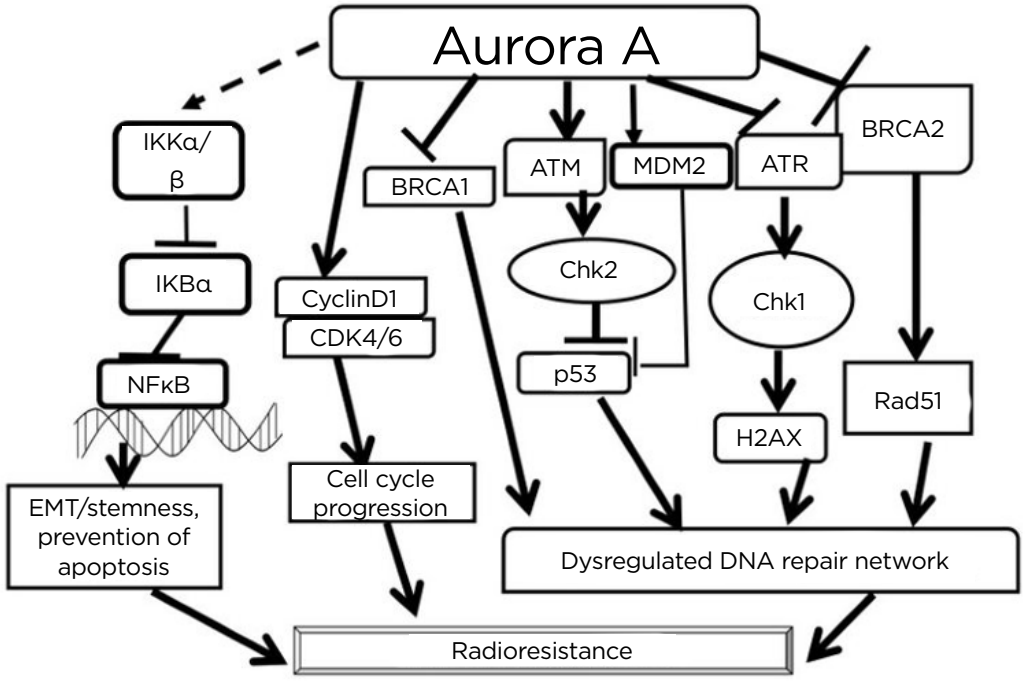

Figure 2: Some of the well-studied interactions of Aurora A that are found to help in acquirement of radioresistance. Aurora A activates NFκB and generates EMT and causes prevention of apoptosis. The kinase can activate cyclin D1 and CDK to allow progression of cell cycle. Aurora A, by interacting with DNA repair regulators (BRCA1, BRCA2, ATM and Rad3-related kinase, Chk 1/2, and p53), causes dysregulated DNA repair. All of these result in changes that lead to radioresistance.

ATM: ataxia–telangiectasia-mutated kinase; ATR: ataxia–telangiectasia-mutated and Rad3-related kinase; BRCA: breast cancer susceptibility protein; CDK4/6: cyclin-dependent kinase 4/6; Chk: checkpoint kinase; EMT: epithelial–mesenchymal transition; MDM2: mouse double minute 2 homolog.

The cell cycle-dependent element and cell cycle gene homology region sequences in *Aurora A* mediate the transcription of *Aurora A* and other crucial G2/M regulators (e.g., cyclin A, cell division cycle 25 phosphatase, cyclin-dependent kinase [CDK] 1, and polo-like kinase).[29]

Post-translational Modifications

Post-translational modification is an important prerequisite for functional activation of the enzyme. Like other serine/threonine kinases, functional regulation of Aurora A occurs through activation loop phosphorylation. Aurora A auto-phosphorylation, a salient post-translational modification, is mediated by several co-factors, of which Ajuba, targeting protein for Xenopus kinesin-like protein 2, protein aurora borealis, and transforming acidic coiled–coil-containing protein 3 are the noteworthy ones. As described earlier, Aurora A has two regulatory sites for phosphorylation in its activation loop (threonine 287 and threonine 288). Phosphorylation of Aurora A in its catalytic domain at threonine 288 is known to trigger the kinase activity of the enzyme.[24] This phosphorylation eventually causes a positive feedback loop, which is responsible for maintaining the activated state of the kinase until anaphase. Maximum activity has been observed from late G2 until pro-metaphase. The function of threonine 287 phosphorylation is still unclear.[30]

RADIORESISTANCE IN CANCER: FUNCTIONAL ROLE OF AURORA A

Apart from its intricate role in regulating mitosis, activated Aurora A also subsequently promotes

a variety of biological functions for maintaining cancer phenotypes. Some of the functions of Aurora A include cell proliferation, migration, invasion, epithelial–mesenchymal transition, and maintenance of cancer stem cell behaviors.[31] Now, it is necessary to understand whether Aurora A has any impact on radiotherapy in cancer. Ectopic expression of Aurora A led to increased sensitivity to ionising radiation in MCF10A normal breast epithelial cells.[30] In contrast, in cancer cells, a plethora of evidence suggests that excessive Aurora A attenuates the radiosensitivity of cells, while silencing or inhibition of Aurora A with small interfering RNA or selective inhibitors enhances radiosensitivity.[32] The possibility of involvement of Aurora A in contributing radioresistance has been experimentally tested in several cancers. Overexpression of Aurora A in cervical squamous cell carcinoma showed a strong positive correlation with cancer cell invasion and metastasis. Furthermore, Aurora A is considered to serve as an independent prognostic factor, which affects disease-free survival and overall survival.[33] In one study, patients with cervical cancer were treated with Aurora A inhibitors. Treatment outcomes included increased cell apoptosis after X-irradiation and downregulation of the expression of cyclin D1, CDK2, and CDK6, which eventually induced cell cycle arrest at the G2/M phases.[34] These findings indicate that Aurora A activation gives rise to radiation resistance by allowing cell cycle progression in cervical cancer. Therefore, Aurora A may be regarded as one of the therapeutic targets and an independent prognostic factor for increasing the sensitivity of cervical squamous cell carcinoma radiotherapy. A predominant finding of Shen et al., who studied hepatocellular carcinoma (HCC) cell lines, revealed lower expression of nuclear IκBα protein in parental HCC cells at the same time as higher expression levels of p65 protein in radioresistant counterparts. Knockdown of Aurora A led to increased expression of nuclear IκBα proteins by way of decreased expression of p65 proteins in radioresistant HCC cells. The expression of downstream effectors of the NF-κB pathway, such as B-cell lymphoma 2, myeloid cell leukaemia 1, cleaved poly(ADP-ribose) polymerase, and caspase-3 (cysteine-aspartic proteases), is enhanced by hyperproduction of Aurora A. Triggering apoptosis in radioresistant cells was attained by knockdown of Aurora A, which resulted in downregulated B-cell lymphoma 2 and myeloid leukaemia 1 protein expressions as well as upregulated cleaved poly(ADP-ribose) polymerase and caspase-3 expressions in radioresistance.[35] To explore whether Aurora A contributes to radioresistance, a study was conducted by Sun et al., using Aurora A complementary DNA/short hairpin RNA or the specific inhibitor VX-680 (Vertex Pharmaceuticals, Inc., Boston Massachusetts, USA). This study confirmed that Aurora A positively regulates cell proliferation, cell cycle progression, and anchorage-independent cell growth in order to establish resistance against X-rays. Simultaneous promotion of the expression of ataxia–telangiectasia-mutated kinase/checkpoint kinase 2 and suppression of the expression of breast cancer susceptibility protein 1/2, ataxia–telangiectasia-mutated and Rad3-related kinase/checkpoint kinase 1, p53, phospho-p53 (serine 15), H2AX, γH2AX (serine 139), and RAD51 by Aurora A resulted in a dysregulated DNA repair mechanism. The formation of a γH2AX focus, which is considered as one of the prognostic markers of radiation-induced DNA damage, was found to be minimised by Aurora A. These reports account for supportive evidence of the hypothesis that Aurora A is a negative biomarker of radiosensitivity.[36] Similar results were observed in HeLa cells, which were irradiated with 4 Gy of γ-rays. The electrophoretic mobility shift assay, luciferase reporter gene assay, immunoblot analysis, small interfering RNA-based gene knockdown, and overexpression studies concluded that Aurora A enhances the binding of NF-κB to DNA, thereby increasing the gene transcription by NF-κB and decreasing the radiosensitivity of the cells.[37] Equivalent results were obtained in radioresistance of lung adenocarcinoma.[38] The effectiveness of radiation-induced cell death often relies on the mechanism of reactive oxygen species-mediated cellular damage. Tumour tissues that are deprived of adequate oxygen supply due to hypoxic conditions lack sufficient amounts of reactive oxygen species, thereby causing a three-fold increase in the chance of acquired radioresistance. The transformed tumor cells get adapted in the hypoxic tumour microenvironment by developing resistant characters in them.[39] Simultaneous overexpression of hypoxia-inducible factor-1α and Aurora A is a remarkable event during hypoxia, which establishes a positive feedback between these two molecules.[40] It has been

suggested that hypoxic cellular proliferation and migration are clinically correlated with increased mRNA and protein expression of Aurora A. Conversely, inhibition of Aurora A could reverse this event.[40] In a further study, it was confirmed that in hypoxia, hypoxia-inducible factor-1α binds at the promoter region of *Aurora A* and enhances its transcription.[41] This associative involvement of Aurora A in both hypoxia and radioresistance is notable, which again provokes the possibility of this kinase in imparting radioadaptive responses during acquirement of radioresistance. Experimental evidence indicated that MLN8237 (Takeda Pharmaceutical Company Ltd., Tokyo, Japan), a selective Aurora A inhibitor, could induce cell cycle arrest at the G2/M phase and significantly reduce radiation-dependent resistance.[42] Similar studies were found in selected lung cancer cell lines, where inhibition of Aurora A enhanced radiosensitivity.[43] Increased expression of Aurora A is negatively correlated with survival in patients with non-small cell lung carcinoma.[43] One of the established Aurora kinase inhibitors, daurinol, targets the kinase and enhances radiotherapy;[44] however, the exact mechanism concerning the functional impact of this Aurora A inhibitor needs to be investigated thoroughly. Whether the inhibitor enhances radiosensitivity by directly blocking Aurora A or through inhibiting cyclin expressions (cyclin D1, CDK2, and CDK6) is yet to be elucidated.[44] Aurora kinase expression was reported to be regulated transcriptionally by radiation because the mRNA and protein expression of such kinases were increased by sub-lethal doses of radiation.[45] The level of Aurora kinases present in pre-treatment biopsies could serve as a predictive factor to identify patients likely to respond to conservative radiotherapies. Pharmacological approaches targeting Aurora kinases in tumors over-expressing these proteins could strongly increase the therapeutic ratio in radiotherapy for cancer treatment. The underlying mechanisms by which targeting aurora kinases may improve the response to radiation seem to be multifaceted and involves cell cycle distribution.[43] In radioresistant pancreatic cancer cells, treatment with an Aurora A inhibitor resulted in co-inhibition of cyclin D1, CDK2, and CDK6 to induce cell cycle arrest at the G1/S and G2/M phases, and also promoted cell apoptosis after γ-irradiation.[46] In laryngeal cancer cells, inhibiting Aurora A by VX-680 induced expression of p53 and potently sensitised cells to radiotherapy, leading to significant cell death, whereas ectopic overexpression of Aurora A reduced p53 levels and rendered cells more resistant to irradiation. Taken together, Aurora A kinase, a negative prognostic marker, promotes migration, and reduces radiosensitivity.[47] The Aurora A signaling axis pertinent to radioresistance is represented in Figure 2.

OTHER PROBABLE INTERACTIONS MEDIATED BY AURORA A IN RADIORESISTANCE

Radioresistance is a collective contribution of several factors, with which Aurora A interacts. Signaling pathways like phosphatidylinositol 3-kinase/protein kinase B, NF-κB, and Wnt/β-catenin in association with stemness markers like sex-determining region Y-box 2, octamer-binding transcription factor 4, and Twist1 guide the cells to obtain epithelial–mesenchymal transition-like characteristics, which accounts for stabilisation of the resistant phenotype.[48-59] Aurora A is found to interact with these molecules during cancer progression. Therefore, there are strong possibilities that such interactions play an essential role in Aurora A-mediated radioresistance. Some of these interactions are summarised in Table 1.

CONCLUSIONS AND PERSPECTIVES

One of the major reasons behind the therapeutic failure of radiation is radioresistance. Cancer cells that survive the effects of radiation acquire adaptations to bypass cell cycle checkpoints and thereby retain their proliferative and invasive properties. Several faulty repair mechanisms accumulate changes in sequences of DNA, which makes this process smoother. The regulatory role of Aurora A in mitotic and non-mitotic events involves several molecules, ranging from DNA repair mediators to signaling modulators. It is more important to highlight that blocking and inactivation of Aurora A activity can reverse the process of

radioresistance and increase radiosensitivity. Treatment of patients using fractionated irradiation determines acquirement of resistance against radiotherapy, which is clinically complemented with overexpression of Aurora A. Thereby, Aurora A can serve as a prognostic marker of radioresistance. This review provides a thought-provoking element to global researchers, encouraging them to design novel experiments in order to explore the mechanistic key regulatory pathway of Aurora A necessary for enhancing the efficiency of treatment. Checking the levels of Aurora A along with administration of Aurora A inhibitors prior to radiotherapy could be applied in the future to enhance the efficacy of radiotherapy. Clinical administration of Aurora A inhibitors as reliable radiosensitisers may serve as a scope of future investigations. The details of several Aurora kinase inhibitors are provided below.

Type of Inhibitor

Pan-aurora inhibitor

Tozasertib (VX-680/MK0457 [Merck & Co., Kenilworth, New Jersey, USA]) is currently in Phase II clinical trials, and exerts its activity by inducing apoptosis and autophagy.[60] Danusertib (PHA-739358), which is also in Phase II clinical trials, blocks the activities of fibroblast growth factor receptor 1, Abl, rearranged during transfection, and tropomyosin receptor kinase A, and increases expression of the p53 protein and its downstream effector protein p21.[61]

Table 1: Interactions of several factors with Aurora A that have a potential to generate radioresistance.

Name of the factor	Interaction with Aurora A	Result	Reference(s)
PI3K/Akt	Aurora A phosphorylates Akt at its activation site (serine 473).	Akt activation eventually activates mTOR pathway, thereby enhancing radioresistance by regulating the level of EMT-related markers.	42
SOX2	Aurora A phosphorylates SOX2 at two important phosphorylation sites: serine 220 and serine 251.	Maintenance of cancer stem cell properties and reduced sensitivity towards radiation.	43
Twist1	Aurora A phosphorylates Twist1 at three sites (serine 123, threonine 148, and serine 184) and stabilises it upon binding. A reciprocal interaction by Twist1 is observed because it prevents Aurora A degradation.	Both the proteins take part in EMT progression. Expression of Twist1 is usually high in radioresistant cancer cells.	44-45
Wnt/β-catenin pathway	Aurora A directly phosphorylates glycogen synthase kinase-3β; activates and stabilises β-catenin.	The Wnt/β-catenin pathway is a major pathway linked with the formation of cancer radioresistance.	46
Myc	Aurora A activates *c-Myc* transcription by interaction with the CCCTCCCCA motif in the NHE III1 region. *c-Myc* also acts as transcriptional activator of Aurora A via physical binding to *Aurora A* promoter in a non-canonical E box, which represents potential Myc binding site (668/400 region of *Aurora A* promoter).	Dysregulation of the DNA repair pathway. Myc also maintains GSH and ROS levels to increase the cancer stem cell-like population and properties, therefore conferring radioresistance.	47

Long, non-coding RNA (*MALAT1*, *TUG1*)	Long, non-coding RNAs are prospective transcriptional regulators, which work in association with chromatin remodeling complex to regulate the expression of Aurora A.	Long, non-coding RNA knockdown enhances radiosensitivity of cancer.	48-51
MicroRNA (microRNA-4715-3p; microRNA-129-3p; microRNA-34/449)	MicroRNAs block the transcription of Aurora A by interacting at the 3'UTR of Aurora A and thereby prevent its expression.	Functional inactivation of microRNAs cause bypass of cell cycle and initiates radioresistance.	52-53

Akt: protein kinase B; EMT: epithelial–mesenchymal transition; GSH: glutathione; *MALAT1*: *metastasis-associated lung adenocarcinoma transcript 1*; mTOR: mechanistic target of rapamycin; NHE III1: nuclease hypersensitive element III1 region; PI3K: phosphatidylinositol 3-kinase; ROS: reactive oxygen species; SOX2: sex determining region Y-box 2; *TUG1*: *taurine up-regulated 1*; 3'UTR: three prime untranslated region.

PHA-680632, CYC-116, SNS-314, R763, and AMG-900 are currently in Phase I clinical trials. PHA-680632 shows additive effects in cancer cells in association with radiation. Treatment with PHA-680632 prior to ionising radiation causes enhancement in apoptosis, micronuclei formation, and breast cancer susceptibility protein 1 foci formation.[62] CYC-116 inhibits Aurora activity by interfering with its autophosphorylation, reducing histone H3 phosphorylation and subsequent polyploidy, and ultimately causing failure in cytokinesis followed by cell death.[63] SNS-314 exhibits potent and sustained responses, including reduced phosphorylated histone H3 levels, increased caspase-3, and appearance of increased nuclear size.[64] R763 causes enlargement of cell size, endoreduplication, and apoptosis.[65] AMG-900 is an ATP-competitive phthalazinamine small molecule inhibitor of Aurora kinases. AMG 900 inhibits autophosphorylation of Aurora kinase and phosphorylation of histone H3 on serine 10. This leads to aborted cell division without a prolonged mitotic arrest, which ultimately results in cell death.[66] AT-9283 is currently in Phase II clinical trials, and promotes a clear polyploid phenotype by inhibiting the activity of Aurora kinase.[67] Finally, PF-03814375, which is in Phase I clinical trials, is a novel, potent, orally bioavailable, reversible inhibitor of Aurora kinase.[68]

Aurora A inhibitor

Alisertib (MLN8237), which is in Phase II clinical trials, performs cell cycle arrest at the G2/M phase, and instigates apoptosis and senescence. It allows up-regulation of p53, p21, and p27, and cleavage of poly(ADP-ribose) polymerase, caspase-3, and caspase-9.[69] ENMD-2076 is also in Phase II clinical trials, and inhibits the activity of Aurora A and B kinases, as well as inducing G2/M cell cycle arrest.[70] Lastly, MLN8054 is an ATP-competitive, reversible inhibitor of Aurora A kinase. Its mechanism of actions includes halting cell proliferation by promoting G2/M accumulation and spindle defects. A recent study showed that MLN8054 sensitises androgen-resistant prostate cancer to radiation by inhibiting Aurora A kinase, which is associated with sustained DNA double-strand breaks.[71,72]

References

1. Murata K et al. Understanding the mechanism underlying the acquisition of radioresistance in human prostate cancer cells. Oncol Lett. 2019;17:5830-8.
2. Norman CC et al. Radiation-induced adaptive response: new potential for cancer treatment. Clin Cancer Res. 2020;26(22):5781-90.
3. Kilic S et al. The relevance of molecular biomarkers in cervical cancer patients treated with radiotherapy. Ann Transl Med. 2015;3(18):261.
4. Akervall J et al. A novel panel of biomarkers predicts radioresistance in patients with squamous cell carcinoma of the head and neck. Eur J Cancer. 2014;50(3):570-81.
5. McIlwrath AJ et al. Cell cycle arrests and radiosensitivity of human tumor cell lines: dependence on wild-type p53 for radiosensitivity. Cancer Res. 1994;54(14):3718-22.
6. Otani K et al. Cell-cycle-controlled radiation therapy was effective for treating a murine malignant melanoma cell line in vitro and in vivo. Sci Rep. 2016;6:30689.

7. Sharda N et al, "Radiation resistance," Bertino J (ed.), Encyclopaedia of Cancer (2002) 2nd edition: Academic Press, pp.1-11.
8. Biau J et al. Altering DNA repair to improve radiation therapy: specific and multiple pathway targeting. Front Oncol. 2019;9:1009.
9. Goldenson B et al. The Aurora kinases in cell cycle and leukemia. Oncogene. 2015;34:537-45.
10. Barr RA et al. Aurora-A: the maker and breaker of spindle poles. J Cell Sci. 2007;120:2987-96.
11. Krenn et al. The Aurora B kinase in chromosome bi-orientation and spindle checkpoint signaling. Front Oncol. 2015;5:225.
12. Adams RR et al. Chromosomal passengers and the (Aurora) ABCs of mitosis. Trends Cell Biol. 2001;11(2):49-54.
13. Quartuccio SM et al. Functions of Aurora kinase C in meiosis and cancer. Front Cell Dev Biol. 2015;3:50.
14. Magnaghi-Jaulin L et al. Aurora A protein kinase: to the centrosome and beyond. Biomolecules. 2019;9(1):28.
15. Asteriti IA et al. The Aurora-A inhibitor MLN8237 affects multiple mitotic processes and induces dose-dependent mitotic abnormalities and aneuploidy aneuploidy. Oncotarget. 2014:5(15):6229-42.
16. Wang X et al. Overexpression of Aurora-A kinase promotes tumor cell proliferation and inhibits apoptosis in esophageal squamous cell carcinoma cell line. Cell Res. 2006;16:356-66.
17. Lin YS et al. Gene expression profiles of the aurora family kinases. Gene Expr. 2006;13(1):15-26.
18. Siddhanta S et al. Surface enhanced Raman spectroscopy of Aurora kinases: direct, ultrasensitive detection of autophosphorylation. RSC Adv. 2013;3:4221-30.
19. Cheetham GMT et al. Crystal structure of Aurora-2, an oncogenic serine/threonine kinase. J Biol Chem. 2002;277(45):42419-22.
20. Brown JR et al. Evolutionary relationships of aurora kinases: implications for model organism studies and the development of anti-cancer drugs. BMC Evol Biol. 2004;4:39.
21. Seeling JM et al. Differential selective pressures experienced by the Aurora kinase gene family. Int J Mol Sci. 2017;19(1):72.
22. Min M et al. Ubiquitination site preferences in anaphase promoting complex/ cyclosome (APC/C) substrates. Open Biol. 2013;3(9):130097.
23. Setny P. Conserved internal hydration motifs in protein kinases. Proteins. 2020;88(12):1578-91.
24. Polverino F et al. The Aurora-A/TPX2 axis directs spindle orientation by regulating NuMa and microtubule dynamics. SSRN Electronic Journal. 2020;DOI:10.2139/ ssrn.3588889.
25. Zhao ZS et al. The GIT-associated kinase PAK targets to the centrosome and regulates Aurora-A. Mol Cell. 2005;20(2):237-49.
26. Walter AO et al. The mitotic serine/threonine kinase Aurora2/AIK is regulated by phosphorylation and degradation. Oncogene. 2000;19(42):4906-16.
27. Mori D et al. An essential role of the aPKC-Aurora A-NDEL1 pathway in neurite elongation by modulation of microtubule dynamics. Nat Cell Biol. 2009;11(9):1057-68.
28. Rannou Y et al. Localization of Aurora A and Aurora B kinases during interphase: role of the N-terminal domain. Cell Cycle. 2008;7(19):3012-20.
29. Tanaka M et al. Cell-cycle-dependent regulation of human Aurora A transcription is mediated by periodic repression of E4TF1. J Bio Chem. 2002;277(12):10719-26.
30. Rowan FC et al. Insights into Aurora-A kinase activation using unnatural amino acids incorporated by chemical modification. ACS Chem Biol. 2013;8(10):2184-91.
31. Chen C et al. AURKA promotes cancer metastasis by regulating epithelial-mesenchymal transition and cancer stem cell properties in hepatocellular carcinoma. Biochem Biophys Res Commun. 2017;486(2):514-20.
32. Liu N et al. Inhibition of Aurora A enhances radiosensitivity in selected lung cancer cell lines. Respir Res. 2019;20(1):230.
33. Ma Y et al. Aurora-A affects radiosenstivity in cervical squamous cell carcinoma and predicts poor prognosis. Oncotarget. 2017;8(19):31509-20.
34. Ma Y et al. Mechanism of cervical squamous cell carcinoma radioresistance conferred by Aurora-A. Int J Clin Exp Pathol. 2017;10:2416-25.
35. Shen ZT et al. Aurora-A confers radioresistance in human hepatocellular carcinoma by activating NF-κB signaling pathway. BMC Cancer. 2019;19(1):1075.
36. Sun H et al. Aurora-A controls cancer cell radio- and chemoresistance via ATM/Chk2-mediated DNA repair networks. Biochim Biophys Acta. 2014;1843(5):934-44
37. Oh ET et al. Aurora-A contributes to radioresistance by increasing NF-κB DNA binding. Radiat Res. 2010;174(3):265-73.
38. Liu JB et al. Aurora-A/NF-κB signaling is associated with radio-resistance in human lung adenocarcinoma. Anticancer Res. 2019;39(11):5991-8.
39. Wang H et al. Hypoxic radioresistance: can ROS be the key to overcome it? Cancers (Basel). 2019;11(1):112.
40. Cui SY et al. The role of Aurora A in hypoxia-inducible factor 1α-promoting malignant phenotypes of hepatocelluar carcinoma. Cell Cycle. 2013;12(17):2849-66.
41. Romain CV et al. Targeting Aurora kinase A inhibits hypoxia-mediated neuroblastoma cell tumorigenesis. Anticancer Res. 2014;34(5):2269-74.
42. Asteriti IA et al. The Aurora-A inhibitor MLN8237 affects multiple mitotic processes and induces dose-dependent mitotic abnormalities and aneuploidy. Oncotarget. 2014;5(15):6229-42.
43. Liu N et al. Inhibition of Aurora A enhances radiosensitivity in selected lung cancer cell lines. Respir Res. 2019;20(1):230.
44. Woo JK et al. Daurinol enhances the efficacy of radiotherapy in lung cancer via suppression of Aurora kinase A/B expression. Oncotarget. 2014;5(15):6229-42
45. Shiomitsu K et al. The radiosensitizing effect of the Aurora kinase inhibitors, ENMD-2076, on canine mast cell tumours in vitro. Vet Comp Oncol. 2016;14(1):13-27.
46. Sun H, Yang G. Mechanistic study of pancreatic cancer cell radioresistance conferred by Aurora-A. China Oncology. 2013;(12):974-9.
47. Guan Z et al. Aurora-A, a negative prognostic marker, increases migration and decreases radiosensitivity in cancer cells. Cancer Res. 2007;67(21):10436-44.
48. Yu CC et al. Targeting the PI3K/ AKT/mTOR signaling pathway as an effectively radiosensitizing strategy for treating human oral squamous cell carcinoma in vitro and in vivo. Oncotarget. 2017;8(40):68641-53.
49. Saigusa S et al. Correlation of CD133, OCT4, and SOX2 in rectal cancer and their association with distant recurrence after chemoradiotherapy. Ann Surg Oncol. 2009;16(12):3488-98.
50. Wang J et al. The Aurora-A-Twist1 axis promotes highly aggressive phenotypes in pancreatic carcinoma J Cell Sci. 2017;130(6):1078-93.
51. Puisieux A et al. A twist for survival and cancer progression. Br J Cancer. 2006:94(1):13-7.
52. Dar AA et al. The Aurora kinase A regulates GSK-3β in gastric cancer cells. Oncogene. 2009;28(6):866-75.
53. Le Grand M et al. Interplay

between MycN and c-Myc regulates radioresistance and cancer stem cell phenotype in neuroblastoma upon glutamine deprivation. Theranostics. 2020;10(14):6411-29.

54. Long Y et al. How do lncRNAs regulate transcription? Sci Adv. 2017;3(9):eaao2110.

55. Fan L et al. Long noncoding RNA MALAT1 contributes to sorafenib resistance by targeting miR-140-5p/Aurora-A signaling in hepatocellular carcinoma. Mol Cancer Ther. 2020;19(5):1197-209.

56. Li T et al. LncRNA TUG1 promotes cells proliferation and inhibits cells apoptosis through regulating AURKA in epithelial ovarian cancer cells. Medicine (Baltimore). 2018;97(36):12131.

57. Jiang H et al. Down-regulation of LncRNA TUG1 enhances radiosensitivity in bladder cancer via suppressing HMGB1 expression Radiat Oncol. 2017;12(1):65.

58. Shen ZT et al. Aurora-A confers radioresistance in human hepatocellular carcinoma by activating NF-κB signaling pathway. BMC Cancer. 2019;19(1):1075.

59. Otto T et al. Cell cycle-targeting microRNAs promote differentiation by enforcing cell-cycle exit. Proc Natl Acad Sci USA. 2017;114(40):10660–5.

60. Chan JY et al. Multiomic analysis and immunoprofiling reveal distinct subtypes of human angiosarcoma. J Clin Invest. 2020;130(11):5833-46.

61. Carpinelli P et al. PHA-739358, a potent inhibitor of aurora kinases with a selective target inhibition profile relevant to cancer. Mol Cancer Ther. 2007;6(12 Pt 1):3158-68.

62. Tao Y et al. Enhancement of radiation response by inhibition of Aurora-A kinase using siRNA or a selective Aurora kinase inhibitor PHA680632 in p53-deficient cancer cells. Br J Cancer. 2007;97(12):1664-72.

63. Wang S et al. Discovery of N-phenyl-4-(thiazol-5-yl)pyrimidin-2-amine aurora kinase inhibitors. J Med Chem. 2010;53(11):4367-78.

64. Arbitrario JP et al. SNS-314, a pan-Aurora kinase inhibitor, shows potent anti-tumor activity and dosing flexibility in vivo. Cancer Chemother Pharmacol. 2010;65(4):707-17.

65. McLaughlin J et al. Preclinical characterization of Aurora kinase inhibitor R763/AS703569 identified through an image-based phenotypic screen. J Cancer Res Clin Oncol. 2010;136(1):99-113.

66. Cota CD et al. Cyclin-dependent kinase 1 and Aurora kinase choreograph mitotic storage and redistribution of a growth factor receptor. PLoS Biol. 2021;19(1):e3001029.

67. Howard S et al. Fragment-based discovery of the pyrazol-4-yl urea (AT9283), a multitargeted kinase inhibitor with potent aurora kinase activity. J Med Chem. 200;52(2):379-88.

68. Jani P J et al. PF-03814735, an orally bioavailable small molecule aurora kinase inhibitor for cancer therapy. Mol Cancer Ther. 2010;9(4):883-94.

69. Görgün G et al. A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma. Blood. 2010;115(25):5202-13.

70. Wang X et al. Preclinical activity of a novel multiple tyrosine kinase and aurora kinase inhibitor, ENMD-2076, against multiple myeloma. Br J Haematol. 2010;150(3):313-25.

71. Manfredi MG et al. Antitumor activity of MLN8054, an orally active small-molecule inhibitor of Aurora A kinase. Proc Natl Acad Sci USA. 2007;104(10):4106-11.

72. Moretti L et al. MLN8054, a small molecule inhibitor of aurora kinase a, sensitizes androgen-resistant prostate cancer to radiation. Int J Radiat Oncol Biol Phys. 2011;80(4):1189-97.

Management of Lower Limb Soft Tissue Sarcomas with Major Neurovascular Involvement: Current and Future Perspectives

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Abstract

Lower limb soft tissue sarcomas are a group of rare mesenchymal tumours that may grow in close anatomical proximity to major neurovascular structures, leading to significant oncological and surgical challenges for treating physicians. This article reviews the current literature on the multidisciplinary approach of treating lower limb soft tissue sarcomas with neurovascular involvement and describes the increasing shift towards limb-sparing surgeries, with an emphasis on improved functional outcomes based on a multimodal treatment approach. In addition to identifying the histological subtype of the tumour, classifying the neurovascular involvement precisely is key in planning the appropriate treatment. Existing classification systems for both vascular and neural involvement are discussed, and a combined neurovascular classification is proposed together with a general treatment algorithm.

INTRODUCTION

Soft tissue sarcomas (STS) are a group of rare mesenchymal tumours that can arise in patients of any age and in a variety of anatomic sites.[1] It is estimated that STS make up 1% of all adult malignancies and that their incidence is on the rise.[2,3] The lower limb is the most commonly affected site, with approximately 28% of STS arising there.[4] With at least 50 different histologic subtypes, STS are considered highly heterogenous in terms of their histopathology and their tendency to metastasise.[5] Undifferentiated pleomorphic sarcomas and liposarcomas are the most common histopathologic subtypes in adult patients.[5]

STS may arise from or grow towards neighbouring vascular and neural structures, leading to significant oncological and surgical challenges. In these cases, the responsible surgeon must

find a balance between the need for a complete tumour resection, with microscopically negative margins, and the desire to limit the invasiveness of the operation and minimise long-term disabilities. In the past, the involvement of major neurovascular structures of the lower extremity was often associated with limb amputations and debilitating surgeries.[6] However, current multimodal treatment strategies pursue the goal of limb preservation, whilst minimising the risk of local or systemic disease recurrence.

There are limited data on the frequency and typical localisation of neurovascular involvement in STS. It appears that the inguinal region, the medial thigh compartment, and the popliteal fossa are common sites of lower limb STS with vascular involvement.[7] The reported frequency of major vascular involvement varies between 5% and 10% of all adult patients with STS of the lower extremity, with femoral vessels being reported as the most commonly involved vascular structures followed by the inguinal and popliteal vessels.[8-10] En bloc tumour resection, with resection of the great vessels, has been reported in up to 5.0% of all patients with lower extremity sarcomas.[7,11-13] In contrast, nerve resection was carried out in only 1.2% of cases of lower limb STS with neural involvement, according to a study by Brooks et al.[14] In a recent study, however, sciatic nerve involvement was reported at 15.0% of all lower limb STS, with 4.5% of all cases of lower extremity STS requiring complete nerve resection.[15]

In this article, the authors aim to review the current literature regarding the multidisciplinary management of lower limb STS, with a focus on diagnostic and therapeutic management strategies of major neurovascular involvement. They also aim to suggest aspects for future research to further assess the role of a limb-preserving multimodal therapeutic approach.

DIAGNOSTIC STRATEGIES

Selection of Imaging Studies

Following the initial clinical examination of a suspicious lesion, further imaging is often necessary in establishing the diagnosis.[16] An initial ultrasound examination of the lesion may be helpful in determining its size and relationship to the fascia.[17] MRI remains the imaging modality of choice for diagnosing soft tissue lesions, providing useful anatomical details necessary in planning the surgical tumour resection.[17] Gadolinium enhancement of the MRI examination is often necessary in determining the vascularity of the tumour and its anatomical relation to blood vessels and nerves.[16] CT imaging can alternatively be used when an MRI examination is contra-indicated. The use of conventional angiography or duplex sonography in addition to magnetic resonance angiography may also be necessary in STS with vascular involvement.[8] Tumour-induced anatomical changes in surrounding vessels can be shown using digital subtraction angiography.[7] PET scanning is being increasingly employed as an imaging modality in the investigation of STS. In addition to screening for metastatic disease, particularly lymph node involvement, fluorodeoxyglucose PET scans may also be used as a prognostic tool in patients with STS due to the demonstrated correlation between tumour grade and fluorodeoxyglucose uptake.[18,19]

The pre-operative radiological imaging and intra-operative findings ultimately determine whether and to what extent a nerve or vessel resection is necessary.[8] Pre-operative staging of the tumour is essential when planning the surgical tumour resection and the surgical margins.[20] The gold standard for local staging of the tumour is MRI examination.[17] When screening for metastatic disease, radiographic or CT imaging of the lungs is essential as STS primarily metastasise to the lungs.[17]

Tumour Biopsy and Histological Confirmation

When planning the appropriate course of treatment, and particularly the choice of neoadjuvant or adjuvant radiation or chemotherapy, the initial accurate tumour diagnosis and identification of the correct histopathologic subtype is paramount.[20] Due to the high rate of misdiagnoses, with reported rates of up to 30%, a reference pathological examination to confirm the tumour histopathology, particularly in community pathology, is highly recommended.[21]

A biopsy of the tumour is usually the first step in accurately identifying its histopathological subtype. The biopsy is usually obtained via an open biopsy as the diagnostic accuracy of the histologic cell type and grade of an open biopsy

is superior to that of a needle biopsy, despite the lower rate of complications associated with needle biopsies.[22] An MRI of the tumour should be performed prior to the open biopsy to avoid traumatic injury of the surrounding tissues and for a qualitatively superior interpretation of the MRI images.[17] When performing an open biopsy of the tumour, the incision should be longitudinal and be in line with future surgical incisions.[17] A transverse incision in the extremities and the exposure of neurovascular structures should always be avoided.[23,24] It is also recommended that the surgeon who is planning to perform the definitive tumour resection also carries out the biopsy of the tumour to ensure the correct placement of the incision.[20]

Classification of Vascular Involvement

Schwarzbach et al.[8] proposed a four-stage classification system and treatment algorithm for extremity STS with vascular involvement. Arterial and venous tumour invasion of the great vessels is classified as Type I vascular involvement. These tumours are treated with an en bloc tumour resection, along with resection of the involved vessels followed by an arterial reconstruction. A venous reconstruction is not necessary when the greater saphenous vein is patent, enabling a collateral venous drainage. Type II vascular involvement refers to tumours with arterial encasement, attachment, or infiltration, which are treated with arterial and tumour resection followed by arterial reconstruction. Tumours that only involve the great veins are classified as Type III and are treated with a resection of the tumour and the involved veins. As with Type I tumours, a venous reconstruction is only required if the collateral venous drainage is impaired. STS of the extremities without vascular involvement are classified as Type IV and are treated with marginal resection of the tumour without vascular resection. This classification system and treatment algorithm has been summarised in Figure 1.[8] The histopathological proof of tumour vessel infiltration, in addition to tumour grade and margin of resection, has been demonstrated as a negative predictor of survival.[8] Tumour grade and resection margins were also found to be important prognostic factors for survival and development of metastases in patients with lower limb STS with sciatic nerve involvement.[15]

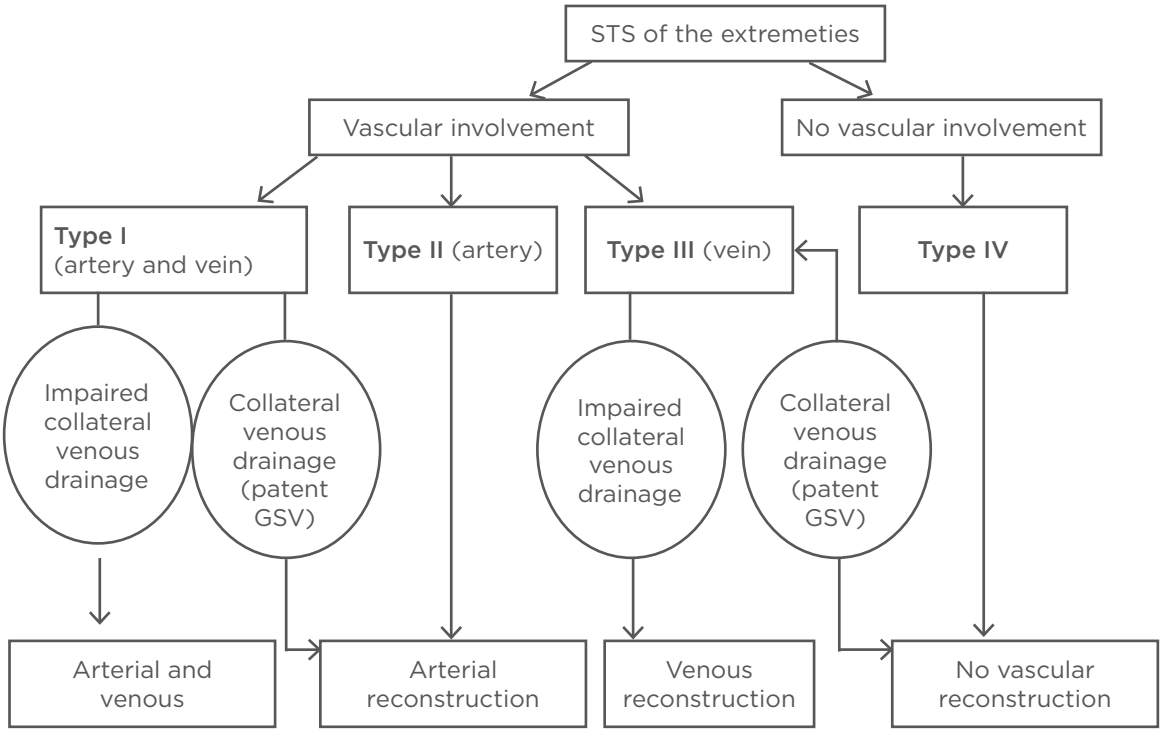


Figure 1: Classification of vascular involvement and treatment algorithm for patients with soft tissue sarcomas of the extremities.[8]

GSV: great saphenous vein; STS: soft tissue sarcomas.

Classification of Neural Involvement

A recent study by Sweiti et al.[15] classified lower limb STS with sciatic nerve involvement into three main categories. Type A tumours were referred to as ≥180° tumour encasement of the nerve based on MRI or CT imaging. These tumours were reassessed intra-operatively by either visually analysing and palpating the relationship of the nerve to the tumour where possible or visualising the extent of nerve contact with ultrasound guidance. If a Type A tumour was intra-operatively confirmed, patients underwent en bloc compartmental resections together with the nerve. STS with direct nerve contact (<180°) were classified as Type B and underwent compartmental resections of the tumour with an epineural nerve dissection. STS without nerve involvement were classified as Type C and were treated with a tumour resection without nerve dissection or resection. This classification of lower limb STS with neural involvement and the suggested treatment approach are summarised in Figure 2.[15]

MULTIMODAL TREATMENT STRATEGIES

The treatment of lower limb STS with neurovascular involvement presents a unique challenge, which requires multidisciplinary management and close co-ordination between surgical, medical, and radiation oncologists. The ultimate goal for patients with non-metastatic STS should be to maintain long-term, disease-free survival, while keeping limitations of limb function to a minimum. Due to the inferior outcomes demonstrated in patients receiving surgical interventions, including biopsies, prior to referral to a multidisciplinary centre, early referral to a specialist centre is strongly recommended to ensure an optimal holistic treatment strategy, which has been associated with improved patient outcomes.[23-27]

Limb-Salvage Surgery

There has been a continuous shift towards multimodal treatment and preservation of limb function following the results of the National Cancer Institute's (NCI) randomised prospective study in 1982, which found no significant difference in the survival rates of patients with STS of the extremities when comparing limb amputation with limb-sparing surgery combined with radiation therapy.[28,29] Limb-sparing surgery with resection of the sciatic nerve in STS of the lower extremity was first reported in 1984, with the hypothesis that the use of ankle–foot orthoses leads to superior functional outcomes when compared to hip disarticulation.[30]

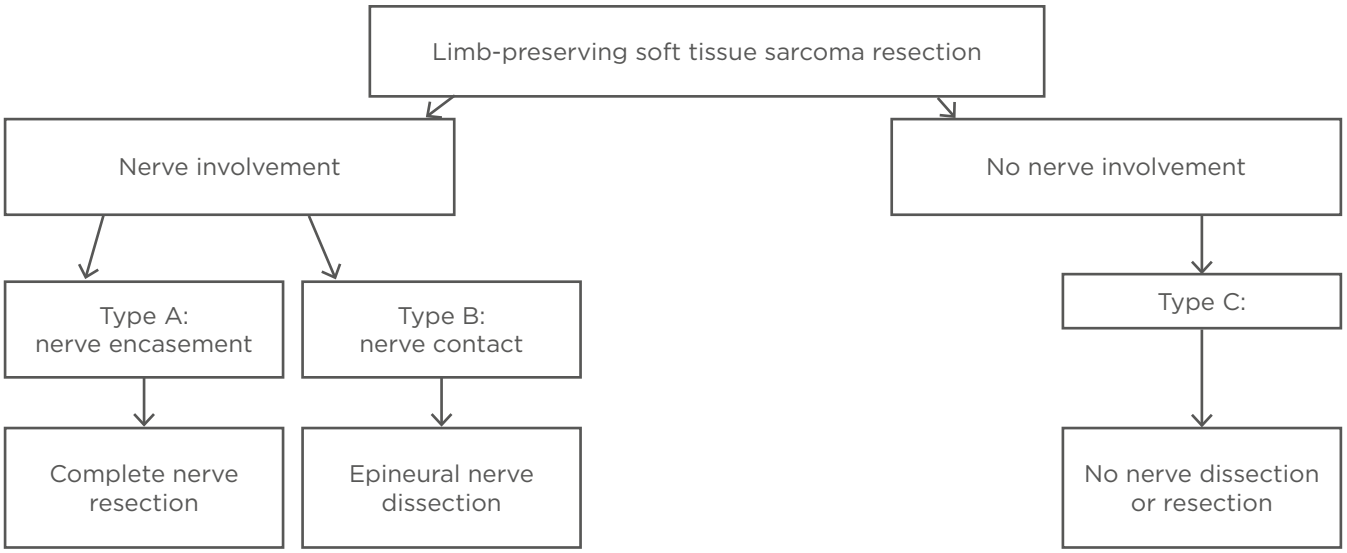


Figure 2: Classification of sciatic nerve involvement and surgical treatment algorithm for lower limb STS.[15]

Tumour involvement of the great vessels or nerves in the lower extremity was previously an indication for limb amputation,[6] but more recent studies have shown comparable oncological outcomes and superior functional outcomes in limb-sparing surgery with vessel reconstruction[8,9,31-34] and partial or complete sciatic nerve resection.[14,15,35-37] Limb-sparing surgery is, therefore, considered the current standard of surgical treatment for STS of the lower extremity.[8] Currently, acknowledged contraindications for limb-sparing surgery include an expected patient survival of <3 months, the presence of a pathological fracture, local or systemic sepsis, as well as a significant contamination of adjacent tissues due to poorly performed biopsies or excisions.[20]

Local disease control is essential for disease-free survival, with surgical resection being the only treatment modality capable of achieving a local disease-free state.[38] The risk of a local recurrence is significantly reduced in tumour resections with wide margins.[39] Obtaining wide, microscopically negative margins is, however, particularly challenging if the tumour is in close contact with major neurovascular structures.[15] A marginal margin of 1–2 mm is, therefore, generally accepted when trying to preserve functional tissue, such as when dissecting a major nerve.[38]

Due to the growth pattern of STS, it is more important to achieve wider margins when excising the tumour longitudinally when compared to the transverse excision during surgical tumour resection.[38] Drains are usually placed in line with the skin incision and exit distally, which is important for any necessary future surgeries such as a secondary limb amputation.[5] It is also important that previous incisions or tracts from biopsies or drains are completely excised in the definitive tumour resection.[38]

Adequate margins and oncological outcomes have been reported in STS of the extremities with vascular involvement treated with limb-sparing surgery, with local recurrence rates ranging from 9–15%.[8,9,31-34] STS with vascular involvement usually requires resection of the corresponding vessels.[7] An exception is when only the aponeurosis of the vessel is invaded by the tumour, allowing tumour resection by sub-adventitial separation, which preserves the continuity of the great vessels.[40] Due to the possibility of vessel damage caused by separation of the aponeuroses and the high risk of tumour contamination, sub-adventitial separation is regarded as an acceptable technique in selected cases such as low-grade tumours that have invaded <50% of the involved great vessel's diameter.[41]

When reconstructing a resected vessel, there is a choice between using autogenic vessels such as the great saphenous and femoral veins, allogenic vessels, or artificial vessels.[7] The advantage of artificial vessels such as polytetrafluoroethylene and Dacron include a reduced duration of surgery and the avoidance of sampling morbidity as with autogenic vessel sampling.[7] Artificial vessels can also be used when an autogenic vessel cannot be sampled and are more suitable than autogenic vessels when the vessel to be reconstructed has a large diameter.[7] Artificial vessels are, however, associated with a high rate of infection.[42] Allogenic vessels are also associated with a reduced duration of surgery compared to autogenic vessels, as well as a low incidence of complications.[42] The long-term patency of reconstructed arteries is higher than that for venous reconstruction, with reports of patency rates between 60–100%.[7,12,33,43] Venous reconstruction, on the other hand, remains controversial and depends on the bilateral status of venous return pre-operatively and on the residual venous return post-operatively.[7] Both the tendency for some veins to become occluded early post-reconstruction and the high risk of chronic venous disease following limb-salvage surgery with extensive venous resection must be taken into consideration.[7]

Unlike vascular reconstruction, reconstruction of nerves involved in STS of the lower extremity does not guarantee preservation of function and remains controversial.[7] Some authors do not advocate for the reconstruction of the sciatic nerve due to the prolonged duration of surgery and thus increased risk of post-operative complications such as delayed wound healing and infections, with no guarantee of preserving function.[7,36] Autogenic nerves are the nerve grafts of choice when reconstructing nerves.[7] Positive functional outcomes were shown in five patients undergoing autogenic common peroneal nerve reconstruction due to STS of the thigh with sciatic nerve involvement.[44] All five patients recovered metatarsal sensation and could walk with the aid of an ankle brace. Further research regarding the

regeneration potential of reconstructed sciatic nerves under the influence of chemotherapy and radiation therapy is necessary.[36]

The most commonly reported complications following limb-sparing surgery are infections, delayed wound healing, or wound dehiscence.[20,45,46] The risk for these complications is higher with prolonged duration of surgery, patients over 40 years of age, and in the presence of neoadjuvant radiotherapy or chemotherapy.[20,45,46] A wound morbidity rate of 34.4% has been reported by Skibber et al.[45] in en bloc resections without adjuvant therapy. A similar wound morbidity rate of 37.0% was reported in a recent study in a cohort of 27 patients with lower limb STS and neural involvement who were treated with limb-sparing surgery.[15] Other complications of limb-sparing surgery of the lower extremity include unplanned neurovascular injury, particularly in confined anatomical spaces such as the popliteal fossa, the formation of hematomas or seromas, devascularisation of soft tissue flaps, joint dislocations, and fractures.[15,20]

The complexity of reconstructive limb-salvage surgery and its potential risks should be taken into consideration when planning surgical tumour resection. In cases where the risks of limb-salvage surgery outweigh the potential benefits in preserving limb function, an amputation may be more appropriate. This is especially relevant in distal lower limb STS, particularly of the foot, where amputation and early prosthetic fitting still have a role in the management of these tumours.[47]

Chemotherapy

The use of adjuvant chemotherapy is not considered a standard treatment in STS, but rather an individual and interdisciplinary decision, even in patients with an increased risk of developing metastatic disease.[45] Local or distant disease recurrence and certain histopathologic entities such as synovial sarcomas or paediatric rhabdomyosarcomas are factors that favour the administration of adjuvant chemotherapy.[5] Relative indications for adjuvant chemotherapy include high-grade, deeply located tumours larger than 5 cm in size, or intermediate-grade, deeply located tumours larger than 10 cm in size, especially in younger patients.[48]

Results from two meta-analyses of multiple randomised controlled trials point to an overall survival benefit of 5–10% for adjuvant treatment with doxorubicin and ifosfamide.[49,50] However, results of these studies need to be cautiously interpreted as pooled trials had conflicting results, posing an important limitation. Current guidelines from the National Comprehensive Cancer Network® (NCCN) as well as the European Society of Medical Oncology (ESMO) reflect on conflicting data as they refer to adjuvant chemotherapy as a legitimate option for high-risk STS but acknowledge the lack of consensus.[21,51]

In certain cases of STS with major neurovascular involvement, pre-operative chemotherapy, with the aim of local cytoreduction, may be a reasonable option, converting a potentially mutilating surgery to a less-invasive limb-sparing operation.[52,53]

Radiation Therapy

The goal of limb-sparing surgery is to achieve complete tumour resection with wide margins. Surgery as a single treatment modality for high-grade STS has, however, been associated with high local failure rates of 70–90%.[54] Surgical resection has been demonstrated to be a sufficient single treatment modality in low-grade subcutaneous STS of the extremities.[55] Baldini et al.[56] reported a local recurrence rate of 7% in a cohort of 74 patients with STS of the trunk or extremities with low- or intermediate-grade small tumours managed with surgical resection alone, which is comparable with the reported local recurrence rates in STS treated with a combination of surgery and adjuvant radiotherapy.

The beneficial effects of adjuvant radiation therapy in patients with STS are generally well documented in the literature, with reported local control rates of 90% or greater.[5] The development of neoadjuvant and adjuvant radiation therapy has led to comparable local control rates, even with focally positive marginal resections.[57] Some studies have compared neoadjuvant radiation with post-operative radiation therapy and found no significant difference in local and distant disease control or disease-free survival.[58,59] Several authors favour neoadjuvant radiation therapy as it has been associated with superior

long-term functional outcomes compared to adjuvant therapy, especially in the lower extremity, despite the higher rates of wound complications.[5,17,58] Flugstad et al.[38] reported major wound complications in 18% of patients treated with adjuvant radiation therapy compared to an incidence of up to 37% in patients treated with neoadjuvant radiation therapy as reported by Bujko et al.[60] Reported complications of adjuvant radiotherapy include an increased incidence of skin fibrosis, oedema, joint stiffness, and fractures.[58] However, it has been suggested by some authors that radiation therapy is most effective when delivered to a low tumour load and should, therefore, be administered as adjuvant therapy, particularly in bulky tumours.[1] The dose of radiation has not been found to significantly influence local disease control.[61] The use of brachytherapy in STS, which is usually administered through the insertion of a catheter over a 3-day period, has been shown to decrease local recurrence rates in some studies.[62,63]

Palliative radiotherapy for symptomatic relief is an important consideration in patients with advanced local and/or systemic disease.[64]

FUTURE CONSIDERATIONS

Schwarzbach et al.[8] have proposed a classification system and treatment algorithm for STS of the extremities with vascular involvement, and a recent study has also classified STS of the lower extremity with sciatic nerve involvement.[8,15] It is essential to validate the proposed classifications in prospective studies and assess the potential role of prognostic parameters such as tumour grade in further optimising the suggested treatment algorithms. Tumour grade is a recognised important prognostic factor in STS, which may influence the extent of surgical resection and any planned adjuvant therapies.[1,15,61,65] The role of the histopathologic subtype of STS as an independent prognostic factor has also been previously emphasised by Pisters et al.[65] Low-grade liposarcomas, for example, rarely metastasise and could potentially be treated with a nerve-sparing surgical resection, despite sciatic nerve encasement (Type A neural involvement), followed by adjuvant radiotherapy to reduce the risk of a local recurrence.[15] The proposed vascular and neural classifications could also be combined into a single classification system for lower limb STS with neurovascular involvement.[15] For example, a tumour of the lower extremity with involvement of the femoral vein, no arterial involvement, and encasement of the sciatic nerve <180° would be classified as a Type IIIB STS and would be treated with an epineural dissection of the sciatic nerve, resection of the femoral vein, and potentially venous reconstruction if the collateral venous drainage is impaired.

CONCLUSION

Limb-sparing surgery has been established as the standard surgical treatment for lower limb STS, even in tumours with major neurovascular involvement. A multimodal treatment approach in a specialist centre is essential in treating these rare tumours, in addition to thorough pre-operative assessment and planning. The use of classification systems in lower limb STS with neurovascular involvement can be integrated into the pre-operative planning of tumour resection, enabling a more precise treatment strategy.

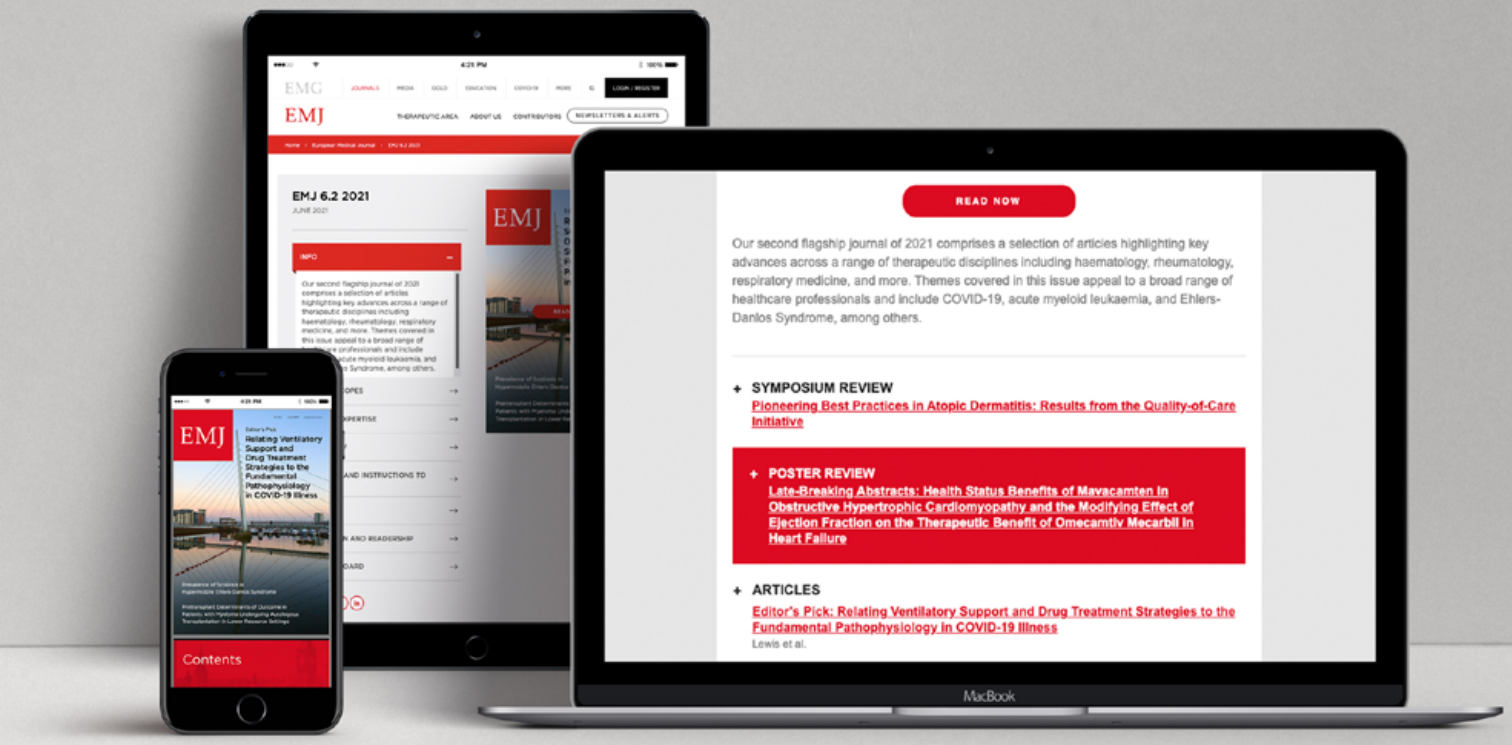
References

1. Elias EG et al. Experience in the management of 52 patients with soft tissue sarcoma. The results of a median follow-up of seven years. J Cancer Ther. 2008;6:47-54.
2. Stiller CA et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer. 2013;49(3):684-95.
3. Siegel R et al. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.
4. Brennan MF et al. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg. 2014;260(3):416-22.
5. Nystrom LM et al. Multidisciplinary management of soft tissue sarcoma. ScientificWorldJournal. 2013;2013:852462.
6. Thomas JE et al. Neurogenic tumors of the sciatic nerve. A clinicopathologic study of 35 cases. Mayo Clin Proc. 1983;58(10):640-7.
7. Lun DX et al. Management of great vessels and nerves in limb-salvage surgery for bone and soft tissue tumors. Orthop Surg. 2013;5(4):233-8.
8. Schwarzbach MH et al. Results of limb-sparing surgery with vascular replacement for soft tissue sarcoma in the lower extremity. J Vasc Surg. 2005;42(1):88-97.
9. Karakousis CP et al. Major vessel resection during limb-preserving surgery for soft tissue sarcomas. World J Surg. 1996;20(3):345-9
10. Ceraldi CM et al. Vascular reconstruction in the resection of soft

tissue sarcomas. Perspect Vasc Surg Endovasc Ther. 2000;12(2):67-83.

11. Ghert MA et al. The surgical and functional outcome of limb-salvage surgery with vascular reconstruction for soft tissue sarcoma of the extremity. Ann Surg Oncol. 2005;12(12):1102-10.
12. Sternheim A et al. Space sarcomas: extra compartmental soft tissue tumors of the lower extremities a systematic approach to sarcomas of the femoral triangle, sartorial canal, and popliteal space. J Surg Oncol. 2009;99(5):281-91.
13. Tsukushi S et al. Results of limb-salvage surgery with vascular reconstruction for soft tissue sarcoma in the lower extremity: comparison between only arterial and arterovenous reconstruction. J Surg Oncol. 2008;97(3):216-20.
14. Brooks AD et al. Resection of the sciatic, peroneal, or tibial nerves: assessment of functional status. Ann Surg Oncol. 2002;9(1):41-7.
15. Sweiti H et al. Limb-salvage surgery of soft tissue sarcoma with sciatic nerve involvement. Sarcoma. 2018;2018:6483579.
16. Moser RP, Parish WM, "Radiologic evaluation of soft tissue tumors," Weiss SW, Goldblum JR (eds.) Enzinger and Weiss's Soft Tissue Tumors (2001) 4th edition, Philadelphia: Mosby.
17. Pike J et al. Soft tissue sarcomas of the extremities: how to stay out of trouble. BCMJ. 2008;50(6):310-7.
18. Schwarzbach MH et al. Prognostic significance of preoperative [18-F] fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging in patients with resectable soft tissue sarcomas. Ann Surg. 2005;241(2):286-94.
19. Schwarzbach MH et al. Clinical value of [18-F] fluorodeoxyglucose positron emission tomography imaging in soft tissue sarcomas. Ann Surg. 2000;231(3):380-6.
20. Choong, PF. Principles of limb sparing surgery in bone and soft tissue sarcoma. Cancer Forum. 2010;34(3):145-8.
21. ESMO/European Sarcoma Network Working Group. Soft tissue and visceral Sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):102-12.
22. Mankin HJ, Hornicek FJ. Diagnosis, classification, and management of soft tissue sarcomas. Cancer Control. 2005;12(1):5-21.
23. Mankin HJ et al. The hazards of the biopsy, revisited. Members of the Musculoskeletal Tumor Society. J Bone Joint Surg Am. 1996;78(5):656-63.
24. Simon MA, Biermann JS. Biopsy of bone and soft-tissue lesions. J Bone Joint Surg Am. 1993;75(4):616-21.
25. Conrad EU et al. "Pelvis," Simon MA, Springfield D (eds.) Surgery for Bone and Soft Tissue Tumors (1998) Philadelphia: Lippincott-Raven, pp.323-41.
26. O'Sullivan B, Pisters PW. Staging and prognostic factor evaluation in soft tissue sarcoma. Surg Oncol Clin N Am. 2003;12(2):333-53.
27. Noria S et al. Residual disease following unplanned excision of soft-tissue sarcoma of an extremity. J Bone Joint Surg Am. 1996;78(5):650.
28. Giuliano AE et al. The management of locally recurrent soft-tissue sarcoma. Ann Surg. 1982;196(1):87-91.
29. Rosenberg SA et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg. 1982;196(3):305-15.
30. Nambisan RN et al. Malignant soft tissue tumors of nerve sheath origin. J Surg Oncol. 1984;25(4):268-72.
31. Koperna T et al. Vascular reconstruction for limb salvage in sarcoma of the lower extremity. Arch Surg. 1996;131(10):1103-7.
32. Nambisan RN, Karakousis CP. Vascular reconstruction for limb salvage in soft tissue sarcomas. Surgery. 1987;101(6):668-77.
33. Leggon RE et al. Limb salvage surgery with vascular reconstruction. Clin Orthop Relat Res. 2001;387:207-16.
34. Williard WC et al. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Ann Surg. 1992;215(3):269-75.
35. Bickels J et al. Sciatic nerve resection: is that truly an indication for amputation? Clin Orthop Relat Res. 2002;399:201-4.
36. Fuchs B et al. Sciatic nerve resection in the thigh: a functional evaluation. Clin Orthop Relat Res. 2001;382:34-41.
37. Clarkson PW et al. Epineural dissection is a safe technique that facilitates limb salvage surgery. Clin Orthop Relat Res. 2005;438:92-6.
38. Flugstad DL et al. Importance of surgical resection in the successful management of soft tissue sarcoma. Arch Surg. 1999;134(8):856-61.
39. Gerrand CH. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br. 2001;83(8):1149-55.
40. Wang Z et al. Functional outcomes and complications of reconstruction of the proximal humerus after intra-articular tumor resection. Orthop Surg. 2010;2(1):19-26.
41. Fortner JG et al. Limb-preserving vascular surgery for malignant tumors of the lower extremity. Arch Surg. 1977;112(4):391-4.
42. Faenza A et al. Vascular homografts for vessel substitution in skeletal and soft tissue sarcomas of the limbs. Transplant Proc. 2005;37(6):2692-3.
43. Nishinari K et al. Vascular reconstruction in limbs associated with resection of tumors. Ann Vasc Surg. 2003;17(4):411-6.
44. Melendez M et al. Sciatic nerve reconstruction: limb preservation after sarcoma resection. Ann Plast Surg. 2001;46(4):375-81.
45. Skibber JM et al. Limb-sparing surgery for soft tissue sarcomas: wound related morbidity in patients undergoing wide local excision. Surgery. 1987;102(3):447-52.
46. Arbeit JM et al. Wound complications in the multimodality treatment of extremity and superficial truncal sarcomas. J Clin Oncol. 1987;5(3):480-8.
47. Ferguson PC. Surgical considerations for management of distal extremity soft tissue sarcomas. Curr Opin Oncol. 2005;17(4):366-9.
48. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet. 1997;350(9092):1647-54.
49. American Academy of Orthopaedic Surgeons. "Musculoskeletal tumours 2," Orthopaedic Knowledge Update (2007) Illinois: Rosemont.
50. Pervaiz N et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008;113(3):573-81.
51. von Mehren M et al. Soft tissue sarcoma, version 2.2014. J Natl Compr Canc Netw. 2014;12(4):473-83.
52. Casali PG. Adjuvant chemotherapy for soft tissue sarcoma. Am Soc Clin Oncol Educ Book. 2015:629-33.
53. Baldini EH et al. Neoadjuvant chemotherapy, concurrent chemoradiation, and adjuvant chemotherapy for high-risk extremity soft tissue sarcoma. Am Soc Clin Oncol Educ Book. 2018;38:910-5.
54. Lindberg RD. Treatment of localized soft tissue sarcomas in adults at M.D. Anderson Hospital and Tumor Institute. Cancer Treat Symp. 1985;3:59-65.
55. Gibbs CP et al. Oncological outcomes of operative treatment of subcutaneous soft-tissue sarcomas of the extremities. J Bone Joint Surg Am. 1997;79(6):888-97.

56. Baldini EH et al. Long-term outcomes after function-sparing surgery without radiotherapy for soft tissue sarcoma of the extremities and trunk. J Clin Oncol. 1999;17(10):3252-9.
57. Dagan R et al. The significance of a marginal excision after preoperative radiation therapy for soft tissue sarcoma of the extremity. Cancer. 2012;118(12):3199-207.
58. O'Sullivan B et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002;359(9325):2235-41.
59. Cheng EY et al. Soft tissue sarcomas: preoperative versus postoperative radiotherapy. J Surg Oncol. 1996;61(2):90-9.
60. Bujko K et al. Wound healing after preoperative radiation for sarcoma of soft tissues. Surg Gynecol Obstet. 1993:176(2):124-34.
61. Herbert SH et al. Limb-preserving treatment for soft tissue sarcomas of the extremities. The significance of surgical margins. Cancer. 1993;72(4):1230-8.
62. Clarke DH, Martinez A. An overview of brachytherapy in cancer management. Oncology (Williston Park). 1990;4(9):39-46.
63. Schray MF et al. Soft tissue sarcoma integration of brachytherapy, resection, and external irradiation. Cancer. 1990;66(3)451-56.
64. Tween H et al. Radiotherapy for the palliation of advanced sarcomas-the effectiveness of radiotherapy in providing symptomatic improvement for advanced sarcomas in a single centre cohort. Healthcare (Basel). 2019;7(4):120.
65. Pisters PW et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol. 1996;14(5):1679-89.



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