ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2020 December 24; 11(12): 968-1083

Published by Baishideng Publishing Group Inc

WJCO

World Journal of Clinical Oncology

Contents

Monthly Volume 11 Number 12 December 24, 2020

World Journal of Clinical Oncology

Monthly Volume 11 Number 12 December 24, 2020

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NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel

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https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
December 24, 2020

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World Journal of Clinical Oncology

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World J Clin Oncol 2020 December 24; 11(12): 968-975

DOI: 10.5306/wjco.v11.i12.968

ISSN 2218-4333 (online)

EDITORIAL

COVID-19 and information and communication technology in radiation oncology: A new paradigm

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Author contributions: All authors have read and approve the final manuscript.

Conflict-of-interest statement: Authors declare no potential conflict of interests for this article.

Manuscript source: Invited manuscript

Specialty type: Oncology

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

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Abstract

Due to coronavirus disease 2019 pandemic caused by severe acute respiratory syndrome coronavirus 2, there has been a major reallocation of resources that has impacted the treatment of many diseases, including cancer. The growing use of information and communication technologies (ICT), together with a new approach to work aimed at ensuring the safety of health care professionals and patients alike, has allowed us to maintain the quality of care while ensuring biosecurity. The application of ICT to health care (eHealth) aims to significantly improve the quality, access to, and effectiveness of medical care. In fact, the expanded use of ICT has been recognized as a key, cost-effective priority for health care by the World Health Organisation. The medical speciality of radiation oncology is closely linked to technology and as a consequence of coronavirus disease 2019, ICT has been widely employed by radiation oncologists worldwide, providing new opportunities for interaction among professionals, including telemedicine and e-learning, while also minimizing treatment interruptions. Future research should concentrate on this emerging paradigm, which offers new opportunities, including faster and more diverse exchange of scientific knowledge, organizational improvements, and more efficient workflows. Moreover, these efficiencies will allow professionals to dedicate more time to patient care, with a better work-life balance. In the present editorial, we discuss the opportunities provided by these digital tools, as well as barriers to their

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 4, 2020
Peer-review started: June 4, 2020
First decision: October 6, 2020
Revised: October 9, 2020
Accepted: October 30, 2020
Article in press: October 30, 2020
Published online: December 24, 2020

P-Reviewer: Georgiev T, Patel HR
S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang YL

implementation, and a vision of the future.

Key Words: Radiation oncology; COVID-19; Telemedicine; Telehealth; Distance learning; Medical education; Patient care; Information technology; Social media

Core Tip: We believe that the current crisis is an opportunity to take advantage of the momentum towards the greater implementation of electronic health, to improve care through telemedicine, remote work, and e-learning. The emergence of information and communication technologies has transformed the speciality of radiation oncology into teleradiotherapy. Future research should focus on this emerging paradigm, which allows greater flexibility, thereby freeing up time for more efficient and humane patient care.

Citation: Fernández C, Ruiz V, Couñago F. COVID-19 and information and communication technology in radiation oncology: A new paradigm. *World J Clin Oncol* 2020; 11(12): 968-975
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/968.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.968

INTRODUCTION

Current situation in radiation oncology pre-COVID

Progress is impossible without change, and those who cannot change their minds cannot change anything (George Bernard Shaw).

During coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2, technologies are playing a crucial role in keeping our society functional. And these technologies may have a long-lasting impact beyond COVID-19.

We start from the advantage the medical speciality of radiation oncology is closely linked to technology, which continues to advance at a rapid pace. The advent of computed-tomography based contouring led to the transition from two-dimensional to three-dimensional treatment planning in the 1980s and 1990s. Due to continuous technological progress, the field of radiation oncology has had to continually evolve and adapt to changing technologies[1], which include advances in radiological imaging, engineering, and computerization. This has led to remarkable advances in the precision of radiotherapy delivery, including novel modalities such as intensity-modulated radiotherapy, volumetric intensity-modulated arc therapy, stereotactic radiosurgery, stereotactic body radiotherapy, and proton therapy. Moreover, all of these advanced techniques are guided by imaging or surface-guided radiotherapy.

Despite the important role of technology in radiation oncology, this speciality involves much more than just machines[2], which are no substitute for real people in clinical practice. Behind increasingly sophisticated linear accelerators are dedicated professionals who continually work to keep up to date with the latest tools and treatments provide patients with the best possible care. The clinical setting requires close teamwork and an established workflow, which starts with the initial consultation followed by computed-tomography simulation, dosimetry and planning, treatment administration, follow-up for potential toxicity, and post-treatment consultations.

Information and communication technologies (ICT) have become an essential component of our profession, leading to changes in how we communicate with each other and with patients. Telemedicine and telehealth services facilitated through video-conferencing software are becoming increasingly accepted in routine medical practice. Although most professional training continues to be done in person (*e.g.*, at medical congresses), a growing number of health care professionals and medical associations now use social media and other online or offline channels, with a good example being the use of Twitter at congresses[3,4].

The COVID-19 pandemic

The COVID-19 pandemic has altered many aspects of our personal and professional

lives, and health care systems are no exception. This pandemic has forced hospitals and clinics to reorganize their health care activity practically overnight. Most health care professionals in primary care, the emergency department, and intensive care units have successfully adapted to meet the unprecedented demands imposed by the crisis.

The clinical management of life-threatening illnesses unrelated to COVID-19, such as cancer, has required a profound and highly challenging redistribution of resources[5]. This has been especially relevant in oncology due to the immunosuppressive effects of many cancer treatments, as cancer patients have an elevated risk of infection with the syndrome coronavirus 2 virus and of developing serious complications from COVID-19[6]. Moreover, given that cancer patients tend to be older with more comorbidities than younger people, the risks posed by COVID-19 are even greater.

Approximately 50% of all cancer patients are treated with radiotherapy. During the COVID-19 epidemic, the role of radiotherapy in the management of oncological patients has become even more important due to delays in chemotherapy and surgery. To minimize treatment interruptions, radiation oncology departments have adopted a range of solutions, including prioritization of treatment according to the urgency, and an increased use of ICT and shorter treatment schemes (hypofractionated or ultrahypofractionated)[7]. Other measures include personal protective equipment, shift changes, and remote work from home, all of which have helped to maintain the quality of care while ensuring the safety of both patients and health care professionals. Clinical trials have even been performed to evaluate a role for radiotherapy outside of cancer therapy, such as the use of low-dose radiotherapy to treat pneumonia associated with COVID-19[8]. Recommendations to optimize radiotherapy during the epidemic can be summarized by the acronym RADS[9] (Remote, Avoid, Defer, Shorten), which recommends performing remote consultations when possible, and avoiding (if clinically appropriate or an effective alternative exists), deferring (when clinical feasible), or shortening radiotherapy treatments.

Electronic health, ICT, and teleradiotherapy

Once the mitigation phase of the COVID-19 pandemic has passed, the next phase is containment. In this phase, it is essential to prevent crowded waiting areas, which means that patients must come unaccompanied, and masks are essential. Before a patient is allowed to enter the waiting area, it is important to continue to check for fever, and to ask patients about symptoms (fever, cough, respiratory distress, anosmia) and/or contact with symptomatic individuals. Proper hand hygiene and disinfection of common spaces will also continue. Clearly, given the need for these precautionary measures, we cannot immediately return to the previous status quo, and thus we are forced to rethink how we organize our departmental workflows and processes.

Electronic health (eHealth) has been defined as ICT applied to health care. Its objective is to significantly improve the quality, access, and effectiveness of health care for all. The World Health Organization has recognized eHealth as a fundamental and cost-effective priority. The 58th World Health Assembly[10] took a historic step in support of eHealth when it approved a resolution to recognize the role of ICT to strengthen health care systems[11,12]. Following this resolution, the use of eHealth-related terminology[13] has exploded, with the most common terms being telemedicine; telehealth; mobile health; electronic medical or health records; digital imaging and communication in medicine; videoconferences and distance learning; Big Data; "wearables" (internet of things); and artificial intelligence. The general term that encompasses all the other concepts is eHealth. According to the European Coordination Committee of the Radiological, Electro-medical and Healthcare IT Industry[14], telemedicine encompasses concepts such as telehealth, telecare, and telediscipline. Telehealth refers to the diagnosis, monitoring, management and empowerment of patients with chronic conditions.

The increasing use of social networks and eHealth in oncology (Figure 1) offers new opportunities for health care professionals and institutions to interact with patients or other professionals through various different channels: (1) Distance learning[15] (e-learning), which offers the opportunity for professional development and knowledge exchange among professionals through both telephone and videoconferences; (2) Tumour board telemeetings; (3) Telehealth including education and health promotion; and (4) Telemedicine and teleconsultation.

The speciality of radiation oncology is currently undergoing a paradigm shift due to the growing use of ICT. Radiation oncology is transforming into a telediscipline known as teleradiotherapy (Figure 1), which allows specialists to conduct consultations, contouring, and treatment planning remotely. In some centres, this teleradiotherapy model was already in place prior to the pandemic, mainly to manage

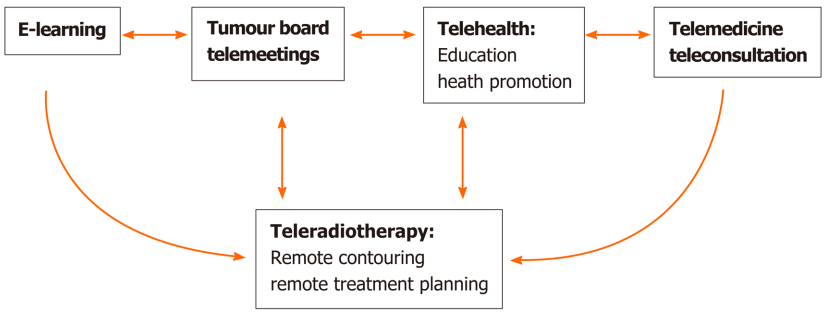

Figure 1 Use of social networks and eHealth in oncology and teleradiotherapy.

patients who live at a great distance from the cancer treatment centre[16]. The teleradiotherapy model can reduce the number of patient consultations requiring a physical presence by combining, in a single visit, the initial consultation with treatment simulation. In addition, follow-up can also be performed remotely through the use of imaging tests, blood tests, and biopsy result in patients in who do not require a physical examination. During the COVID-19 pandemic, we have also witnessed and participated in new ways of working, including online congresses, videoconferences with other professionals, remote management and treatment of patients, and new forms of healthcare management.

The COVID-19 pandemic has precipitated a series of changes in the physician-patient relationship[17], as well as in the work environment of radiation oncology departments[18,19]. Due to the high risk of contagion in the hospital setting, especially during the mitigation phase of the epidemic, it is important to minimize exposure to the hospital environment in order to reduce the risk of infection with this novel virus. As a result, there has been an increased use of existing tools (*e.g.*, remote contouring, remote planning, teleconsultation, telemeetings.) that were previously underutilized, mainly due to the inertia (resistance to change) that is common in many large institutions, including hospitals.

In these exceptional circumstances, working from home has enabled healthcare professionals to minimize physical contact with patients (who could be infected with the virus), and also allowed patients to avoid unnecessary travel. The conditions imposed by the pandemic have obliged us to take a much more flexible and proactive attitude to health care, pushing us ever closer towards the telemedicine model, which offers greater flexibility for both physicians and patients. In short, in this context, the availability of ICT has been a blessing that will surely continue to provide benefits in the future, even after the pandemic has passed.

Social networks such as Twitter have proven to be powerful tools, with an immense potential to transform continuing medical education[20], which has also been accelerated by COVID-19[21]. Nor can we overlook the emergence of mobile health applications[22] used for patient follow-up. These applications have proven invaluable to assess side effects, quality of life, and treatment satisfaction, thus improving workflows[23].

The changes that are here to stay and barriers to change

Given the highly technical nature of our speciality, radiation oncologists are accustomed to adapting to continuous technological advances in equipment, planning systems, imaging devices, and software. Nevertheless, our workflow and clinical practices remain practically unchanged and conventional.

The unprecedented historical impact of the COVID-19 epidemic will require a profound analysis in the near future. However, this crisis has provided us with an opportunity to reinterpret the physician-patient relationship, as well as to rethink our approach to work as radiation oncologists. Clearly, without the assistance of ICT, the consequences of the epidemic would have been much more severe. Paradoxically, in this time of forced confinement, mobile technology, the possibility of videoconferencing and telephone calls have brought us closer together. The availability of electronic devices such as smartphones has provided the means for isolated patients to communicate with their physicians and their families. We have even been able to obtain real-time information from other countries going through similar circumstances. Radiation oncologists have learned to create telematic (*i.e.*, online and mobile) communication and work networks, to receive training sessions

through webinars and social networks, as well as to access emerging research through open access publications. All of these tools have contributed to our knowledge about COVID-19 and the dimensions of the epidemic.

Despite the many advantages of telemedicine, there are numerous potential barriers to consider[24,25]. Barriers to implementing remote consultations are summarized in Table 1.

Once these barriers have been overcome, then we will be ready to develop new models of healthcare that are more efficient, versatile, convenient, and welcoming. The key is to learn new skills, to improve access to the available technology, and simply to get started.

Areas to target for improvement and improvements specific to radiation oncology are summarized in Table 2.

We believe that telemedicine is here to stay. It would be wrong to believe that telemedicine is only a temporary response to a crisis and that we will return to the pre-epidemic status quo. We must seize the opportunity to improve our healthcare work processes in a new era. Numerous health care issues (unrelated to COVID-19) can be resolved online or through mobile devices, thus reducing unnecessary travel and saving valuable time. Studies have found that patients are highly satisfied with remote consultations. For example, a survey conducted by Hamilton *et al*[16] found that 54.7% of patients preferred telemedicine for future consultations, while 34.9% preferred a mix of online and in-person consultations, with less than 1% expressing a preference for in-person access only.

Our work experience during the COVID-19 crisis has largely been positive. Patients generally feel that they are well-cared for and that their physicians listen to them, both of which give patients peace of mind. They have even congratulated professionals, thanking them for making the effort to transform their usual clinical practices in record time. Patients appear to understand that, in this new world, they need to be more proactive in regard to their own health, and they are more aware of the benefits of self-care. For physicians, remote work has allowed us to continue our clinical practice without causing major delays in treatment or in accumulating pending visits. It has also allowed us to more clearly identify what is urgent and what is not. In short, this crisis has allowed us to eliminate practices that add little value.

Future directions

In radiation oncology, radiotherapy treatment planning can be performed remotely, with no need to be physically present at the hospital. By enabling physicians to work from home (*i.e.*, teleconsultations or remote treatment planning), we have been able to continue our clinical practice uninterrupted. This versatility and convenience has undoubtedly reduced stress levels. The option to work remotely has been especially critical for professionals in quarantine and for those who needed to stay home for family or personal reasons. Moreover, it has allowed us to avoid prolonged exposure to the hospital environment, thus minimizing the risk of contagion. Future research should concentrate on evaluating this new paradigm, which offers new opportunities, including faster and more diverse exchange of scientific knowledge, organizational improvements, more efficient workflows, and more time to dedicate to patient care. Importantly, this new paradigm allows us to better balance our personal and professional lives, something that is always difficult to achieve. The digitization of our work will make it more flexible, faster, safer, and more efficient. In short, this shift marks a revolution for the better for all parties involved.

CONCLUSION

Information and communication technologies allow us to offer patients more frequent and more efficient clinical consultations. Patients now have the ability to contact us through a wide range of different channels: Face-to-face, online (videoconference or telephone consultation), or offline (email), eliminating classic space/time barriers. However, it is essential that we continue striving to be good communicators, innovators, and creative people. We must also, first and foremost, be good, humane providers of quality health care for our patients. ICT can help us achieve all of these aims by strengthening the bonds between health care professionals and patients using a novel and dynamic approach.

Table 1 Barriers to implementing remote consultations

Technological barriers
Availability of smart phones or mobile devices
Mobile network coverage
Lack of a dedicated, properly-equipped office in the hospital to conveniently and rapidly program and conduct a remote visit that is comparable to a real-life consultation. This equipment would include videoconferencing software to allow for a proper anamnesis, with hands-free headphones to allow the physician to record data on the eMR, and automatic telephone dialling
Electronic medical record formats and the capability to order complementary tests through the software
Physical barriers
Telephone consultation and difficult anamnesis in some cases, such as patients with a laryngectomy, cognitive impairment, hearing loss, neurological diseases, or poor language skills (*i.e.*, foreigners), *etc*;
Impossibility of performing a correct physical examination of patients
Communication barriers
Physicians
Use of technical jargon
Semantic barriers: Inability to understand the language used by the sender or the receiver
Lack of body language signals (telephone consultations)
Potential lack of empathy in telephone consultations
External interruptions
Patients
Mental ("not thinking clearly") and emotional blocks
Fear of asking questions
Lack of family support during the teleconsultation
Potential misinterpretation of the message
Feelings of inferiority
Misinformed or "overinformed" (infodemia)
External interruptions
Difficulties in understanding how to behave in this unique setting: Respect, cordiality and a collaborative attitude
Psychological barriers
Physicians
Feelings of insecurity due to work processes outside of routine practices;
Perceived deterioration in the doctor-patient relationship, in which it is necessary to cede more power and autonomy to the patient with more open dialogue (and a less paternalistic relationship)
The need to use an appropriate tone of voice, ask clear and concise questions, use warm and friendly language, and practice active listening when communicating with patients
Potential to perceive a certain loss of humanity due to the lack of physical presence
Patients
If the patient cannot see the physician (*e.g.*, telephone call), this can produce feelings of depersonalization
The patient may be accustomed to letting the physician make health-related decisions
The patient may have difficulties describing symptoms in a virtual setting
Bioethical barriers
Confidentiality and privacy
Data protection
The remote consultation cannot replace a face-to-face visit, but rather complements it
Risks related to computer security and hacking

Table 2 Areas to target for improvement and improvements specific to radiation oncology

Areas to target for improvement
Specific agenda only for remote consultations that is separate from face-to-face consultations
Ensure that video-assisted consultations include automatic dialling, headphones, a camera and a microphone
Implementation of electronic prescriptions
Ability to directly order complementary tests telematically
Possibility of sending notifications and reminders to the patient's mobile phone
Health care education and promotion directly from primary care
Increased digital literacy in the general population
Computer security measures
Provision of technology in rural areas: Mobile coverage, access to devices, *etc*
Remote consultations considered as a complement to face-to-face visits
Emotional support for the patient, family involvement, motivation and commitment
Provide legal safeguards for these tools
Improvements specific to radiation oncology
Regulation of remote work ("work from home") options in the radiation oncology. For example, it would be feasible to work from home one day each week to perform remote contouring or other work that does not require a physical presence. Working from home should be considered a natural extension of our work, although potential disadvantages must be considered: Failure to disconnect from work, lack of clarity regarding work organization, and difficulties in the work-life balance
To apply Big Data in our work, we need appropriate electronic medical records and data reporting formats that provide us with feedback on our results, which can then be used to improve clinical care

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World Journal of Clinical Oncology

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World J Clin Oncol 2020 December 24; 11(12): 976-982

DOI: 10.5306/wjco.v11.i12.976

ISSN 2218-4333 (online)

EDITORIAL

Practice change in the management of metastatic urothelial carcinoma after ASCO 2020

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Author contributions: Gajate P, Torres-Jiménez J, Bueno-Bravo C, and Couñago F wrote the paper.

Conflict-of-interest statement: Gajate P has served as an advisor for Roche and Janssen, has served as a speaker for Pfizer, Roche and Janssen. Torres-Jimenez J, Bueno-Bravo C and Couñago F have nothing to disclose.

Manuscript source: Invited manuscript

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Abstract

Metastatic urothelial carcinoma (mUC) is an incurable and aggressive disease. In the past decades there have been few effective treatment options that have impacted the prognosis of mUC patients. However, in the last few years, several drugs have emerged as new treatment choices that are changing the therapeutic landscape of mUC. Immune checkpoint inhibitors (ICIs) and targeted agents are useful treatment strategies that have been incorporated into our clinical practice. Nevertheless, cisplatin-based chemotherapy is still the standard of care in the first-line of metastatic disease. The results of the JAVELIN Bladder 100 phase 3 trial were presented at ASCO 2020, this trial evaluated the role of avelumab, an ICI, as maintenance therapy in patients who had not progressed after first-line platinum-based chemotherapy. The trial met its primary endpoint demonstrating an overall survival benefit with avelumab maintenance. In addition, new drugs and combinations are being evaluated to improve the outcomes of second and subsequent lines. Fibroblast growth factor receptor (FGFR) inhibitors and immunotherapy combinations were some of the strategies presented at ASCO 2020 that have shown promising results. Finally, the development of predictive biomarkers that help us in the decision-making process will be one of the most important challenges in the next years.

Key Words: Metastatic urothelial carcinoma; Immune checkpoint inhibitors; Avelumab; JAVELIN Bladder 100; FGFR inhibitors; ASCO 2020

Specialty type: Oncology

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: July 2, 2020
Peer-review started: July 2, 2020
First decision: October 23, 2020
Revised: November 1, 2020
Accepted: November 11, 2020
Article in press: November 11, 2020
Published online: December 24, 2020

P-Reviewer: Huo Q, Shomura M
S-Editor: Huang P
L-Editor: Webster JR
P-Editor: Wang LL

Core Tip: The landscape of urothelial carcinoma treatment has changed significantly in the last 5 years. Several drugs with different mechanisms of action have emerged as new therapeutic opportunities. At ASCO 2020, avelumab, an immune checkpoint inhibitor, was evaluated as maintenance therapy in the JAVELIN Bladder 100 trial: This was the first clinical trial that improved overall survival in the metastatic setting since the 80s. Moreover, new drugs and combination strategies have shown their potential role as new therapeutic alternatives to increase survival in this disease which has a poor prognosis.

Citation: Gajate P, Torres-Jiménez J, Bueno-Bravo C, Couñago F. Practice change in the management of metastatic urothelial carcinoma after ASCO 2020. *World J Clin Oncol* 2020; 11(12): 976-982
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/976.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.976

INTRODUCTION

Bladder cancer is the 10th most common cancer worldwide with an estimated 550000 new cases and 200000 deaths in 2018[1]. Urothelial carcinoma is the predominant histologic type, with approximately 90% of bladder cancers in the United States and Europe[2].

Cisplatin–based chemotherapy has been the standard of care first-line treatment for metastatic urothelial carcinoma (mUC) since 1980[3,4]. However, 50% of patients with mUC are ineligible for cisplatin treatment, and a carboplatin-based regimen is the standard chemotherapy alternative[3,5]. In addition, new drugs, such as immune checkpoint inhibitors (ICIs) and molecular targeted agents, have emerged as new therapeutic choices in the last 5 years and have changed the therapeutic landscape of mUC. ICI is a frontline option for PD-L1 positive metastatic tumors[6-8] and the standard treatment for second-line patients with disease progression after platinum-containing chemotherapy[9,10]. Furthermore, the Food and Drug Administration (FDA) has recently approved two targeted agents, erdafitinib and enfortumab vedotin, for patients with locally advanced or mUC who have previously received platinum-based chemotherapy[11,12].

At ASCO 2020, the JAVELIN Bladder 100 trial was presented as an attractive treatment strategy, which assessed an ICI as maintenance therapy after achieving an objective response or stable disease with first-line chemotherapy. New drugs and combination strategies have also shown their potential role as new therapeutic options to prolong survival in this disease which has a poor prognosis. Our objective is to summarize the most important studies in mUC that have just been presented at ASCO 2020, and how they modify the standard clinical practice.

MOST RELEVANT STUDIES PRESENTED AT ASCO 2020

JAVELIN Bladder 100 was one of the most important studies presented at ASCO 2020[13](Table 1). It is a randomized phase 3 trial, which assessed avelumab (anti-PD-L1 treatment) as maintenance therapy in patients with mUC whose disease had not progressed with first-line platinum–based chemotherapy. Seven hundred patients with unresectable or mUC were randomized 1:1 to receive avelumab (10 mg/kg intravenously every two weeks) and best supportive care (BSC) or BSC alone. Crossover was not allowed within the study. Patients had to achieve an objective response or stable disease after at least four cycles of gemcitabine and cisplatin or carboplatin. A maximum of 6 cycles were allowed. Patients were stratified by best response to first-line chemotherapy (complete/partial response *vs* stable disease) and localization of metastatic disease (visceral *vs* non-visceral). The co-primary endpoint was overall survival (OS) assessed from randomization in all patients and in the PD-L1 positive population. Progression-free survival (PFS), objective response rate (ORR) and safety were secondary endpoints. After a median follow-up of 19 mo avelumab plus BSC significantly prolonged OS *vs* BSC alone in the overall population [21.4 *vs* 14.3

Table 1 Results of the most relevant studies at ASCO 2020

	JAVELIN Bladder 100[13]	FORT-2[16]	BLC2001[14]	COSMIC-021[18]	PEANUT[19]
Phase	3	1b/2	2	1b	2
Treatment	Avelumab + BSC *vs* BSC	Rogaratinib + atezolizumab	Erdafitinib	Cabozantinib + atezolizumab	Pembrolizumab + nab-paclitaxel
Inclusion criteria	Response or stable disease after 1st line platinum-based chemotherapy	Treatment naive	≥ 1 line or cisplatin unfit	≥ 1 line	1-2 lines
		Cisplatin ineligible	FGFR genetic alteration	Prior ICI not allowed	Prior ICI not allowed
		FGFR mRNA overexpression	Prior ICI allowed		
Study population (*n*)	700	31	101	30	70
PFS (mo)	3.7 *vs* 2.0		5.52	5.4	5.0
OS (mo)	21.4 *vs* 14.3		11.3		
ORR (%)	9.7 *vs* 1.4	44	40	27	38.6
Duration of response		NR	5.98	NR	NR

BSC: Best supportive care; ICI: Immune checkpoint inhibitor; FGFR: Fibroblast growth factor receptor; PFS: Progression-free survival; OS: Overall survival; ORR: Objective response rate.

mo; hazard ratio (HR) 0.69, 95%CI: 0.56-0.86; one-sided $P = 0.0005$]. Fifty-one percent of tumors were PD-L1 positive, 189 in the experimental arm and 169 in BSC arm. In this PD-L1 positive population, avelumab treatment also significantly increased OS (not reached *vs* 17.1 mo; HR 0.56, 95%CI 0.40-0.79; one-sided $P = 0.0003$). In addition, in the subgroup analysis, OS was longer with avelumab *vs* the control arm across all prespecified subgroups.

Erdafitinib is a novel pan-fibroblast growth factor receptor (FGFR) kinase inhibitor recently approved by the FDA for patients with locally advanced or mUC with susceptible FGFR3 or FGFR2 genetic alterations who have progressed during or following platinum-based chemotherapy. Approval was based on data from the primary analysis of the BLC2001 study, a phase II trial that assessed erdafitinib in this group of patients[11]. The final results of this trial were presented at ASCO 2020, including long-term outcomes and safety data. With a median follow-up of 24 mo, the investigators confirmed an ORR of 40%, with a median duration of response of 6 mo. Furthermore, 31% of responders had a response duration of over 12 mo[14]. Median PFS was 5.52 mo and median OS was 11.3 mo. Central serous retinopathy (CSR) is a known class effect of FGFR inhibitors. CSR occurred in 27% (27/101) of patients, but 85% of those (23/27) were grade 1 or 2. In addition, a phase III trial is evaluating erdafitinib compared to pembrolizumab or chemotherapy in patients with mUC and FGFR alterations who have progressed after 1 or 2 prior treatments[15].

FORT-2 is a phase Ib/II study that evaluates the safety and efficacy of rogaratinib in combination with atezolizumab as first-line treatment in cisplatin–ineligible patients with mUC and FGFR mRNA overexpression[16]. Rogaratinib is a highly selective FGFR1-4 inhibitor that has shown good tolerability and clinical activity as monotherapy in a previous phase I trial[17]. Eleven patients were treated with rogaratinib 800 mg twice daily and atezolizumab 1200 mg every 3 wk, and 16 patients were treated with rogaratinib 600 mg twice daily and atezolizumab 1200 mg every 3 wk. The ORR was 44%, with a disease control rate of 68%. The duration of response was not reached. The safety profile was manageable with diarrhea (58%), hyperphosphatemia (45%) and urinary tract infection (36%) being the most common treatment-emergent adverse events.

The COSMIC-021 and PEANUT trials assessed the combination of an ICI with a targeted-agent or chemotherapy, respectively, in patients with mUC previously treated. COSMIC-021 is a multi-cohort phase 1b study that evaluates the immunomodulatory effect of cabozantinib (40 mg daily) in combination with

atezolizumab (1200 mg every 3 wk)[18]. Thirty patients with mUC were included. The ORR was 27% including 2 patients with a complete response. The median duration of response was not reached. The median PFS was 5.4 mo. Asthenia (37%), diarrhea (27%), lower appetite (23%), increased transaminases (23%) and mucosal inflammation (20%) were the most frequent treatment-related adverse events (TRAEs). PEANUT is a phase 2 study evaluating the combination of pembrolizumab and nab-paclitaxel in patients previously treated with chemotherapy[19]. Sixty-five patients were included. The median PFS was 5 mo, with an ORR of 38.6%. The median duration of response was not reached. This combination showed an expected safety profile with alopecia (71%), neutropenia (32%) and peripheral neuropathy (34%) as the most common TRAEs.

Finally, at ASCO 2020 the analysis of tumor microenvironment biomarkers from the IMvigor130 study was presented[20]. This phase 3 trial compared atezolizumab with or without platinum-based chemotherapy *vs* placebo plus platinum-based chemotherapy in the first-line treatment of mUC. The addition of atezolizumab to platinum-based chemotherapy prolonged PFS, which was one of the co-primary endpoints of the trial. In the biomarker analysis, clinical outcomes were evaluated by PD-L1 status, T-effector and TGF-β-response gene expression signature, tumor mutational burden and APOBEC mutation analysis. This exploratory analysis provided additional evidence for biomarkers previously associated with response and resistance to ICI.

HOW WILL ASCO 2020 CHANGE CLINICAL PRACTICE IN MUC?

Cisplatin-based chemotherapy is the standard first-line treatment for mUC. JAVELIN Bladder 100 met its primary endpoint, demonstrating significantly longer OS with first-line maintenance avelumab plus BSC compared to BSC alone, in both the overall and PD-L1 positive populations. In addition, all prespecified subgroups benefited from this treatment. According to these data, first-line maintenance avelumab should be offered in patients with mUC who achieved an objective response or stable disease with platinum-based chemotherapy. This includes approximately 85% of patients that start first-line platinum-based chemotherapy[4,5]. Those with primary refractory disease (15%) should receive second-line treatment with ICIs. Nevertheless, only 25%-55% of patients that progress after first-line treatment receive new therapy[21-23]. A maintenance strategy is a chance to increase the number of patients that will receive ICI therapy. In this context, there are other trials assessing the combination of ICI and chemotherapy in first-line treatment. The IMvigor130 study has recently been published[24]. Its co-primary endpoints were PFS and OS. The combination of atezolizumab with platinum-based chemotherapy as first-line treatment prolonged PFS in patients with mUC. A statistically significant OS advantage was not observed in the interim analysis, however, these data are immature and a longer follow-up is needed. First-line maintenance avelumab in patients with mUC whose disease has not progressed with platinum-based chemotherapy should be considered a new standard of care.

Despite the approval of erdafitinib by the FDA, the European Medicines Agency (EMA) has not authorized it yet. The benefit from FGFR inhibitors in mUC patients with FGFR alterations has been demonstrated in different clinical trials. The long-term outcomes from the phase II erdafitinib study confirm the efficacy results observed in the interim analysis. In addition, new strategies are being evaluated such as combinations with other drugs and their role in prior lines or earlier stages. Although data from phase 3 trials are pending and some strategies are still under development, FGFR inhibitors will probably be included in the treatment algorithm of mUC in the near future.

ICI is the standard of care for the second-line treatment of mUC. Despite this, only a subset of patients responds to these therapies. The research for new strategies to increase the number of patients that benefit from ICI is one of the most important points in mUC management. In this direction, several clinical trials are assessing different combinations with promising results in phase II studies. Nevertheless, no randomized trials have shown superiority over ICI monotherapy. However, the probable position of immunotherapy in the first-line setting could modify these strategies.

PD-L1 expression in ineligible cisplatin patients is the only biomarker that has been integrated in clinical practice regarding ICI use in mUC[6]. The development of biomarkers could be useful to identify patients who will benefit from the different treatment strategies, focusing on their potential predictive role rather than their solely

prognostic nature. Biomarkers associated with response and intrinsic resistance to ICIs have previously been identified in urothelial cancer. However, predictive biomarkers for combination regimens or maintenance therapy remain uncertain. It is necessary to integrate biomarker analysis in every clinical trial to identify patients who will benefit from each treatment strategy.

CONCLUSION

JAVELIN Bladder 100 was one of the most important studies presented at ASCO 2020. Avelumab maintenance treatment after first-line chemotherapy will change our standard of practice. Other clinical trials in this setting could offer new treatment strategies. Biomarker analysis should help us to identify the best treatment option in every single patient. Moreover, new drugs are being incorporated in the therapeutic landscape of mUC. The integration of all these treatment opportunities for our patients will be one of the most important challenges in mUC management.

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World Journal of Clinical Oncology

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World J Clin Oncol 2020 December 24; 11(12): 983-989

DOI: 10.5306/wjco.v11.i12.983

ISSN 2218-4333 (online)

EDITORIAL

Stereotactic body radiation therapy: A good dance partner of oligometastatic non-small cell lung cancer to the sound of SINDAS study

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Author contributions: All authors contributed equally to the manuscript.

Conflict-of-interest statement: Mielgo-Rubio X has received fees for serving as a speaker, a consultant and/or an advisory board member for BMS, Roche, MSD, Kiowa Kirin, Astra Zeneca, Boehringer Ingelheim, Abbott. Mielgo-Rubio X hast received research funding from BMS for a ISR.

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Abstract

The European Organization for Research on Treatment of Cancer Research published a consensus statement to establish the key criteria to define oligometastatic disease (OMD). According to those criteria, all lesions (both primary and metastatic) should be amenable to radical intent treatment with acceptable toxicity. Several retrospective studies have shown that adding local ablative therapy to the treatment of OMD improves outcomes; however, due to the diverse selection criteria and treatment strategies used in those studies, it is difficult to compare directly results to draw definitive conclusions. In recent years, prospective phase II trials, such as the SABR-COMET and "Oligomez" trials, have shown that stereotactic body radiation therapy (SBRT) improves outcomes in patients with OMD. More recently, interim results of the randomised phase 3 SINDAS trial were reported at the annual meeting of the American Society of Clinical Oncology 2020 demonstrating that upfront SBRT added to systemic treatment with tyrosine kinase inhibitors yielded a significant benefit in both progression-free survival and overall survival in patients with epidermal growth factor receptor-mutant oligometastatic non-small cell lung cancer. In the present editorial, we review the definition and historical context of advanced non-small

Manuscript source: Invited manuscript

Specialty type: Oncology

Country/Territory of origin: Spain

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: July 25, 2020
Peer-review started: July 25, 2020
First decision: October 6, 2020
Revised: October 21, 2020
Accepted: October 27, 2020
Article in press: October 27, 2020
Published online: December 24, 2020

P-Reviewer: Kang KM, Liu Y
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Zhang YL

cell lung cancer with OMD. In addition, we review the scientific evidence for local ablative therapy and SBRT and discuss the results of recently published prospective studies. We also discuss in depth the results of the SINDAS study, including the strengths and weaknesses of the study and the barriers to extrapolating these results to routine clinical practice.

Key Words: Oligometastatic; Non-small cell lung cancer; Stereotactic body radiation therapy; SINDAS; Local ablative therapy; Epidermal growth factor receptor mutations; Epidermal growth factor receptor-mutated

Core Tip: In this editorial, we review the definitions and historical context of advanced non-small cell lung cancer with oligometastatic disease. We also review the scientific evidence for local ablative therapy and stereotactic body radiation therapy as well as the results of recently-published prospective studies. Finally, we provide an in-depth analysis of the interim results of the SINDAS trial, particularly its strengths and weaknesses, and the barriers to extrapolating these findings to real-life clinical practice.

Citation: Mielgo-Rubio X, Garde-Noguera J, Juan O, Couñago F. Stereotactic body radiation therapy: A good dance partner of oligometastatic non-small cell lung cancer to the sound of SINDAS study. *World J Clin Oncol* 2020; 11(12): 983-989
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/983.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.983

INTRODUCTION

Concept and historical context of oligometastatic non-small cell lung cancer

The concept of oligometastatic disease (OMD) was first coined by Hellman and Weichselbaum to describe patients with a limited number of metastatic lesions and sites, representing an intermediate state between localised and disseminated disease[1]. Depending on how OMD is defined, the number of metastases can vary from a single metastatic lesion in one organ to several metastases in several organs[2]. Recently, the European Organization for Research on Treatment of Cancer Research published a consensus statement to establish the key criteria to define OMD. According to those criteria, all lesions (both primary and metastatic) should be amenable to radical intent treatment with acceptable toxicity[3]. That consensus statement also established the maximum number of metastatic lesions (n = 5) and involved organs (n = 3) detected by 18F-fludeoxyglucose positron-emission tomography-computed tomography and brain magnetic resonance imaging. Due to differences in the criteria used to define OMD, it is difficult to ascertain the true incidence, although estimates suggest that approximately 25% of patients present five or fewer metastases at diagnosis[2]. Numerous studies, mostly retrospective[4], have shown that ablative therapies are an effective treatment to achieve disease control and to extend survival in patients with OMD. A meta-analysis of seven retrospective studies involving a total of 776 patients diagnosed with OMD (one to five metastases) found that ablative therapy significantly improved survival outcomes[5]. Nevertheless, data obtained from the application of next-generation sequencing techniques, which allow for phylogenetic analysis of the tumour and metastases, suggest that even a limited number of metastases (one to three) can rapidly multiply, leading to disseminated disease over time[6]. For this reason, ablative therapy applied to those limited number of progenitor cells could prevent the development of polymetastatic disease[6].

For many years, the most common treatment approach (55% of cases) in these patients was surgical resection of the metastatic lesions[7]. Due to technological advances in radiation therapy — mainly the emergence of stereotactic body radiation therapy (SBRT) — it is now possible to administer high dose, highly conformal radiation to small volumes. Consequently, we can now treat brain metastases as well as lesions in other locations (lung, liver, spine, and even multiple sites), achieving local control rates ranging from 70% to 90% with low rates (< 10%) of grade 3 or higher

toxicity[8].

SBRT is less aggressive than surgery but with comparable effectiveness, which explains why interest in this treatment modality for OMD continues to grow. Advances in our understanding of lung cancer, the development of more efficacious therapies such as targeted treatments for genetic mutations [epidermal growth factor receptor (EGFR) and anaplastic lymphocyte kinase, among others], and the emergence of immunotherapy have altered the course of metastatic non-small cell lung cancer (NSCLC). Nonetheless, prospective data supporting the value of ablative therapy remain scant, and most of the available evidence for this strategy comes from retrospective studies showing that local ablative therapy (LAT) yields better outcomes than systemic treatment alone[7].

The first prospective phase II trial of LAT (surgery or radiotherapy) was conducted in 39 patients with NSCLC with ≤ metastases, with most patients having only a single lesion (n = 37; 87%). In that trial, median overall survival (OS) was 13.5 mo, with a 12-mo survival rate of 56.4%[9]. In a recent update of that trial, 5.1% of patients were still alive at 6 years of follow-up[10]. It is important to note that SBRT was not widely available when that study was performed and was not used in the trial. More recently, findings from several prospective randomised trials have provided valuable data to facilitate treatment decision-making in this clinical setting.

THE MAIN PROSPECTIVE STUDIES

The SABR-COMET study was a prospective phase II clinical trial involving 99 patients with different types of oligometastatic tumours (maximum of five metastatic sites). Patients were randomised to receive SBRT plus standard systemic therapy or systemic therapy alone[11]. Median OS and progression-free survival (PFS) were significantly longer in patients treated with SBRT *vs* conventional treatment [OS: 41 mo *vs* 28 mo; hazard ratio (HR) 0.57, 95% confidence interval (CI), 0.30-1.10, P = 0,09; PFS: 12 mo *vs* 6 mo; HR 0.47, 95%CI, 0.30-0.76, P = 0.0012]. That study used a randomised phase 2 screening design with a two-sided α of 0.20 and power of 80%, which is higher than the 0.05 level used in phase 3 designs, recognising that positive results should not be considered definitive. However, only 18 patients had a primary lung tumour, so it is difficult to reach any definitive conclusions about the true value of SBRT in this population. Moreover, the SBRT group was comprised mainly of patients with breast or prostate cancer, both of which have a less aggressive natural history than lung cancer, which could have influenced the results. A post-hoc analysis that excluded patients with breast and prostate cancer found a significant benefit for LAT, with a 5-year survival rate of 33% *vs* 16% in patients who received standard treatment.

The findings from several phase II clinical trials in patients with lung cancer have recently been reported. Iyengar *et al*[12] carried out a phase II trial of 29 patients with oligometastatic NSCLC who showed disease response/stabilization after induction chemotherapy. Patients were randomised to maintenance chemotherapy or consolidation SBRT to all metastatic sites followed by maintenance chemotherapy. A significant increase in PFS was observed for patients who received radical treatment (9.7 *vs* 3.5 mo; P = 0.01), with excellent local control in the irradiated sites and no increase in toxicity. Gomez *et al*[13] reported the findings from a phase II trial involving 49 randomised patients with advanced lung cancer and ≤ 3 metastases at diagnosis. After completion of induction chemotherapy, patients were randomised to consolidation SBRT and maintenance with systemic therapy *vs* systemic therapy alone. The combined treatment yielded significantly better PFS (14.2 mo *vs* 4.4 mo; P = 0.022) and OS (41.2 mo *vs* 17 mo; P = 0.017). More recently, the interim results of the SINDAS trial were reported at the annual meeting of the American Society of Clinical Oncology 2020. SINDAS is a randomised phase III trial designed to explore the role of upfront SBRT in combination with first- or second-generation EGFR tyrosine-kinase inhibitors (EGFR-TKI) *vs* EGFR-TKI alone as first-line treatment in patients with oligometastatic (≤ 5 metastatic lesions) lung cancer with EGFR activating mutations[14]. In that trial, 136 patients were randomised to receive TKI (n = 65) or TKI plus SBRT (n = 68). The interim findings showed a significant benefit for the experimental arm in both PFS (20.2 *vs* 12.5 mo; HR 0.61, 95%CI, 0.3949-0.9697, P < 0.001) and OS (25.5 *vs* 17.4 mo; HR 0.68, 95%CI, 0.4654-1.001, P < 0.001), without any additional toxicity. Moreover, there were no between-group differences in the distribution of adverse effects ≥ grade 3 nor in toxicity-related mortality (Table 1).

Table 1 Prospective clinical trials in oligometastatic disease

Trial	Ref.	Design	Population	Number of lesions	Local treatment	PFS	OS
SABR-COMET	Palma *et al*[11]	Phase II, *n* = 99	≤ 5 locations; different tumour types (lung cancer; *n* = 18)	1-5	SABR	12 mo *vs* 6 mo, (*P* = 0.0012)	41 mo *vs* 28 mo, (*P* = 0.09)
	Iyengar *et al*[12]	Phase II, *n* = 29	Lung cancer patients treated with induction chemotherapy followed by standard maintenance treatment (+/-SBRT)	1-5	SABR	9.7 mo *vs* 3.5 mo, (*P* = 0.01)	Not reported
"Oligomez"	Gomez *et al*[13]	Phase II, *n* = 49	Lung cancer patients treated with induction chemotherapy followed by standard maintenance treatment (+/-SBRT)	1-3	XRT or Surgery	14.2 mo *vs* 4.4 mo, (*P* = 0.022)	41.2 mo *vs* 17 mo, (*P* = 0.017)
SINDAS	Wang e *et al*[14]	Phase III, *n* = 133	Front line treatment for EGFR + NSCLC patients with ≤ 5 metastases. EGFR-TKI *vs* SBRT + EGFR-TKI	1-5	SBRT	20.2 mo *vs* 12.5 mo, (*P* < 0.01)	25.5 mo *vs* 17.4 mo, (*P* < 0.01)

EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; SBRT: Stereotactic body radiation therapy; TKI: Tyrosine kinase inhibitor.

DISCUSSION

The SINDAS trial provides new, high-grade evidence to support the benefits of LAT with SBRT at diagnosis for the treatment of oligometastatic NSCLC[14]. The main strength of that trial is the randomised phase III design. Other important strengths include the homogeneous population (NSCLC with EGFR mutations) and the well-balanced patient cohort (despite a few exceptions, discussed below). In addition, the timing of SBRT (applied at diagnosis) was the same in all patients. This aspect is important because it eliminates the possible interference of SBRT timing on outcomes. Notwithstanding these advantages, one of the main limitations of that trial is that it is not possible to extrapolate the results to routine clinical practice due to the high screening failure rate. Only 136 of the 631 patients screened over a 3-year period were eligible for randomisation, a screening failure rate of nearly 78%, which underscores the difficulty of identifying "ideal" oligometastatic candidates. Other limitations are the inclusion of patients with EGFR exon 20 insertions. These patients received first-generation TKIs rather than the more modern, superior systemic treatment strategies involving second and third-generation TKIs or combination therapy (chemotherapy + TKIs). In addition, the trial excluded patients with brain metastases, which is one of the most common metastatic sites[15].

Another notable limitation of the SINDAS trial is the lack of balance between treatment arms in the proportion of patients with exon 20 insertions (12% of the control arm *vs* only 4% in the SBRT group), a relevant difference given the worse prognosis in these patients[16]. This was confirmed on the multivariate analysis (exon 19 *vs* exon 20/21; HR 0.091, 95%CI, 0.022-0.381, *P* = 0.001) and for which we will probably have a more effective targeted treatment in the future[17]. In addition, patients in the control arm received proportionally more gefitinib than erlotinib. Although these agents are both first-generation inhibitors, no comparative studies have been performed and thus they may present small differences in efficacy and toxicity. Other factors that could limit the validity of the results and their extrapolation to real-world clinical settings are the small number of patients and the fact that the trial involved only Chinese patients, who may differ in some ways from western populations. In addition, we do not know the proportion of patients with the T790M resistance mutation, which is a relevant point given that patients with progressive disease were treated with chemotherapy alone as salvage therapy, a suboptimal treatment in patients with the T790M mutation, which could have had a major impact on OS[18].

The SINDAS trial did not clarify the role of local treatment of the primary tumour, since that was not included in the protocol. There is some evidence from a meta-analysis of retrospective studies suggesting that aggressive thoracic therapy is associated with better survival[5,15,19]. Despite these limitations, the results of the SINDAS trial demonstrate that the strategy of adding upfront SBRT to systemic treatment with TKIs yielded a significant benefit in both PFS and OS. Given the effectiveness of this treatment strategy, this approach merits consideration in treatment decision-making in the context of routine clinical practice; however, further studies, including randomised clinical trials, are warranted to provide more definitive data.

FUTURE DIRECTIONS

There is a growing body of evidence to support the addition of LAT (such as SBRT) to the treatment of OMD. The current evidence includes retrospective studies showing that LAT provides a survival benefit[19], randomised phase II trials that have prospectively confirmed this benefit with long-term data[11,20,21], and the first randomised phase III trial (SINDAS) whose results provide robust support for this strategy, demonstrating an increase in both PFS and OS[14].

Many doubts remain with the regard to the optimal use of LAT in OMD. The term OMD is still too broad; as a result, the optimal treatment may differ depending on the specific patient subgroup. The multivariate analysis in the SINDAS trial showed that patients with the largest tumours (T3-4 *vs* T1-2; HR for OS 2.06, 95%CI, 1.08-5.5, P = 0.017) and a greater number of metastases (≥ 3 *vs* < 3; HR for OS 1.95, 95%CI, 1.2-3.07, P = 0.04] had worse survival[14]. Moreover, we still do not know which LAT technique is best for the various clinical scenarios due to a lack of head-to-head studies comparing surgery to SBRT or radioablation. That said, if we were forced to select a single approach, it seems reasonable to opt for the least aggressive treatment, which would support the use of SBRT due to its favourable toxicity and morbidity profile.

The optimal timing of SBRT is also unclear. SBRT could be administered as the initial therapy—the approach used in the SINDAS and SABR-COMET trials[11,14]—or as consolidation therapy, as in the "Oligomez" and Iyengar trials[12,13]. The benefit of local treatment of the primary tumour should be confirmed prospectively. The effect of adding immunotherapy in this clinical scenario remains unknown; similarly, the biomarker and molecular profiles that could help to identify the patients most likely to benefit from LAT are not known. In tumours with EGFR mutations, there may be a high degree of discordance between the primary tumour and metastases (Lee *et al*[22] found a discordance rate of 45% between the primary tumour and bone metastases). Indeed, this discordance provides the rationale for treating these foci of TKI-resistant cell clones with LAT and explains why this strategy is effective. Several phase III trials currently underway will help resolve these questions. The NRG LU002 trial (NCT03137771) is being performed to evaluate local ablative consolidation therapy in NSCLC. The SABR-COMET-3 (NCT03862911) and SABR-COMET-10 (NCT03721341) trials are evaluating upfront SBRT in multi-tumour OMD with one to three or four to ten metastases, respectively. A new post-hoc analysis of the SABR-COMET trial data is expected when all patients have reached at least 10 years of follow-up. Other phase II trials are also underway, including CHESS (NCT03965468), which is evaluating the application of immunotherapy, chemotherapy, and radiotherapy, and the NCT03905317 trial, which is evaluating antiangiogenic therapy combined with radiotherapy.

CONCLUSION

In conclusion, although the strong results published in recent years have generated great enthusiasm for including SBRT in the treatment of oligometastatic NSCLC, more research is essential to improve patient selection, identify molecular biomarkers (not only clinical), and determine the optimal timing of SBRT. While SBRT is not likely to be applicable to most patients with oligometastatic NSCLC, it may be an ideal treatment for well-defined subgroups.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 990-995

DOI: 10.5306/wjco.v11.i12.990

ISSN 2218-4333 (online)

EDITORIAL

New standard in locally advanced rectal cancer

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Author contributions: All authors contributed equally to designing and performing this research, and all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest.

Manuscript source: Invited manuscript

Specialty type: Oncology

Country/Territory of origin: Chile

Peer-review report's scientific quality classification

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Abstract

In the following review we intend to ascertain the optimal neoadjuvant therapy in patients with locally advanced rectal cancer. In 2004, a study revealed that chemoradiotherapy (CRT) resulted in better local control when performed preoperatively rather than postoperatively, thus neoadjuvant treatment was established as a standard treatment. Subsequently, the Polish study and the Trans-Tasman Radiation Oncology Group showed no statistically significant difference between concomitant CRT over 5 wk *vs* short-course radiotherapy (RT). Therefore, both were established as standard neoadjuvant treatments. Later, the Stockholm III study demonstrated that short-course RT had a higher complete pathological response than long-course RT. It also showed that a delay between RT and surgery presented fewer complications. This opened a window of time to provide an early and effective systemic treatment to prevent distant metastases. Studies show that short-course RT plus oxaliplatin-based chemotherapy could achieve this. When comparing this total neoadjuvant treatment (TNT) *vs* concomitant CRT, the former showed greater complete pathological response and lower acute toxicity. Studies presented during 2020 have also shown the benefits of TNT in terms of complete pathological response, as well as disease and metastasis-free survival. Our review suggests that probably TNT should be the new standard treatment for these patients. However, we will have to wait for the full text publications of these studies to confirm this statement.

Key Words: Locally advanced rectal cancer; Total neoadjuvant treatment; Short-course radiotherapy; Oxaliplatin; Neoadjuvant chemoradiotherapy; Long-course radiotherapy

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

Received: July 31, 2020
Peer-review started: July 31, 2020
First decision: September 17, 2020
Revised: October 1, 2020
Accepted: October 20, 2020
Article in press: October 20, 2020
Published online: December 24, 2020

P-Reviewer: Fabozzi M, Vosmik M
S-Editor: Huang P
L-Editor: Webster JR
P-Editor: Zhang YL

Core Tip: In this review we intend to ascertain the optimal neoadjuvant therapy in patients with locally advanced rectal cancer. In terms of chemotherapy (CT) it has recently been demonstrated that oxaliplatin-based CT after short-course radiotherapy results in greater pathological response and lower acute toxicity than concomitant chemoradiotherapy. Studies presented during 2020 have also shown this benefit, as well as better disease and metastasis-free survival. Our review suggests that probably total neoadjuvant treatment should be the new standard treatment for these patients. However, we will have to wait for the full text publications of these studies to confirm this statement.

Citation: Solé S, Baeza R, Gabler C, Couñago F. New standard in locally advanced rectal cancer. *World J Clin Oncol* 2020; 11(12): 990-995
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/990.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.990

INTRODUCTION

Since the Gastrointestinal Tumor Study Group study was published in the *New England Journal of Medicine* in 1985, we have known that locally advanced rectal cancer surgery alone is not sufficient[1]. This research demonstrated a clear benefit in the addition of radiotherapy (RT) at around 5 wk and concomitant chemotherapy (CT) after surgery (adjuvant). In Sweden, they performed preoperative or neoadjuvant RT treatment. Thus, in 1997, they published a randomized study of surgery alone *vs* RT 2500 centi-gray (cGy) delivered in 5 fractions in 1 wk (short-course RT) followed by surgery within one week. Patients who received RT had better local control and higher overall survival[2].

Up to that date, two randomized studies existed which showed the benefit of adding treatments to surgery for both neoadjuvant short-course RT and concomitant adjuvant chemoradiotherapy (CRT). It was not clear whether it was better to carry out this treatment before or after resection. In 2004, a study performed by Sauer *et al*[3] was published showing that CRT treatment over 5-6 wk was better when performed preoperatively in comparison to postoperatively as it resulted in better local control and was better tolerated. At this point, neoadjuvant treatment was established as the standard.

Taking this into consideration, what is the best neoadjuvant treatment? Concomitant CRT over 5 wk (dose of 5000-5040 cGy delivered in 25-28 fractions in 5-5.5 wk) *vs* short-course RT. Two randomized studies were performed on this subject, the Polish study and the TROG[4,5] trial. Both studies showed that there was no statistically significant difference between these neoadjuvant treatments and so both were established as standard treatments.

It seems counter-intuitive that a short-course RT treatment with 2500 cGy is equivalent to a concomitant CRT treatment with double the dose. However, when analyzing this from a radiobiological perspective, these doses are equivalent as the 2500 cGy are administered in doses of 500 cGy per session *vs* the 180-200 cGy per session for concomitant CRT. In addition, the treatment is completed in only 1 wk *vs* 5-5.5 wk. In fact, the 1 wk treatment administers a dose equivalent to 3570 cGy in comparison to 3440 cGy, which is the dose administered in the long-course treatment, if one uses the linear quadratic model and factors in total treatment time[6].

This was clinically demonstrated in the Stockholm III study, which compared long-course RT at 5 wk, without concomitant CT, *vs* short-course RT, both neoadjuvant treatments followed by surgery after 4-8 wk. Pathology study results confirmed the radiobiology calculations. The pathological complete response was better in the short-course RT group, reaching 10.4% *vs* only 2.2% in the long-course RT group[7]. The same study compared short-course RT with and without pre-surgical delay (following week *vs* a delay of 4-8 wk) and showed that the oncological results were similar but that a delay allows for fewer surgical and post-operative complications[8]. The authors concluded that a pre-resection delay should be made. This delay opens a window of time to provide effective systemic treatment early in the course of treatment that

prevents the development of distant metastases. This is very relevant because randomized studies consistently show an incidence of distant metastases of around 30% in patients who are treated for locally advanced rectal cancer[9].

NEW PARADIGM

The new paradigm is to advance useful systemic treatment with oxaliplatin (OXA)-based CT in order to prevent the development of distant metastases. In this regard, the ideal is to be able to perform all adjuvant treatments preoperatively. This concept is known as total neoadjuvant treatment (TNT). The main objective of this is to prevent distant metastases by instructing the patient to use effective systemic treatment early in the course of their disease. Other benefits of TNT are improved local response that can manifest itself in improved clinical and pathological complete response, improved tolerance and adherence to treatment, and reduced total time for complete treatment with earlier ostomy resolution. In fact, this last point was demonstrated in a study presented at the American Society of Clinical Oncology (ASCO) 2019 in patients who received TNT through short-course RT and CT with OXA[10].

In 2016, the STELLAR study was presented at the American Society of Radiation Oncology, which compared short-course RT followed by CT with OXA for 4 cycles with concomitant CRT, as neoadjuvant treatments. After surgery in both treatments, CT with OXA was recommended, 2 cycles for the short-course RT group and 6 cycles for the concomitant CRT group. The experimental group that underwent short-course RT followed by CT was superior in terms of pathological complete response, which was obtained in 25.7% of cases *vs* only 7.9% of cases in the concomitant CRT control group. There was also a difference in complete clinical response of 11.7% in the experimental group *vs* 0% in the control group[11]. These preliminary data were updated at the European Society for Medical Oncology 2018 Congress. A benefit continued to be exhibited in pathological complete response for the short-course RT group followed by CT which turned out to be 26.2% *vs* 5.3% for the group that received concomitant CRT[12].

In 2016, the Polish study II was published, which compared short-course RT followed by OXA-based CT *vs* concomitant OXA-based CRT in patients with fixed cT4 or cT3 cancer. In this study, 56% of patients had tumors located in the lower rectum. Overall survival at 3 years was superior in the short-course RT group with 73% *vs* 65% for the concomitant CRT group[13]. The long-term results of this study with 7 years of follow-up showed a median overall survival of 89 mo for the short-course RT group *vs* 81 mo for the concomitant CRT group, with no statistical difference[14]. This second publication shows that only 70% of patients in both groups received OXA because during the course of the study, other studies appeared that showed greater toxicity due to concomitant CRT with OXA. This is probably why the benefit initially shown, when most of the randomized patients had received OXA, was lost when a significant percentage of admitted patients later switched to OXA-free treatment. In this new scenario, the benefit that the short-course RT group followed by OXA-based CT has to start early effective systemic treatment during disease progression that may prevent the development of metastases is lost. In any case, this study reinforces that short-course RT is at least equivalent to concomitant CRT in locally advanced rectal cancer. It is important to note that concomitant CRT was not superior to short-course RT in any outcome, but acute toxicity was lower for short-course RT (P = 0.006). When treatments are equivalent in oncological outcome, we must opt for the treatment with lower toxicity, which in this case was the short-course RT.

At IRAM Clinic (Santiago, Chile), we started TNT in 2015 with short-course RT followed by 4 cycles of folinic acid/5-fluorouracil/oxaliplatin (FOLFOX) for 2 mo[15]. To date, we have 58 patients with pathological results, where 77.5% had cT3 or cT4 cancers and 86.2% were classified as N+. A total of 82.7% of patients were classified in stages using CT scans of the chest, abdomen and pelvis and 62% with pelvic magnetic resonance imaging (MRI). Pathological complete responses were obtained in 22.4% of patients and 65.5% of patients were down staged from stage III to a lower stage (stage II, I or 0). Compared to the study performed by Sauer *et al*[3] of concomitant CRT, they showed pathological complete response rates of 8% and downstaging of 15%.

At ASCO 2020, results were presented from the RAPIDO study that randomized patients with high-risk features for failure on MRI to undergo TNT with short-course RT followed by CT with OXA-based CT for 18 wk followed by surgery *vs* concomitant CRT followed by surgery and then 24 wk of OXA-based CT. The TNT group tolerated the treatment well with the following grade 3 or higher adverse events: Diarrhea in

17.6% of the group, vascular disorders in 8.5%, all other adverse events affected under 5%. The primary focus was treatment-related failure, which was 23.7% in the group receiving TNT *vs* 30.4% in the control group (P = 0.019). The pathological complete response doubled in the TNT group, reaching 28.4% *vs* 14.3% (P < 0.001) and distant metastases occurred in 20% of patients in the TNT group *vs* 26.8% of patients in the concomitant CRT group (P = 0.005). These results were found in a patient population with very high risk of recurrence with cT4 disease in 31.8%, N2 in 65.4% and a compromised mesorectal fascia in 61.7%[16].

In addition, the PRODIGE 23 study was presented where TNT and FOLFIRINOX was randomized for 3 mo, followed by concomitant CRT, then total mesorectal excision (TME) and then CT with FOLFOX or capecitabine for 3 mo *vs* a control group with concomitant CRT followed by TME and then CT with adjuvant FOLFOX or capecitabine for 6 mo[17]. It is important to note that in the pre-operative re-staging, 4.7% of control group patients became metastatic *vs* 1% of those in the experimental group (P = 0.03). This reinforces the fact that the classical approach of starting treatment with concomitant CRT does not prevent the development of distant diseases and that is why we must stop treating patients in this way and shift the paradigm towards TNT. The grade 3 or higher adverse events in adjuvant treatment alone were 44.4% for the TNT group. This seems a little high considering that these data do not consider the adverse effects of other stages of treatment (neoadjuvant) and that only 70.6% were able to receive adjuvant treatment and, of these, only 80.4% completed all cycles. This is equivalent to only 56.7% of patients randomized to TNT. However, TNT resulted in better disease-free survival at 3 years with 75.7% *vs* 68.5% (P = 0.034) and better metastasis-free survival at 3 years with 78.8% *vs* 71.7% (P = 0.017).

Another study presented at ASCO 2020 was the Organ Preservation of Rectal Adenocarcinoma (OPRA) study[18]. Patients with rectal cancer with a better prognosis than in the RAPIDO and PRODIGE 23 studies with stage II or III were randomized to concomitant CRT and then OXA-based CT for 4 mo *vs* OXA-based CT for 4 mo and then concomitant CRT. Patients were then re-staged and, if they achieved a clinical response, they entered an active follow-up protocol. Those who had no response went on to TME. With a median follow-up of 2.2 years, surgery-free survival at 3 years was better for the group that started with RT (P = 0.007). Grade 3 or higher toxicity occurred in 45.5%-49% of patients. The author concluded that further follow-up is required but that organ preservation in rectal adenocarcinoma could be a safe alternative in some patients.

CONCLUSION

Considering both the historical and recent evidence, probably the new standard treatment for locally advanced rectal cancer will be TNT as it shows better results than concomitant CRT in at least 2 randomized studies. However, we will have to wait for the full text publications to confirm this statement. Among the TNT options, the best alternative is short-course RT followed by OXA-based CT for 18 wk following the RAPIDO study protocol, since it achieves similar metastasis-free survival rates at 3 years as PRODIGE 23 (80% RAPIDO *vs* 78.8% PRODIGE 23), despite the fact that the included patients had a worse prognosis since cT4 disease was 31.8% in RAPIDO *vs* 17.8% in PRODIGE 23 and a greater risk of a positive lateral margin (compromise of mesorectal fascia in 61.7% in RAPIDO *vs* predicted lateral margin < 1 mm 26% in PRODIGE 23) with a toxicity profile that seems to be lower (Table 1). The OPRA study is not comparable because it included patients with a much better prognosis (T1-2 13%, N0 28% in the best group) and still has little follow-up (2.2 years), but suggests that we need to start with RT and then follow with OXA-based CT, and not the other way round.

Table 1 Comparison between Sauer's, PRODIGE 23 and RAPIDO study

	T4	N+	Predicted lateral margin < 1 mm	Pathologic complete response	Metastasis-free survival
Sauer (%)	6	54		8	70.2
PRODIGE 23 (%)	17.8	89.1	26	27.8	78.8
RAPIDO	31.8	90	61.7	28.4	80

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 996-1007

DOI: 10.5306/wjco.v11.i12.996

ISSN 2218-4333 (online)

MINIREVIEWS

Predictive indicators of successful tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia

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Author contributions: Stuckey R and López-Rodríguez JF wrote the review; Sánchez-Sosa S updated the CML registry and patient data; Segura-Díaz A and Gómez-Casares MT treated patients with CML; Stuckey R, Sánchez-Sosa S, and Sánchez-Farías N coordinated TKI discontinuation clinical trials; Bilbao-Sieyro C and Gómez-Casares MT supervised the investigational and medical aspects, respectively, of discontinuation studies at our center; All authors approved the final version of the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Abstract

Clinical trials have demonstrated that some patients with chronic myeloid leukemia (CML) treated for several years with tyrosine kinase inhibitors (TKIs) who have maintained a molecular response can successfully discontinue treatment without relapsing. Treatment free remission (TFR) can be reached by approximately 50% of patients who discontinue. Despite having similar levels of deep molecular response and an identical duration of treatment, the factors that influence the successful discontinuation of CML patients remain to be determined. In this review we will explore the factors identified to date that can help predict whether a patient will successfully achieve TFR. We will also discuss the need for the identification of predictive biomarkers associated with a high probability of achieving TFR for the future personalized identification of patients who are suitable for the discontinuation of TKI treatment.

Key Words: Biomarkers; Tyrosine kinase inhibitors; Treatment discontinuation; Molecular monitoring; Duration of therapy; Leukemia; Myelogenous; Chronic; BCR-ABL positive

Core Tip: Clinical trials have shown that approximately 50% of patients with chronic myeloid leukemia who reach a deep molecular response (MR) following treatment for several years with tyrosine kinase inhibitors (TKI) can discontinue and remain in treatment-free remission (TFR). Factors such as the duration of TKI treatment and duration and depth of the patient's MR prior to discontinuation appear to be important in determining whether TFR is achieved. However, it is clear that other biological

Manuscript source: Invited manuscript

Specialty type: Oncology

Country/Territory of origin: Spain

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 21, 2020
Peer-review started: March 21, 2020
First decision: September 24, 2020
Revised: September 28, 2020
Accepted: October 21, 2020
Article in press: October 21, 2020
Published online: December 24, 2020

P-Reviewer: D'Orazi G
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Zhang YL

factors must determine whether an individual will remain in TFR after discontinuation. Future studies should aim to elucidate biomarkers predictive of TFR.

Citation: Stuckey R, López-Rodríguez JF, Sánchez-Sosa S, Segura-Díaz A, Sánchez-Farías N, Bilbao-Sieyro C, Gómez-Casares MT. Predictive indicators of successful tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia. *World J Clin Oncol* 2020; 11(12): 996-1007
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/996.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.996

INTRODUCTION

Chronic myeloid leukemia (CML) is a neoplasia of the pluripotent hematopoietic progenitor cells characterized by the clonal expansion of differentiated cells in the myeloid lineage[1] and classified by the World Health Organization within the group of chronic myeloproliferative neoplasms[2].

The constitutive activation of tyrosine kinases in hematopoietic stem cells is a common molecular basis of the myeloproliferative neoplasms. CML is defined by the presence of a reciprocal translocation between chromosomes 9 and 22 *t*(9; 22)(q34; q11), resulting in a shortened chromosome 22 known as the Philadelphia chromosome, which leads to the expression of the fusion oncogene *BCR-ABL1* encoding a constitutively active tyrosine kinase[3,4].

Imatinib mesylate (Gleevec®) was the first tyrosine kinase inhibitor (TKI) developed to target specifically the BCR-ABL1 oncoprotein. Physicians now have five approved TKIs available for the treatment of patients with CML: Imatinib (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®) for first- or second-line therapy and ponatinib (Iclusig) for patients with resistance or intolerance to prior therapy[4].

The outcome for CML patients has improved dramatically as a result of treatment with imatinib and other TKIs. In fact, most patient life expectancy is almost equivalent to that of the general population[5]. Despite their effectiveness in controlling the disease, TKIs are not considered to be curative, as they are not capable of eradicating the BCR-ABL1$^+$ leukemic stem cell. In fact, these cells do not depend on BCR-ABL1 for their survival and represent a reservoir capable of restoring CML, justifying the requirement for CML patients to take life-long daily oral TKI therapy[6-9].

However, recent clinical trials have demonstrated that approximately 50% of patients with CML treated for several years with TKIs and that reach a deep molecular response (MR) (DMR) (BCR-ABL1/ABL1 ≤ 0.01%, MR^4 or better) can successfully maintain remission after the discontinuation of TKI treatment, known as treatment free remission (TFR)[10]. Importantly, a 2017 survey determined that 81% of CML patients would be willing to attempt discontinuation[11].

Here, we will discuss which patients can discontinue TKI treatment and explore the factors that may predict whether a patient successfully achieves TFR.

Why discontinue TKI treatment?

One disadvantage associated with the use of these drugs is the development of side effects. Many patients experience mild to moderate non-hematologic TKI-related side effects, such as fatigue, nausea and vomiting, edema, diarrhea, headache, skin rash, muscle cramping, joint pain, night sweats, weakness, lack of appetite and myelosuppresion, especially when commencing TKI therapy. Indeed, only 60% of patients continue on the standard daily dose of 400 mg imatinib after 6 years due to intolerance or resistance[12], and approximately one-third of patients suffer moderate to severe TKI-related adverse effects[13] including neutropenia, thrombocytopenia and anemia.

In some cases, long-term treatment is associated with more serious off-targets despite not being reported in the initial clinical studies[14-16]. Such events comprise hepatic toxicity and coronary atherothrombotic, cerebrovascular and peripheral arterial events associated with nilotinib[17,18]; arterial and venous occlusive events with ponatinib[19,20]; pulmonary hypertension and pleural effusion with dasatinib use[21,22].

Adverse events can contribute to an impaired quality of life for patients with

CML[23,24], particularly for patients aged under 60 years, with the largest effects of TKI treatment on quality of life observed in patients aged 18-39 years[23]. Therefore, the successful discontinuation of TKI treatment would allow patients with CML to live a completely normal life.

Moreover, TKI treatment can affect fertility, and no TKI is recommended for women who wish to conceive or during pregnancy or lactation. Indeed, there is a higher tendency for women to interrupt TKI treatment than men[25]. Thus, the discontinuation of TKI therapy would allow women to have a normal pregnancy and be able to breastfeed.

Is TKI discontinuation feasible?

Various studies have demonstrated the viability of the discontinuation of TKI treatment[10]. As a result, TKI discontinuation has now become a feasible objective among clinicians in the management of patients with CML. For patients treated with imatinib, the STIM1 and STIM2 studies showed that a large proportion of patients with CML can benefit from the long-term suspension of TKIs (between 40% and 70% according to prognostic factors)[26,27]. In the case of patients treated with "newer" TKIs, such as nilotinib and dasatinib, recent clinical trials suggest a percentage of TFR equal or superior to trials with imatinib (see Table 1 for a non-exhaustive list of discontinuation trials). According to the results of studies in which our research group has participated, 52% of patients who discontinued nilotinib (ENESTFreedom) reached TFR[28], while for dasatinib (DASFREE) the TFR rate at 24 mo was 46%[29]. Interestingly, although clinical experience with the discontinuation of second-generation TKIs such as nilotinib and dasatinib is shorter, study results seem to indicate that the percentage of patients successfully achieving TFR will be higher than for imatinib and that a shorter duration of treatment may be needed prior to a discontinuation attempt[28,30,31].

All of these studies include the close monitoring of patients (monthly BCR-ABL1 transcript determinations during the first 12 mo), with the aim of detecting the signs of relapse as soon as possible. Importantly, practically all the patients who did relapse after discontinuation responded well to re-treatment[26,27]. Moreover, a meta-analysis of discontinuation studies determined that the suspension of imatinib neither increased the probability of disease progression nor the risk of death, with all CML patients alive after 2-year follow-up (only one patient had progressed to blast crisis, 0.8%)[32].

Prognostic variables for TFR

To date, the variables shown to be predictive of a higher probability of TFR success are those related with CML characteristics and TKI treatment, such as the Sokal score, duration of TKI treatment, and duration and depth of MR[10].

Sokal score: The percentage of patients with a low, intermediate or high Sokal score who achieved TFR in the TWISTER study was 51%, 37% and 25%, respectively[33]. Likewise, patients with a low or intermediate Sokal score who discontinued imatinib in the STIM1 study were found to have a higher probability of obtaining TFR[26].

Duration of TKI treatment: Results from the STIM1 study also revealed a higher probability of obtaining TFR for patients who had received more than 4.5 years of TKI therapy[26]. This observation was confirmed by the KID study and the EURO-SKI study, the latter of which revealed that patients who had reached at least a MR^4 during 1 year and had received TKI treatment for longer than 5.8 years had a higher TFR rate than those who had received imatinib for less than 5.8 years (65% *vs* 42.6%, respectively)[34-36]. Moreover, according to European Society for Medical Oncology (ESMO), the "stability of TFR is improved with longer TKI therapy and longer DMR"[37]. Of note, the DASFREE study reported a TFR at 12 mo of 54% for patients who discontinued dasatinib as first-line TKI treatment compared to a TFR of 43% for patients who discontinued dasatinib in the second-line. Moreover, no significant association was found between TFR and duration of prior TKI therapy[29]. This result suggests that first-line treatment with second generation TKIs may help improve the probability of reaching TFR.

Duration and depth of MR: Results from several studies have revealed a positive association between the level (or depth) of molecular response and the probability of TFR success. For example, the Japanese STAT2 trial found that the TFR rate after 36 mo was significantly higher in patients with undetectable molecular residual disease than in patients without (76.6% *vs* 48.6%, respectively)[38]. This finding was confirmed by the JALSG-STIM213 study, which discontinued CML patients who had received imatinib for at least 3 years and had a sustained DMR for at least 2 years, and reported

Table 1 Summary of level (depth) of molecular response required prior to discontinuation attempt in discontinuation clinical trials, for all of these studies, molecular relapse was considered to be loss of major molecular response

Molecular response	Trial	TKI	TFR, %	TFR at month
MMR	Destiny	Dasatinib	39	24
DMR	JALSG-STIM213	Imatinib	68	12
DMR	DASFREE	Dasatinib	63	12
DMR	ENESTFreedom	Nilotinib	52	12
DMR	ENESTop	Nilotinib	58	12
DMR	EURO-SKI	Mixed	61	6
CMR[1]	STIM1[2]	Imatinib	43	6
UMRD	ISAV[3]	Imatinib	48	36
UMRD	STOP 2G-TKI[4]	Mixed	61	12
UMRD	STIM2[5]	Imatinib	64	6
UMRD	KIDS[6]	Imatinib	62	12
UMRD	TWISTER[6]	Imatinib	47	24

[1]Complete molecular response should not be detectable but could be MR^4 or $MR^{4.5}$ depending on the sensitivity of the BCR-ABL1 transcript quantification technique used[63].
[2]> 5-log reduction.
[3]Limit of detection log4-4.5.
[4]Undetectable BCR-ABL1 by real-time quantitative polymerase chain reaction, with at least 20,000 copies of the control gene.
[5]Undetectable BCR-ABL1 with sensitivity ≥ 50000 amplified copies of *ABL1* control gene.
[6]Limit of detection log4.5. CMR: Complete molecular response; DMR: Deep molecular response MR^4 or better (< 0.01%); MMR: Major molecular response, MR^3 (0.1%); TFR: Treatment free remission; TKI: Tyrosine kinase inhibitor; UMRD: Undetectable molecular residual disease.

a TFR rate of 72% after 3 years for patients with undetectable molecular residual disease (UMRD) compared to 35.7% for patients with $MR^{4.5}$ prior to discontinuation[39]. This association was also indicated by the ISAV study, which employed digital polymerase chain reaction (dPCR) to predict relapses after imatinib discontinuation in CML patients who had maintained complete molecular response (CMR) (defined as undetectable BCR-ABL1 transcripts by quantitative PCR, with a limit of detection of 4–4.5 Logs) during at least 18 mo. The study reported a TFR rate at 36 mo of 48% and although no association was found between the risk of molecular relapse and Sokal score, duration of imatinib treatment, or duration of CMR–dPCR positivity was significantly associated with relapse[40]. Finally, the analysis of data from the EURO-SKI study suggested that a longer duration of deep molecular response was positively associated with TFR[35,37].

The predictive value of these variables was confirmed by two recent meta-analyses that collectively considered 22 TKI discontinuation studies comprising 3300 chronic myeloid leukemia patients and concluded that depth of molecular response trials[41] (specifically trials whose eligibility criteria required $MR^{4.5}$ or better prior to discontinuation[42]) and duration of DMR[41] (specifically trials that required at least 24 mo of DMR[42]) were associated with higher TFR rates.

Imatinib resistance: One important result from the STOP 2G-TKI study was that resistance to imatinib or poor response was associated with a significantly lower probability of achieving TFR after TKI discontinuation[30].

Nevertheless, it is difficult to compare the results of many discontinuation studies due to the different criteria used in each case, in terms of the length of TKI treatment as well as the level and duration of molecular response required prior to discontinuation. Even the definition of molecular relapse varies considerably from study to study, depending on the criteria of each clinical trial (Table 1). For example, prior to TKI discontinuation, DMR was required by the DASFREE[29], EURO-SKI[36] and ENESTFreedom[28] studies; whereas the KIDS[34] and TWISTER[33] studies required a depth of MR as stringent as UMRD.

As a consequence of these findings on variables that are predictive of TFR success (and many others that have not been named in this review due to space restrictions),

both the United States National Comprehensive Cancer Network (NCCN) and the ESMO developed guidelines for the safe discontinuation of TKI treatment for patients with CML[37,43]. The criteria for patient selection for a discontinuation attempt according to the NCCN guidelines from 2018 include TKI treatment for at least 3 years and a maintained MR^4 or above for at least 2 years, as well as no history of TKI resistance[43]. The 2017 ESMO guidelines also require a maintained DMR for at least 2 years but require at least 5 years of TKI therapy prior to the discontinuation attempt and the achievement of $MR^{4.5}$[37].

Real-life discontinuation studies

As previously discussed, numerous clinical trials have endeavored to establish criteria for the safe discontinuation of TKI treatment in patients with CML. Although the evidence related to the applicability of such criteria to clinical practice is limited, several groups have attempted to evaluate the safety of TKI discontinuation outside of controlled trials.

The Spanish Group on CML (GELMC) analyzed a series of 236 discontinued patients from 33 national centers and reported that 164 patients maintained a major molecular response (MMR) after a median follow-up of 21.5 mo, while 67 patients (28%) had to reinitiate TKI treatment due to loss of MMR (at two consecutive controls with an increase > 1 Log of BCR-ABL1). The probability of reaching TFR at 12 and 48 mo was 72.5% and 64%, respectively[44]. A similar observational study of 293 Italian patients who discontinued TKI, with a median follow-up of 34 mo, reported that 39% had to reinitiate treatment, due to loss of MR^4 (19%), loss of MMR (70%) or loss of cytogenetic response (9%). Moreover, a multivariate analysis revealed that the discontinuation of second-generation TKIs (28% of patients) had superior TFR rates than imatinib (73% *vs* 68% at 12 mo, respectively)[45]. Finally, the study conducted at the MD Anderson Cancer Center on 100 patients who had reached $MR^{4.5}$ prior to discontinuation reported a TFR rate of 70% at 2 years, and determined that patients with a duration of $MR^{4.5}$ of 2 years had a probability of losing MMR of 29% compared to only 7% for patients with a duration of $MR^{4.5}$ of 6 years[46].

Together, the results of these real-life studies confirm that the discontinuation of TKI treatment in clinical practice is viable and safe for many CML patients. It is important to note that they also support the duration of TKI treatment and particularly the duration of DMR prior to discontinuation as clinical variables that are positively associated with TFR.

Selection of patients for TKI discontinuation

Although the seminal discontinuation studies of imatinib (EURO-SKI) commenced in 2010, and those for nilotinib (ENESTFreedom) and dasatanib (DASFREE) in 2013, there is still no European or international consensus regarding what criteria are important for selecting patients for a discontinuation attempt. Despite this (and although discontinuation of TKI therapy is still largely conducted in controlled clinical trials), our hospital, in collaboration with the Canarian CML Group, has developed a standard protocol for TKI discontinuation in clinical practice based on the current NCCN[43] and ESMO guidelines for the selection of CML patients for TKI discontinuation[37].

To be eligible for consideration for TKI discontinuation at our center or other hospital in the Canary Islands, CML patients must meet the criteria as set out in the "TKI Treatment Discontinuation in Patients with Chronic-phase CML"–Canarian CML Group protocol (Table 2), which has the aim of assuring the maximum rate of discontinuation success.

The importance of molecular factors for the prediction of TFR

There is a real clinical need to study CML patients who successfully achieve TFR and those who suffer molecular relapse in order to identify the molecular factors that have a significant role in remission. Such molecular factors could potentially be used as biomarkers to predict which patients are likely to reach TFR. The identification of predictive factors for TFR in CML will also help define criteria for safer discontinuation attempts with a greater probability of success.

Although the global duration and other variables related to TKI treatment prior to discontinuation are associated with TFR[10,41,42], it is clear that other biological factors must exist that determine whether an individual will or will not remain in TFR when the TKI is withdrawn. To date, very few studies have investigated this at the molecular level, although some suggest a possible role of the immune system[35]. For example, a maintained TFR following the discontinuation of imatinib was associated with high

Table 2 Inclusion and exclusion criteria for patient selection from the Canarian-chronic myeloid leukemia "Tyrosine kinase inhibitor treatment discontinuation in patients with chronic-phase chronic myeloid leukemia" protocol

Inclusion criteria, all should be met	Exclusion criteria
Aged 18 yr or over, with diagnosis of CML in chronic phase	Resistance to any TKI or insufficient response to imatinib
Received 5 yr or more of TKI treatment (imatinib, bosutinib, nilotinib or dasatinib)	Accelerated phase or blastic crisis in any moment
Maintained a $MR^{4.5}$ (BCR-ABL1/ABL1 < 0.0032%) or better in all samples taken during the last 3 yr (with at least one recent sample certified in a centralized laboratory)	Detection of BCR-ABL1 kinase domain mutations in any moment
Present a typical BCR-ABL1 transcript at diagnosis that permits quantifiable molecular monitoring	
A low or intermediate Sokal index at diagnosis	
Give written informed consent	

CML: Chronic myeloid leukemia; MR: Molecular response; TKI: Tyrosine kinase inhibitor.

levels of NK cells[47-50], increased CD3(+)CD8(+)CD62L(+) T cells[48], increased expression of CD56 and NKG2D in NK cells and lower expression of CD86[51].

Interestingly, Caocci *et al*[52] recently described an association between the presence of specific polymorphisms of the killer immunoglobulin-like receptor (KIR) and TFR[52]. The authors analyzed 36 CML patients with a $MR^{4.5}$ and observed that after discontinuation, those with the homozygotic haplotype KIR A/A had a significantly higher TFR than those with haplotype B/x. These results suggest that specific mutations may cause an increased expression of tumoral antigens and thus change the vulnerability of the tumor cells to the immune system. However, these results did not coincide with those of the EURO-SKI study, in which the authors observed no differences in TFR in relation to KIR haplotype[35].

To the best of our knowledge, only one preliminary study has specifically searched for mutations in CML patients who achieved TFR using exome sequencing[53]. The study compared the exome sequence of three patients who achieved TFR with three patients who relapsed after TKI discontinuation and identified a variant in *PARP9* in the TFR group and variants in *CYP1B1, ALPK2* and *IRF1* in the relapsed group[53]. Although only a small number of patients' exomes were sequenced, making the formation of scientific conclusions difficult, the study demonstrates that the existence of variants in genes of diverse functions may contribute to the maintenance of TFR.

Other intriguing results have linked high miR-126 levels with higher numbers of quiescent CML stem cells[54]. Therefore, it would be interesting for future studies to analyze the role of the expression of certain microRNAs with the successful obtention of TFR.

FUTURE RESEARCH DIRECTIONS

Need to determine molecular factors associated with TFR

As mentioned above, there is a real need to identify molecular factors associated with TFR to identify patients with CML with a higher probability of reaching TFR. Studies indicate that the incidence of deep molecular responses, a prerequisite for TFR in many studies and one of the patient selection criteria according to the ESMO 2017 guidelines, is quite low. For example, in the IRIS[55], DASISION[21] and ENESTnd[56] studies, the $MR^{4.5}$ rates after 5 years of TKI treatment were 23.3%, 33% and 31%, respectively. As such, current patient selection criteria may be overly restrictive and thus limit the number of patients who can currently make a discontinuation attempt.

In addition, the identification of molecular factors predictive of TFR would bring substantial savings for national health systems. The current price of TKI treatment in most European countries is approximately 2500–3500 € *per* month[10], although this is substantially reduced in the case of generic imatinib (approximately 100 € *per* month). In actual fact, the savings would be even greater, since the health system would not have to treat the appearance of adverse effects often associated with TKI treatment, including serious cardiovascular comorbidities. CML has an incidence of 1–1.5 cases per 100000 inhabitants per year and the average age of patients presenting with CML is 60–65 years. Thus, these potential savings could become critical in the future for

national health systems due to the increased aging of the global population[57], which will result in an estimated 35-fold rise in incidence of CML, with a peak in prevalence around the year 2050[58].

Influence of second discontinuation attempt

The evidence to support the safety and viability of a second discontinuation attempt in patients with CML who lost molecular response in a first discontinuation attempt is scarce. The prospective RE-STIM study reported the second discontinuation attempt of 70 patients with TFR rates at 12 and 24 mo of 48% and 42%, respectively[59]. Importantly, no patient progressed toward advanced-phase CML and 76% of patients regained at least a $MR^{4.5}$ with a median of 6.5 mo, while 18% regained MMR with a median of 4.6 mo. The treatment-free remission accomplished by dasatinib (TRAD) study aimed to determine whether patients could reach TFR in a second discontinuation attempt after failing a first discontinuation attempt with imatinib and re-initiating treatment with dasatinib. However, the preliminary second discontinuation results were disappointing, with 84% of patients losing molecular response after a median of 3.7 mo[60]. However, these data argue in favor of the safety of a second discontinuation attempt.

Since the molecular factors associated with TFR are yet to be determined for a first discontinuation attempt, it is too early to indicate possible factors that may influence the success of a second TKI discontinuation attempt. Nevertheless, analysis of RE-STIM data revealed that for patients who had remained in DMR within the first 3 mo upon TKI re-initiation following a first unsuccessful TKI discontinuation attempt, the TFR rate at 24 mo was 72% compared to 36% who did not[59]. Also, results from the TRAD study suggested that one additional month of first TFR duration correlated with a 51.5% reduced risk of molecular relapse in the second discontinuation attempt[60].

Patient perspective

It is important that medical practitioners consider the patient's psychological and emotional factors, in addition to clinical variables, when selecting patients for discontinuation. The discontinuation of TKI treatment should have a positive effect on patient quality of life, which should be the primary objective of any discontinuation attempt.

Clinicians should inform patients of the possible disadvantages of a discontinuation attempt. For example, during the first years following TKI cessation, and particularly during the first 12 mo, patients are required to undertake more frequent molecular monitoring to detect possible loss of MR as soon as possible, meaning more blood tests and visits to the clinician. For example, patients in maintained DMR undergo controls every 3 or 6 mo, whereas for patients who discontinue TKI treatment, the controls are monthly for the first year, every 6–8 wk for the following 6 mo, and every trimester from 18 mo onwards. Moreover, approximately 30% of patients may experience temporary TKI withdrawal side effects, particularly during the first weeks after TKI suspension, such as musculoskeletal pain[61].

Indeed, there is a real need for quality of life analysis since current discontinuation guidelines do not address the psychological issues related to discontinuing TKI therapy and attempting TFR, such as the fear of disease recurrence or progression[62]. Studies are required that monitor the physical and psychological impact of discontinuation on the quality of life of patients who discontinue TKI treatment using a standardized and accredited questionnaire, such as the "Change of Health-related Profiles after Imatinib Cessation in Chronic Phase Chronic Myeloid Leukemia Patients" validated questionnaire[63], to help determine emotional characteristics that should be included in the eligibility criteria for patients and thus help refine criteria for future discontinuation attempts. Similarly, very little information exists on the impact on quality of life of patients treated with second-generation TKIs. It is a possibility that those patients with a higher incidence of adverse effects would be more willing to attempt discontinuation[62] and that experiencing certain adverse effects could even be a factor in reaching TFR. For example, among patients with the myeloproliferative neoplasm essential thrombocythemia, the manifestation of pruritus, a common side effect for this neoplasia, was associated with a more proliferative and aggressive form of the disease[64].

CONCLUSION

To date, clinical trials and real-life discontinuation studies have confirmed the viability

and safety of the discontinuation of TKI treatment in the majority of patients with CML who undergo such an attempt. However, the current selection criteria for TKI discontinuation, as recommended by the NCCN and ELN guidelines, are quite restrictive and so the number of eligible CML patients are limited.

The identification of predictive factors for TFR in CML will inform the clinic on the best candidates to include in future discontinuation attempts and will help define criteria for safer discontinuation attempts with a greater probability of success. Moreover, it would potentially give more patients a chance at stopping TKI treatment. The identification of CML patients with a higher probability of achieving TFR after TKI discontinuation would bring with it substantial savings for national health systems. At present, TKI treatment costs approximately 30000-45000 € per year per patient in most European countries, although this is substantially reduced in the case of generic imatinib. Indeed, the saving would be even greater, since the health system would not have to treat the appearance of adverse effects often associated with TKI treatment, including important cardiovascular comorbidities, hepatic toxicity, or pleural effusion.

Current predictive indicators of the maintenance of TFR include factors related to the duration of TKI treatment and the duration and depth of the patient's MR prior to discontinuation. Some immune factors also appear to be important in determining whether TKI discontinuation is successful.

However, future studies are required to elucidate biomarkers predictive of TFR after discontinuing TKI treatment. Besides increasing our understanding of the underlying molecular mechanisms of this pathology, such studies would help refine the discontinuation criteria and may identify novel prospective therapeutic targets for CML. Thus, the determination of the molecular factors that influence TFR would be a significant advancement in personalized medicine.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 1008-1017

DOI: 10.5306/wjco.v11.i12.1008

ISSN 2218-4333 (online)

MINIREVIEWS

Fluoropyrimidine-induced cardiotoxicity

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Author contributions: Deac AL performed the majority of the writing, designed the tables and figures; Deac AL, Burz CC, Bocsan IC, Buzoianu AD designed the study; Deac AL performed the research on medical literature; all authors have read and approved the final manuscript.

Conflict-of-interest statement: No conflict of interest.

Manuscript source: Unsolicited manuscript

Specialty type: Oncology

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Abstract

Cardio-oncology is a discipline based on early screening, monitoring, and treating chemotherapy-induced cardiotoxicity. There are many chemotherapeutics known for their cardiac toxic effects, including fluoropyrimidines. Fluoropyrimidine represents the cornerstone of many types of cancer and each year almost two million cancer patients undergo this treatment. Fluoropyrimidine-induced cardiotoxicity can be manifested in several forms, from angina pectoris to sudden death. This paper is a review of how the cardiotoxicity of fluoropyrimidines is presented, the mechanisms of its occurrence, its diagnosis, and management.

Key Words: Fluoropyrimidines; Cancer treatments; Cardiotoxicity; Rechallenge; Prevention; Antidote

Core Tip: There are several reviews and cases which showed fluoropyrimidine-induced cardiotoxicity. However, this mini-review includes useful information on clinical manifestations, pathophysiological mechanisms, diagnosis, and management of fluoropyrimidine-induced cardiotoxicity.

Citation: Deac AL, Burz CC, Bocsan IC, Buzoianu AD. Fluoropyrimidine-induced cardiotoxicity. *World J Clin Oncol* 2020; 11(12): 1008-1017

URL: https://www.wjgnet.com/2218-4333/full/v11/i12/1008.htm

Country/Territory of origin: Romania

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 8, 2020
Peer-review started: June 8, 2020
First decision: September 18, 2020
Revised: September 27, 2020
Accepted: October 20, 2020
Article in press: October 20, 2020
Published online: December 24, 2020

P-Reviewer: Ebrahimifar M, Lee JI
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Wang LL

DOI: https://dx.doi.org/10.5306/wjco.v11.i12.1008

INTRODUCTION

Fluoropyrimidine-based treatments are one of the most frequently used methods of chemotherapy worldwide. The fluoropyrimidine drugs include 5-fluorouracil (5-FU), Capecitabine, Tegafur, S-1, and TAS-102. Fluoropyrimidines are useful in the treatment of head and neck cancer, breast cancer, esophageal cancer, gastric cancer, pancreatic cancer, and colorectal cancer, and it is estimated that more than 2 million patients are being treated with fluoropyrimidines[1,2]. The toxicity associated with fluoropyrimidine chemotherapy affects almost 30% of patients with more than 10% severe toxicity (CTC-AE grade ≥ 3) requiring hospitalization, and in 0.5%-1% of cases, the toxicity is lethal[3,4].

The most known cause of fluoropyrimidine toxicity is the deficiency of dihydropyrimidine dehydrogenase (DPD), a crucial enzyme in fluorouracil metabolism, which is encoded by the *DPYD* gene[4]. DPD levels show an important intra- and inter-individual variability which influences the patient's response to fluoropyrimidine in terms of efficacy, resistance, and toxicity[5]. Deleterious polymorphism of *DPYD* represents the main cause of DPD deficiency. The most common *DPYD* variants associated with toxicity during treatment with fluoropyrimidine are DPYD*2A (IVS14+1G>A, c.1905+1G>A), DPYD*9B (c.2846A>T), DPYD*13 (c.1679T>G), and HapB3 (c.1129-5923C>G)[6-9].

Fluoropyrimidine toxicity can be manifested through hematological non-cumulative toxicity most common in bolus infusion (anemia, neutropenia, thrombocytopenia), immediate digestive toxicity (nausea, vomiting, diarrhea, stomatitis, ileitis), alopecia in the case of continuous perfusion, thrombophlebitis and photosensitivity along the vein pathway, neurological toxicity if in high doses (cerebellar ataxia), ophthalmological toxicity through tear excretion (conjunctivitis, tear hypersecretion), skin toxicity usually aggravated by sun exposure (hand-foot syndrome, hyperpigmentation, hives, rash), and reversible cardiac toxicity following continuous perfusion (angina pectoris, unstable angina pectoris, arrhythmias, myocardial infarction, heart failure, myocardial necrosis)[10].

CARDIOTOXICITY GENERALITIES

Chemotherapy-related cardiac dysfunction is one of the chemotherapy side effects that can appear even 20 years after treatment with an incidence of 10%[11]. Chemotherapy-related cardiotoxicity can be due to the direct effect of chemotherapeutic agents on the entire cardiovascular system or indirectly through thrombogenic status or alteration of hemodynamic flow during treatment[12]. The European Society of Cardiology (ESC) defines cardiotoxicity as the decrease in left ventricular ejection fraction with more than 10% of the normal value or a decrease of more than 15% of the overall longitudinal deformation of the cord while preserving the ejection fraction[13]. Two types of cardiotoxicity have been described: (1) Type I, irreversible, dose-related, and caused by free radical formation, oxidative stress and myocyte fiber rearrangements, and mitochondrial dysfunction, *e.g.*, anthracycline-induced toxicity; and (2) Type II, reversible, not dose-related and is not associated with structural changes and can be induced by biological therapy, *e.g.*, Trastuzumab[12-15]. Cardiotoxicity manifests itself in the form of hypertension, arrhythmias, myocardial dysfunction, coronary artery disease, sinus node dysfunction, atrioventricular block, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension, pericardial complications, and heart failure[12,13].

FLUOROPYRIMIDINE-INDUCED CARDIOTOXICITY

Fluoropyrimidines produce type II, reversible cardiotoxicity. The incidence of fluoropyrimidine-induced cardiotoxicity ranges from 1% to 18%[16,17]. The most common symptom of fluoropyrimidine cardiotoxicity is chest pain[16,17]. Other symptoms that may occur are palpitations, dyspnea, hypertension, or hypotension, while less common manifestations include myocardial infarction, reversible

cardiomyopathy, myopericarditis, congestive heart failure, tachyarrhythmias, coronary dissection, cardiogenic shock, and sudden death[18]. Another manifestation of cardiotoxicity is the development of silent cardiac ischemia. Prospective and retrospective studies have reported electrocardiography (ECG) changes of silent ischemia ranging from 4% to 88%[18].

Among the proposed risk factors for fluoropyrimidine cardiotoxicity are older age, concurrent radiotherapy or history of chest radiotherapy, concurrent administration of cardiotoxic drugs, history of cardiovascular diseases or the presence of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking[17]. Studies have shown that the continuous infusion of 5-FU compared with bolus administration is associated with a higher incidence for cardiac adverse events[17,19]. Kosmas *et al*[19] also demonstrated that the addition of Leucovorin (LV), a potentiator of 5-FU activity in 24 h continuous infusion and five days of 5-FU, may increase the incidence of cardiac adverse events (13%) compared with the same schedule of 5-FU administration but without LV addition (5%). Furthermore, de Forni *et al*[28] examined 367 patients receiving a continuous infusion of 5-FU at doses between 600-1000 mg/m^2/day and showed higher toxicity at doses more than 800 mg/m^2/day. Symptoms usually appear in the first 72 h during the first cycle of 5-FU, but they can develop any time during the course of treatment and even a couple of days after the end of treatment[20].

MECHANISM OF CARDIOTOXICITY

The pathogenesis of fluoropyrimidine-induced cardiotoxicity has not been fully elucidated. Several hypotheses have been proposed, such as vasoconstriction, direct myocardial toxicity, endothelial dysfunction, and a hypercoagulable status leading to thrombosis, all of them leading to cardiac damage (Figure 1)[16].

The coronary vasospasm and the ischemic events it produces are probably the most studied cardiac adverse events of fluoropyrimidines. Patients usually present symptoms and signs of acute coronary syndrome, possibly increased troponin in blood levels, and often ST segment changes on ECG[16,21]. ST-T wave changes are seen in 65% of cases and elevated cardiac enzymes only in 7%[21]. Luwaert *et al*[22] in one of the first reports of coronary vasospasm associated with fluoropyrimidine cardiotoxicity, performed angiography during the 5-FU infusion and observed vasospasm of the left circumflex artery, which was resolved by an intracoronary injection of isosorbide dinitrate. Despite this, coronary angiography was often normal without any evidence of a thrombotic event[23]. Mosseri *et al*[24] showed that the activation of protein kinase C (PK-C), a subcellular mediator of vascular smooth muscle tone, can also be a mediator of 5-FU-induced vasoconstriction and 5-FU causes direct endothelium-independent vasoconstriction of vascular smooth muscle *in vitro*. In other studies, Thyss *et al*[25] and Porta *et al*[26] found high levels of endothelin-1, a regulatory vasoconstrictor, in patients with 5-FU-induced cardiotoxicity. The vasodilator therapy included non-dihydropyridine calcium channel blockers such as Verapamil or Diltiazem, and nitrates have been shown to be effective in resolving symptoms and ECG changes[27].

Another mechanism of fluoropyrimidine cardiotoxicity is represented by direct myocardial injury highlighted by global systolic dysfunction[28]. Following a ventricular biopsy, Kuropkat *et al*[29] reported the role of sarcoplasmic reticulum dilatation in cardiotoxicity, a mechanism similar to the cardiotoxicity of anthracyclines.

The accumulation of alpha-fluoro-beta-alanine (FbAL), a metabolite of 5-FU metabolism, which is converted to fluoroacetate and then to fluorocitrate, can cause an impairment in the Krebs cycle leading to citrate accumulation and downstream depletion of ATP resulting in ischemia[30,33]. FbAL involvement as a direct mediator of cardiotoxicity was demonstrated by Muneoka *et al*[30] who showed elevated levels of FbAL in a patient suffering from a myocardial infarction after administration of 5-FU. The same patient was later treated with S-1, a combination of ftorafur (FT), oxonic acid and gimeracil at a molar ratio of 1:0.4:1, and did not experience any associated cardiac adverse effects[30,31]. Kwakman *et al*[32] demonstrated in a series of seven patients that the rechallenge with S-1 after Capecitabine-induced cardiotoxicity was without recurrent cardiac side effects. An explanation for the lack of associated cardiotoxicity of S1 is due to gimeracil, a DPD-inhibitor, which increases the concentration of 5-FU, leading to a lower concentration of FbAL[33,34].

The dysfunction of vascular endothelium followed by thrombosis, independent of vasoconstriction, seems to be a possible mechanism associated with fluoropyrimidine-

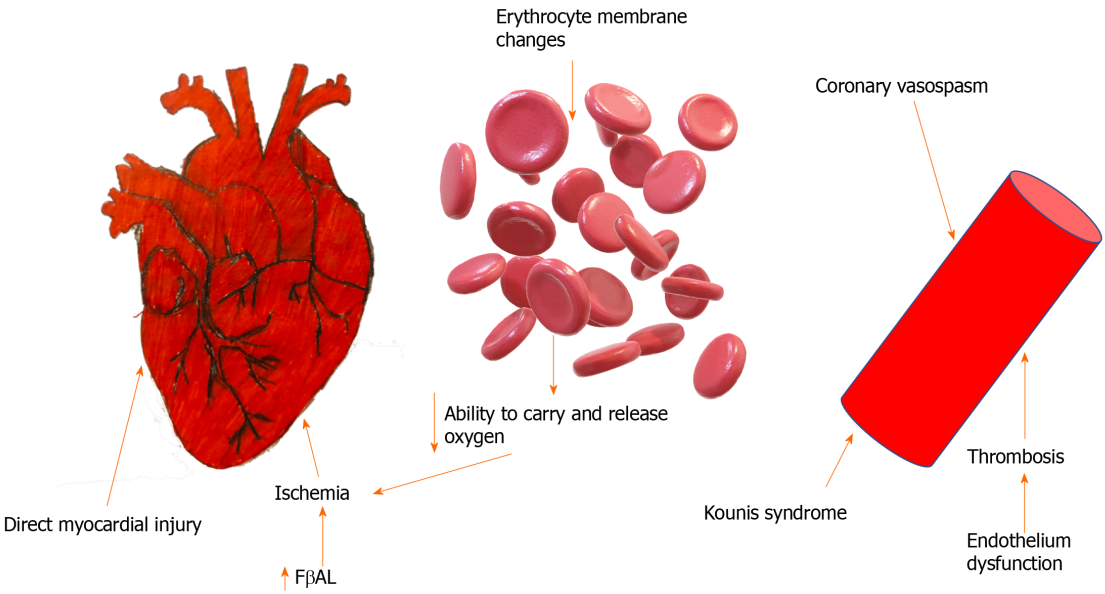

Figure 1 Proposed mechanism of fluoropyrimidine-induced cardiotoxicity.

induced cardiotoxicity. Many studies on animals have analyzed the effect of 5-FU on vascular endothelial cells and showed direct endothelial dysfunction and platelet and fibrin accumulation[34]. Kuzel *et al*[35] reported an increase in fibrinopeptide A and a decrease in protein C in the presence of 5-FU, which together confer a more susceptible environment for thrombus formation.

In another study, Spasojević *et al*[36] demonstrated that 5-FU can cause changes in the shape of the erythrocyte membrane and lead to increased blood viscosity and decreased ability to carry and release oxygen, thus causing myocardial ischemia. Focaccetti *et al*[37] demonstrated increased reactive oxygen species (ROS) in cardiomyocytes and endothelial cells, leading to 5-FU induced apoptosis. In guinea pig hearts treated with 5-FU, decreased levels of superoxide dismutase and glutathione peroxidase have been observed, supporting the theory of oxidative stress[38]. Eskandari *et al*[39] support the same theory in their study and demonstrated that fluoropyrimidine cardiotoxicity was associated with the formation of ROS, depletion of glutathione and lipid peroxidation, resulting in an increase in oxidative stress, which correlated with mitochondrial dysfunction that triggers caspase-3 and activates apoptosis or necrosis.

Another mechanism suggested by Karabay *et al*[40] is Kounis syndrome, an acute coronary syndrome caused by an allergic reaction which can precipitate the release of inflammatory mediators that can break the atherosclerotic plaques caused by 5-FU exposure, causing coronary vasospasm which partially responds to antihistamine and corticosteroid therapy.

DIAGNOSIS OF FLUOROPYRIMIDINE-INDUCED CARDIOTOXICITY

There is no specific test for the diagnosis of fluoropyrimidine-induced cardiotoxicity, and it is usually guided by anamnesis of cardiovascular risk factors and diseases followed by a cardiologic examination, electrocardiography, cardiac enzymes, and echocardiography.

In cancer patients with previous coronary artery disease and indications of fluoropyrimidine-based chemotherapy, additional attention must be paid to risk factors such as smoking, hypertension, diabetes mellitus, and dyslipidemia followed by pharmacological treatment, before starting treatment with fluoropyrimidines[13].

Cardiac 12-lead ECG monitoring is the most feasible method for early detection of cardiac adverse events during the course of 5-FU chemotherapy[41]. ECG is recommended for all patients before and during chemotherapy. The most common findings on ECG are ST elevation, ST depression, QT prolongation and inverted T waves[41]. Holter monitoring represents a method with a higher sensitivity, but no recommendations have been made for this technique. ECG changes may occur early during the continuous infusion of 5-FU or in the first days of Capecitabine

administration[42,43].

The brain natriuretic peptide (BNP), troponin I and T (TnI and TnT) and creatine phosphokinases (CK and CK-MB) are well known markers for the diagnosis and prognosis of heart diseases. TnI is a protein specific to the myocardial tissue and a component of the troponin protein complex; an increase in serum TnI level is an early and specific sign of myocardial injury, but no significant changes have been found in patients with fluoropyrimidine-induced cardiotoxicity[42]. The European Society of Medical Oncology (ESMO), in their clinical practice guidelines regarding fluoropyrimidine cardiotoxicity, recommends monitoring of TnI and brain natriuretic peptide (BNP) in patients with symptoms or signs of cardiac ischemia as a grade C III/IV level of evidence[44]. Holubec *et al*[45] determined BNP and TnI before and after 5-FU chemotherapy and showed increased levels of TnI in 57% of cases and BNP in 57% of cases, but no correlations have been made with clinical signs of cardiotoxicity. Data on the clinical relevance of cardiac biomarkers are very controversial; several studies have shown that BNP and troponins remain unchanged despite the occurrence of cardiac adverse events[42,45]. In only one study, out of 26 patients who experienced cardiac adverse events, seven had an increase in CK-MB level; the remaining studies did not show changes in CK-MB in patients with cardiotoxicity[19,46].

Another way to assess fluoropyrimidine cardiotoxicity is by echocardiography and imaging techniques. Fluoropyrimidine-induced cardiotoxicity can affect ventricular systolic and diastolic kinetics by reducing left ventricular ejection fraction[47]. Evidence of the role of echocardiography is also controversial; some authors failed to detect changes in diastolic and systolic function, while others such as Turan *et al*[48] and Wacker *et al*[49] found a significant correlation between a decrease in diastolic and systolic function and fluoropyrimidine cardiotoxicity in 18.7% of patients after the first cycle and in 10.5% of patients three months after chemotherapy[42,46].

MANAGEMENT

In cases of acute fluoropyrimidine cardiotoxicity, the first step should be to stop the treatment immediately and treat the symptoms with antianginal drugs such as nitrates, calcium channel blockers, and antiplatelets[50]. Symptom cessation has been shown in 69% of cases[50]. For high-risk patients with suspected acute coronary syndrome, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend an urgent coronarography with revascularization, and for low risk patients with persistent minor or mild symptoms, it is suggested to consider a stress test or coronary computed tomography angiography[17,51].

Rechallenging a patient with fluoropyrimidine may cause a recurrence of cardiac symptoms in 45%-90% of patients and a death rate of 18%[52,53]. Clavel *et al*[54] reported 4 cases of myocardial necrosis and 4 cases of cardiogenic shock in a series of 28 rechallenged patients. Given all the existing scientific evidence, several strategies have been proposed depending on what other therapeutic options exist and the need to keep fluoropyrimidines in patient treatment. If the patient still needs fluoropyrimidine-based chemotherapy, the following strategies should be considered: (1) Switch from continuous infusion to 5-FU bolus administration; (2) Dose reduction along with antianginal drug prophylaxis; and (3) Other oral fluoropyrimidines such as uracil-tegafur or S-1, both drugs contain either uracil which competes with 5-FU for DPD and therefore reduces the degradation of 5-FU into FbAL, or gimeracil which as we have seen before is a DPD inhibitor and also prevents FbAL formation[52]. Even if we know about the possible benefit of those two prodrugs, we still need more studies to prove the lower cardiotoxicity and trials of equalization with 5-FU and Capecitabine. Another option is TAS-102, the combination of trifluridine (TFD) and tipiracil, the last fluoropyrimidine approved in chemorefractory colorectal cancer. TFD exhibits two anti-tumor mechanisms: Inhibition of TS and the creation of single-strand DNA breaks by incorporating the triphosphate form into DNA in the place of thymidine[55,56]. The addition of tipiracil inhibits trifluridine degradation and increases bioavailability[56]. The fact that TAS-102 is not metabolized by DPD explains the lack of cardiac adverse events[56].

Clasen *et al*[57] in a case series of 11 patients with previous fluoropyrimidine cardiotoxicity, successfully rechallenged with the same drug, and based on their experience, they made the following recommendations: (1) Switch from continuous administration to bolus; (2) Pretreatment with isosorbide mononitrate for 3 to 4 h and extended-release nifedipine before 5-FU administration; (3) Treatment with short-

acting diltiazem and sublingual nitroglycerin during the treatment with 5-FU; (4) Posttreatment with nifedipine and isosorbide mononitrate 12 h after the first dose of antianginal pretreatment; and (5) Posttreatment with nifedipine 24 h after the first dose.

Another alternative to fluoropyrimidine is represented by Raltitrexed (Tomudex), a quinazoline folate analogue, which inhibits thymidylate synthase (TS), thereby blocking DNA synthesis[58]. The results of two prospective studies proposed Raltitrexed as an option for colorectal cancer patients with cardiovascular risk factors or fluoropyrimidine cardiotoxicity. Ransom *et al*[59] published the final results of the Australasian Gastrointestinal Trials Group ARTIC study and reported no cardiac adverse effects attributed to Raltitrexed in 42 patients who previously experienced fluoropyrimidine cardiotoxicity. In the second study, Raltitrexed was used in 111 colorectal cancer patients who presented fluoropyrimidine cardiotoxicity and important cardiovascular risk factors[60]. The study reported five patients who experienced cardiac adverse events during treatment with Raltitrexed[60]. Both of these studies indicate that Raltitrexed can be a safe alternative in patients after cardiac adverse events.

In the desire to counterbalance the severe side effects or fluoropyrimidine overdose, uridine triacetate (UT, Vistogard) was approved by the FDA in 2015 as an antidote based on two open-label, single-arm trials which demonstrated a survival benefit in 96% of cases[61,62]. Uridine triacetate is an oral pyrimidine analogue of uridine, which competes with fluorouridine-triphosphate incorporation into RNA and this way improves fluoropyrimidine toxicity[17,61]. Uridine triacetate can be used in the first 96 h after the last dose of 5-FU or Capecitabine for early-onset, severe or life-threating toxicity such as severe neutropenia, gastrointestinal toxicity or cardiotoxicity unresponsive to drug cessation and antianginal therapy (Table 1)[62,63].

Phenotyping and genotyping DPD activity before starting the treatment with fluoropyrimidine can be useful to detect the patients who are already more predisposed to experiencing severe adverse events. In a case report, Saif *et al*[64] showed the presence of both *DPYD* and *TYMS* gene mutations in a patient who developed a severe Takotsubo cardiomyopathy after receiving fluoropyrimidine treatment. We need more studies to evaluate the possible correlation between DDP deficiency and cardiotoxicity.

CONCLUSION

Fluoropyrimidine cardiotoxicity may be more common than is currently diagnosed due to the multiple indications of this class. Despite the fact that 5-FU and Capecitabine cardiotoxicity is not very common, it can be unpredictable and sometimes fatal. Even if some of the fluoropyrimidine cardiotoxicity mechanisms are known, we still need more studies to discover new mechanisms or to explore the mechanisms already known and the possible relationship with *DPYD* mutation or other genes involved in the metabolism of fluoropyrimidines. There is currently no consensus on the treatment and prophylaxis of these adverse events, the only certainty is the need for immediate discontinuation of fluoropyrimidine chemotherapy and treatment of symptoms. Rechallenging the patient with 5-FU or Capecitabine is feasible, but it comes with certain risks such as the recurrence of cardiac toxicity or more severe forms of it. If a decision is made to continue this treatment, antianginal therapy may prevent ischemic events. In such a scenario, dose reduction is also recommended. We still need more studies and tools to identify the patients who will develop cardiotoxicity due to fluoropyrimidine-based chemotherapy and to determine how we can prevent it.

Table 1 Management of fluoropyrimidine-induced cardiotoxicity and rechallenge

Management of acute cardiotoxicity	Rechallenge with fluoropyrimidine	Antidote
Stop fluoropyrimidine chemotherapy	Switch from continuous infusion to bolus administration	Uridine triacetate
Administration of antianginal drugs and antiplatelets	Dose reduction with antianginal drugs administration: (1) Preatreatment 3 to 4 h before fluoropyrimidine; (2) Administration during the treatment with 5-FU; (3) Posttreatment 12 or 24 h after fluoropyrimidine	
Monitor patient's cardiac enzymes, ECG	Use of alternative fluoropyrimidine agents (S1, TAS-102)	
Coronarography with revascularization if acute coronary syndrome is suspected	Use of alternative non-fluoropyrimidine agents	
Stress test or coronary CT angiography in patient's with persistent minor or mild symptoms		

ECG: Electrocardiography; CT: Computed tomography; 5-FU: 5-fluorouracil.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 1018-1028

DOI: 10.5306/wjco.v11.i12.1018

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Retrospective Study

Forkhead box P3 and indoleamine 2,3-dioxygenase co-expression in Pakistani triple negative breast cancer patients

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Institutional review board statement: The study was

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Abstract

BACKGROUND

Forkhead box P3 (FOXP3) is a specific marker for immunosuppressive regulatory T (T-reg) cells. T-regs and an immunosuppressive enzyme, indoleamine 2,3-dioxygenase (IDO), are associated with advanced disease in cancer.

AIM

To evaluate the co-expression of FOXP3 and IDO in triple negative breast cancer (TNBC) with respect to hormone-positive breast cancer patients from Pakistan.

METHODS

Immunohistochemistry was performed to analyze the expression of FOXP3, IDO, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor on tissues of breast cancer patients (n = 100): Hormone-positive breast cancer (n = 51) and TNBC (n = 49). A total of 100 patients were characterized as FOXP3 negative *vs* positive and further categorized based on low, medium, and high IDO expression score. Univariate and multivariate logistic regression models were used.

RESULTS

reviewed and approved by the Shaukat Khanum Memorial Cancer Hospital and Research Centre Institutional Review Board.

Conflict-of-interest statement: Authors declare no conflict of interests for this manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at kashifasghar@skm.org.pk. Consent was not obtained but the presented data are anonymized and risk of identification is low. No additional data are available.

Manuscript source: Unsolicited manuscript

Specialty type: Oncology

Country/Territory of origin: Pakistan

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 13, 2020
Peer-review started: April 13, 2020
First decision: August 9, 2020
Revised: August 24, 2020
Accepted: October 27, 2020
Article in press: October 27, 2020
Published online: December 24, 2020

Out of 100 breast tumors, 25% expressed FOXP3 positive T-regs. A significant co-expression of FOXP3 and IDO was observed among patients with TNBC (P = 0.01) compared to those with hormone-positive breast cancer. Two variables were identified as significant independent risk factors for FOXP3 positive: IDO expression high (adjusted odds ratio (AOR) 5.90; 95% confidence interval (CI): 1.22-28.64; P = 0.03) and TNBC (AOR 2.80; 95%CI: 0.96-7.95; P = 0.05).

CONCLUSION

Our data showed that FOXP3 positive cells might be associated with high expression of IDO in TNBC patients. FOXP3 and IDO co-expression may also suggest its involvement in disease, and evaluation of FOXP3 and IDO expression in TNBC patients may offer a new therapeutic option.

Key Words: Forkhead box P3; Indoleamine 2,3-dioxygenase; Triple negative breast cancer; T-regs; Immunotherapy; Cancer

Core Tip: Forkhead box P3 (FOXP3) positive cells might be associated with high expression of indoleamine 2,3-dioxygenase (IDO) in triple negative breast cancer (TNBC) patients. Evaluation of FOXP3 and IDO expression in TNBC patients may provide a novel effective therapeutic strategy.

Citation: Asghar K, Loya A, Rana IA, Bakar MA, Farooq A, Tahseen M, Ishaq M, Masood I, Rashid MU. Forkhead box P3 and indoleamine 2,3-dioxygenase co-expression in Pakistani triple negative breast cancer patients. *World J Clin Oncol* 2020; 11(12): 1018-1028
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/1018.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.1018

INTRODUCTION

Forkhead box P3 (FOXP3) is a part of the forkhead/winged-helix family of transcription regulators[1]. FOXP3 is a specific marker for regulatory T cells (T-regs)[2], which are crucial mediators of peripheral tolerance[3]. FOXP3 expression has been reported in breast cancer[4-6], and its quantification in this malignancy can be used as an effective tool to monitor disease progression and predict prognosis[7]. The cell count of FOXP3 expressing T-regs increases steadily in breast cancer with increasing stage of disease[7]. The mechanisms underlying are still not clear. High numbers of FOXP3 expressing T-regs provide poor prognosis for relapse-free survival in patients with invasive carcinoma[7], but Lee *et al*[8] observed the prognostic significance of FOXP3-positive T-regs compared to FOXP3-negative T-regs in triple negative breast cancer (TNBC). Furthermore, they found that improved survival was linked with FOXP3-postive T-regs in TNBC. This finding was in contrast with other types of cancers[8]. Therefore, further studies are required to link FOXP3- positive T-regs to good or worse prognosis.

An immunosuppressive enzyme, indoleamine 2,3-dioxygenase (IDO), catabolizes tryptophan into kynurenines[9,10]. IDO has the ability to inhibit the immune responses and produce immunosuppression through the differentiation and maturation of T-regs[11]. On the other hand, tryptophan depletion by IDO affects the cytotoxicity of T cells[12]. It has been reported that tryptophan downstream metabolites induce apoptosis of T cells *in vitro*[13]. IDO plays a role in the cancer immune-escape mechanism[14,15]. Evidence has suggested that overexpression of IDO has been observed in both antigen-presenting cells and tumor cells in tumor draining lymph nodes[16]. IDO overexpression may lead to recruitment of T-regs in breast tumor microenvironment and promote metastasis[17].

TNBC is characterized by lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2)[18]. TNBC is a more aggressive tumor than other breast cancers types[19]. Our goal was to quantify FOXP3 expression in relation with IDO expression in patients diagnosed with breast cancer

P-Reviewer: Scaggiante B
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Wang LL

from Pakistan. Pakistan has the highest incidence of breast cancer cases in its region. We further investigated the numbers of FOXP3-positive T-regs in TNBC patients compared to hormone-positive breast cancer patients.

MATERIALS AND METHODS

Sampling and patient data

For this retrospective analysis, archived formalin-fixed paraffin-embedded (FFPE) blocks of 100 breast cancer patients were retrieved from the pathology department. The study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC) Lahore, Pakistan. All the patients were diagnosed with breast cancer between 2007 and 2009, and all patients selected were treatment naïve. Tumor grade was allocated using the Nottingham Histologic Score. Immunohistochemistry was performed to identify the expression of ER, PR, and HER2 by using standard methods[20]. Clinico-pathological data were obtained from medical reports of the patients. The current study was approved by the Institutional Review Board (IRB) of the SKMCH&RC (#IRB-16-08) and was exempted from informed consent in agreement with the Declaration of Helsinki Guidelines. We used the specimens of hospital registered patients. The data were recorded in such a manner that the individual identity could not be recognized. This study does not include any procedures that would normally require informed consent outside the context of the study.

Immunohistochemical staining of FOXP3 and IDO

Bond III Leica automated system (Leica Biosystems Melbourne, Australia) was used to perform the immunohistochemistry. Briefly, two sections of FFPE blocks of the same patients were obtained. Bond Dewax solution (#AR922, Leica) was used to deparaffinize the slides. Bond ER-2 (#AR9640, Leica) was used to perform heat induced epitope retrieval on the automated system for 20 min. The primary antibodies FOXP3 (Abcam, #ab22510, Cambridge, United Kingdom) or IDO1 (Abcam, #ab55305) were used at a 1:50 and 1:200 dilution, respectively, in primary antibody diluent and incubated for 5 min. Bond™ polymer refine detection kit was used to visualize FOXP3 and IDO labeling. Peroxidase block was applied for 5min. The slides were then incubated with post primary rabbit anti mouse immunoglobulin G for 8 min, followed by incubation with polymer anti-rabbit poly-horseradish peroxidase-immunoglobulin G for 8 min. Three prime-diaminobenzidine tetrahydrochloride hydrate was applied for 10 min. Counterstaining was performed with hematoxylin for 5 min. Two pathologists were involved in the study, and they conducted a blind histopathologic assessment. The discrepancies between the two pathologists were reviewed mutually to reach the consensus. The mean score of both pathologists was considered as the final score. Staining of at least 25% of cells was considered positive for FOXP3. FOXP3 expression had nuclear localization[6]. IDO staining evaluation was based on two factors: (1) Intensity of cytoplasmic staining (0 to 3); and (2) Percentage of cells staining positive (0 to 3). They were categorized as low (1-3), medium (4-6), and high (7-9).

Statistical analysis

Statistical analysis was carried out using SPSS software (version 20.0; SPSS, Armonk, NY, United States). For continuous variables, mean and standard deviation were used. For categorical variables, percentages (proportions) were used. Chi-square or Fisher exact test was performed for bivariate analysis. Independent *t*-test was performed for continuous explanatory variables such as age. Risk factors were identified by using the univariable and multivariable logistic regression model.

RESULTS

Patient baseline characteristics

A total of 100 breast cancer patients were included in this study with an average age of 48 years. Majority of patients belonged to the Punjab region (88%). Fifty-seven percent of tumors were T2/T3, and 7% tumors were T1 (Tumor Node Metastasis classification). According to the grade distribution, 56% presented grade III. Fifty percent of patients were positive for node, and 49% were positive for metastasis. PR (26%), HER2-neu (26%), and ER (31%) were expressed in the tumor tissue (Table 1).

Table 1 Baseline characteristics of breast cancer patients

Variables	Levels	Total, *n* %
Age	mean ± SD	48.28 ± 11.83
Region	Punjab	88 (88.0%)
	Khyber Pakhtunkhwa	7.0 (7.0%)
	Kashmir	3.0 (3.0%)
	Sindh	2.0 (2.0%)
Histology	Ductal	91 (91.0%)
	Others	9.0 (9.0%)
Grade	II	35 (35.0%)
	III	56 (56.0%)
	UNK	09 (9.0%)
Tumor size	T1	7.0 (7.0%)
	T2/T3	57 (57.0%)
	UNK	36 (36.0%)
Nodes	Negative	37 (37.0%)
	Positive	50 (50.0%)
	UNK	13 (13.0%)
Metastasis	Negative	38 (38.0%)
	Positive	49 (49.0%)
	UNK	13 (13.0%)
Estrogen receptor	Negative	69 (69.0%)
	Positive	31 (31.0%)
Progesterone receptor	Negative	74 (74.0%)
	Positive	26 (26.0%)
HER2 status	Negative	74 (74.0%)
	Positive	26 (26.0%)
TNBC	No	51 (51.0%)
	Yes	49 (49.0%)
Status	Alive	50 (50.0%)
	Death	35 (35.0%)
	Lost to follow-up	15 (15.0%)
FOXP3	Negative	75 (75.0%)
	Positive	25 (25.0%)
IDO score	Low	24 (24.0%)
	Medium	27 (27.0%)
	High	49 (49.0%)

UNK: Indicates missing data. FOXP3: Forkhead box P3; HER2: Human epidermal growth factor receptor; IDO: Indoleamine 2,3-dioxygenase; TNBC: Triple negative breast cancer; SD: Standard deviation.

We have further categorized baseline characteristics based on TNBC and hormone positive breast cancer in Table 2.

Table 2 Comparative characteristics of triple negative breast cancer and hormone positive breast cancer patients

Variables	Levels	Triple negative breast cancer, *n* (%)	Hormone positive breast cancer, *n* (%)
Age	mean ± SD	47.24 ± 11.5	49.27 ± 12.0
Histology	Ductal	46 (50.5)	45 (49.5)
	Others	3 (33.3)	6 (66.7)
	Total	49 (49.0)	51 (51.0)
Grade	II	9 (25.7)	26 (74.3)
	III	37 (66.1)	19 (33.9)
	UNK	3 (33.3)	6 (66.7)
	Total	49 (49.0)	51 (51.0)
Tumor size	T1	4 (57.1)	3 (42.9)
	T2/T3	26 (45.6)	31 (54.4)
	UNK	19 (52.8)	17 (47.2)
	Total	49 (49.0)	51 (51.0)
Nodes	Negative	23 (62.1)	14 (37.8)
	Positive	21 (42.0)	29 (58.0)
	UNK	5 (38.4)	8 (61.6)
	Total	49 (49.0)	51 (51.0)
Metastasis	Negative	23 (60.5)	15 (39.5)
	Positive	21 (42.8)	28 (57.2)
	UNK	5 (38.4)	8 (61.6)
	Total	49 (49.0)	51 (51.0)

UNK: Indicates missing data. SD: Standard deviation.

Clinicopathological characteristics of breast cancer patients with FOXP3 expression

There were 25 out of 100 FOXP3 positive cases (Table 3). Based on immunohistochemistry analysis, FOXP3 expression had nuclear localization. All the cases were invasive ductal carcinoma. Furthermore, 18 out of 25 were TNBC patients. The data of 75 out of 100 FOXP3 negative cases are provided in supplementary data (Supplementary Table 1).

FOXP3 and IDO co-expression is associated with TNBC

In order to validate the immunosuppressive effect of FOXP3 and IDO co-expression, we categorized the patients into TNBC and hormone-positive breast cancer groups. The mean age at diagnosis of FOXP3 positive *vs* negative breast cancer cases was 47.32 ± 14.19 years and 48.60 ± 11.02 years, respectively (P = 0.64). The majority of patients had grade III tumor (n = 18) and grade II tumor (n = 07). There was a statistically significant association between FOXP3 and high expression of IDO (P = 0.01) and TNBC (P = 0.01), respectively. Remaining explanatory variables are presented in Table 4.

FOXP3 and IDO immunostaining

To evaluate the expression of FOXP3 and IDO, we selected FFPE tumor specimens of the same patients (n = 100). Out of 100 patients, 25 expressed FOXP3-positive T-regs, and 75 expressed FOXP3-negative T-regs (Figure 1). IDO positivity was found in all breast tumor specimens. Synchronal expression of FOXP3 and IDO is shown in Figure 1. Immunostaining of low, medium, and high IDO expression is provided in supplementary data (Figure 1).

Univariable and multivariable analysis

Table 5 summarizes the several clinicopathological features that were included in

Table 3 Clinicopathological characteristics of breast cancer patients with nuclear forkhead box P3 expression

Case	Histology	Age in yr	Grade	Nodes	Metastasis	ER	PR	HER2	TNBC
1	Ductal	28	3	0	-	-	-	-	+
2	Ductal	54	3	14	+	-	-	-	+
3	Ductal	67	3	1	+	-	-	-	+
4	Ductal	65	2	UNK	UNK	-	-	-	+
5	Ductal	45	3	13	+	-	-	-	+
6	Ductal	45	3	0	-	-	-	-	+
7	Ductal	55	3	0	-	-	-	-	+
8	Ductal	23	3	0	-	-	-	-	+
9	Ductal	47	2	0	-	-	-	-	+
10	Ductal	73	3	2	+	-	-	-	+
11	Ductal	35	3	0	-	-	-	-	+
12	Ductal	35	3	0	-	-	-	-	+
13	Ductal	52	3	UNK	UNK	-	-	-	+
14	Ductal	39	3	0	-	-	-	-	+
15	Ductal	48	3	0	-	-	-	-	+
16	Ductal	70	3	2	+	-	-	-	+
17	Ductal	40	3	13	+	-	-	-	+
18	Ductal	35	3	13	+	-	-	-	+
19	Ductal	43	3	0	UNK	-	-	+	-
20	Ductal	36	2	1	+	-	-	+	-
21	Ductal	45	3	UNK	UNK	+	+	-	-
22	Ductal	71	2	6	+	+	-	-	-
23	Ductal	30	2	17	+	+	+	-	-
24	Ductal	40	2	UNK	UNK	-	-	+	-
25	Ductal	62	2	0	-	+	+	+	-

UNK: Indicates missing data; Grade: Nottingham Histologic Score; Nodes: No. of nodes involved. ER: Estrogen receptor; HER2: Human epidermal growth factor receptor; PR: Progesterone receptor; TNBC (+): Triple negative breast cancer; TNBC (-): Hormone-positive breast cancer.

unadjusted and adjusted logistic regression model to identify the FOXP3 correlation with IDO expression and TNBC. Two variables were identified as significant independent risk factors for FOXP3 positive: IDO expression high [adjusted odds ratio (AOR) 5.90; 95% confidence interval (CI): 1.22-28.64; P = 0.03) and TNBC (AOR 2.80; 95%CI: 0.96-7.95, P = 0.05) in multivariable analysis.

DISCUSSION

The role of immunosuppression in cancer progression is currently evaluated in various cancers[21-23]. It has been established that immunological factors such as T-regs are involved in the progression of tumor through induction of immune tolerance in the tumor microenvironment[7,22]. T-regs are effective inhibitors of the immune system[22]. T-regs create immunosuppressive environment by suppressing effector immune cells[22]. They are also associated with poor clinical outcomes in various tumors[4,7]. FOXP3 is a specified marker for T-regs[2]. Several studies identified that FOXP3$^+$ T-regs infiltration in tumor microenvironment may affect breast cancer progression[7,24]. Bates *et al*[7] demonstrated that a high ratio of FOXP3 cells predict worse relapse-free survival and shorten overall survival in patients with invasive breast carcinoma[7]. In another

Table 4 Patients and tumor characteristics of forkhead box P3 negative *vs* positive

Variables	Characteristics	FOXP3 negative 75 (75.0%)	FOXP3 positive 25 (25.0%)	*P* value
Age (yr)	mean ± SD	48.60 ± 11.02	47.32 ± 14.20	0.64
IDO score	Low	22 (91.7%)	2 (8.3%)	0.01[a]
	Medium	23 (85.2%)	4 (14.8%)	
	High	30 (61.2%)	19 (38.8%)	
Grade	II	28 (80.0%)	7 (20.0%)	0.21
	III	38 (67.9%)	18 (32.1%)	
Metastasis	Negative	27 (71.1%)	11 (28.9%)	0.45
	Positive	39 (79.6%)	10 (20.4%)	
Tumor size	T1	4 (57.1%)	3 (42.9%)	0.15
	T2/T3	46 (80.7%)	11 (19.3%)	
Lymph nodes involvement	Negative	26 (70.3%)	11 (29.7%)	0.29
	Positive	40 (80.0%)	10 (20.0%)	
Estrogen receptor	Negative	48 (69.6%)	21 (30.4%)	0.06
	Positive	27 (87.1%)	4 (12.9%)	
Progesterone receptor	Negative	52 (70.3%)	22 (29.7%)	0.06
	Positive	23 (88.5%)	3 (11.5%)	
HER2–neu receptor	Negative	53 (71.6%)	21 (28.4%)	0.19
	Positive	22 (84.6%)	4 (15.4%)	
Triple negative breast cancer	No	44 (86.3%)	7 (13.7%)	0.01[a]
	Yes	31 (63.3%)	18 (36.7%)	

[a]*P* < 0.05. IDO: Indoleamine 2,3-dioxygenase; HER2: Human epidermal growth factor receptor; FOXP3: Forkhead box P3; SD: Standard deviation.

Table 5 Univariable and multivariable logistic regression analysis for forkhead box P3-negative (reference) *vs* forkhead box P3-positive

Variables	Characteristics	Univariable analysis odds ratio (95%CI), *P* value	Multivariable analysis odds ratio (95%CI), *P* value
IDO score	Low	Ref.	Ref.
	Medium	1.91 (0.32-11.52), 0.50	2.32 (0.37-14.50), 0.37
	High	6.97 (1.50-33.10), 0.01[a]	5.90 (1.22-28.64), 0.03[a]
Triple negative breast cancer	No	Ref.	Ref.
	Yes	3.65 (1.36-9.80), 0.01[a]	2.80 (0.96-7.95), 0.05[a]

[a]*P* < 0.05. IDO: Indoleamine 2,3-dioxygenase.

study the researchers observed no difference in overall survival among patients expressing high or low FOXP3[25]. There is contradictory data regarding the involvement of FOXP3$^+$ T-regs in breast cancer patients. Nevertheless, we investigated FOXP3 positive *vs* negative expression in the current study. FOXP3 expression was identified in 25 breast cancer patients, and a majority of these patients displayed TNBC phenotype. Overall, 36.73% of TNBC patients expressed FOXP3 positive cells, while 13.72% of hormone positive breast cancer patients expressed FOXP3 positive cells. On the other hand, FOXP3 expression was not detected in 63.26% of TNBC patients and 86.27% of hormone positive breast cancer patients. Our findings of FOXP3 T-regs infiltration in TNBC patients is similar to several studies published before that identified the involvement of FOXP3 positive cells in breast cancer progression[7,24].

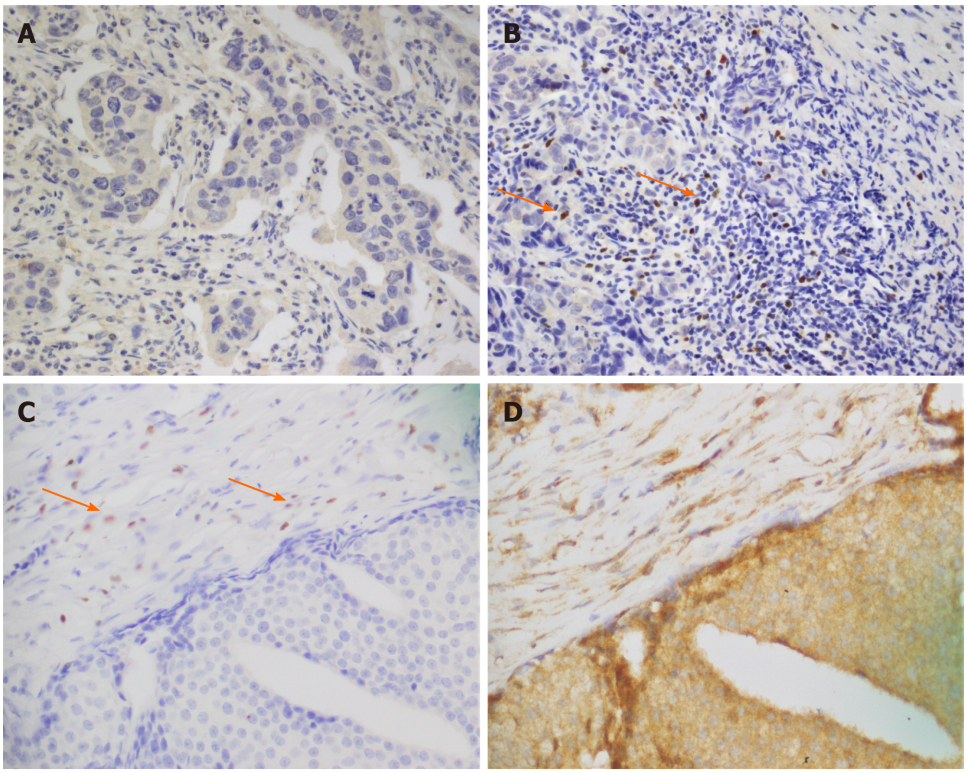

Figure 1 Formalin-fixed paraffin-embedded tumor specimens. A and B: Forkhead box P3 (FOXP3) immunohistochemical staining; A: Invasive ductal carcinoma with FOXP3-negative expression; B: FOXP3-positive lymphocytic infiltration in invasive ductal carcinoma. The staining was nuclear; C and D: Co-expression of FOXP3 and indoleamine 2,3-dioxygenase (IDO), FOXP3 and IDO expression in breast cancer tissues (n = 100) were evaluated; C: FOXP3 positive cells infiltrated in invasive ductal carcinoma (nuclear staining). Sections from matched breast cancer patients were stained for IDO; D: Strong and diffuse IDO staining in invasive ductal tumor cells (cytoplasmic staining). Images were captured at × 40 magnification.

FOXP3$^+$ T-regs can restrain effector T cells by an IDO dependent mechanism[9]. IDO plays a critical role in the pathogenesis of breast cancer[26]. IDO overexpression is linked with shorter overall survival and poor prognosis[27-34]. FOXP3$^+$ T-regs have prognostic implications in TNBC[8]. IDO expression is also associated with TNBC[26]. Previously we showed high IDO expression in TNBC patients from Pakistan[35]. The aim of our current study was to identify the substantial association between FOXP3-positive T-regs and IDO in TNBC patients. There was a statistically significant association of FOXP3 with high IDO expression (P = 0.01) and TNBC (P = 0.01) respectively. Two variables were recognized as significant independent risk factors for FOXP3 positive: IDO expression high (AOR 5.90; 95%CI: 1.22-28.64; P = 0.03) and TNBC (AOR 2.80; 95%CI: 0.96-7.95; P = 0.05) in multivariable analysis. Although several studies focus on the role of immunosuppression in TNBC, our data provide some insight regarding immunosuppression in association with simultaneous expression of FOXP3 and IDO in TNBC patients.

Our study has some limitations, which have to be mentioned. The study population (n = 100) did not permit us to draw any strong conclusion. Forthcoming projects on breast cancer patients from Pakistan with inclusive cohort studies are required to authenticate conclusive associations.

Identification of an appropriate immunotherapeutic target for TNBC is currently a hot-topic. FOXP3 and IDO co-expression has the ability to inhibit anti-tumor immune responses and may be considered one of the hurdles in the development of successful immunotherapy for cancer. The role of FOXP3 and IDO co-expression is still a subject of rigorous research in breast cancer.

CONCLUSION

In conclusion, the current data revealed that FOXP3 positive cells might be associated with high IDO expression in TNBC patients. FOXP3 and IDO expression monitoring in TNBC patients may provide an effective therapeutic strategy.

ARTICLE HIGHLIGHTS

Research background

Forkhead box P3 (FOXP3) and indoleamine 2,3-dioxygenase (IDO) are associated with advanced disease in cancer (*e.g.,* breast cancer).

Research motivation

To quantify FOXP3 expression in relation with IDO expression in patients diagnosed with breast cancer from Pakistan.

Research objectives

Our objective was to identify the co-expression of FOXP3 and IDO in triple negative breast cancer (TNBC) patients.

Research methods

Immunohistochemistry was performed to analyze the expression of FOXP3, IDO, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor in human breast cancer tissues.

Research results

A significant association of FOXP3 and IDO co-expression was observed among patients with TNBC (P = 0.01).

Research conclusions

FOXP3 positive cells might be associated with high expression of IDO in TNBC patients.

Research perspectives

Evaluation of FOXP3 and IDO expression in TNBC patients may be implemented in the future as a therapeutic strategy.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 1029-1044

DOI: 10.5306/wjco.v11.i12.1029

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Retrospective Study

Overall and cause-specific survival for mucoepidermoid carcinoma of the major salivary glands: Analysis of 2210 patients

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Author contributions: Taylor ZC was the primary writing author, and contributed to data analysis and editing; Kaya EA, Bunn JD, Guss ZD, Mitchell BJ, Fairbanks RK, and Lamoreaux WT were responsible for data analysis and editing; Wagner AE and Peressini BJ contributed to biostatistics, data analysis and editing; Lee CM was the supervising author, and contributed to data analysis and editing.

Supported by Community Cancer Fund in Spokane, Washington, United States

Institutional review board statement: This retrospective clinical research project was exempt from Institutional Review Board review as de-identified information was utilized from the Surveillance, Epidemiology, and

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Abstract

BACKGROUND

Mucoepidermoid carcinoma (MEC) is a rare malignancy of the head and neck; however, it accounts for a majority of the tumors of the salivary glands. This study used a national population-based registry to describe the pre-treatment and treatment-related prognostic factors that influence survival in patients with MEC of the major salivary glands. To our knowledge, this is the largest population-based study examining predictors of both overall and cause-specific survival of MEC of the major salivary glands.

AIM

To identify prognostic factors influencing overall survival (OS) and cause-specific survival (CSS) of patients with MEC of the major salivary glands.

METHODS

We used the Surveillance, Epidemiology and End-Results Database of the National Cancer Institute to investigate a variety of factors that could influence survival of patients diagnosed with mucoepidermoid carcinoma of the major salivary glands. A total of 2210 patients diagnosed with MEC of the major salivary glands during the years of 1975-2016 were studied. The primary endpoints were OS and CSS. Cox regression analysis was used to perform univariate and

multivariate analyses of clinical variables such as age at diagnosis, diagnosis year, sex, race, tumor size, stage, grade, treatment with or without surgical excision, and adjuvant radiotherapy treatment.

RESULTS

A total of 2210 patients diagnosed with MEC of the major salivary glands met inclusion criteria. In this study, 95% of patients underwent surgical excision and 41% received adjuvant radiation therapy. Median OS time for Grade I, II, and III/IV was 401 mo (± 48.25, 95%CI), 340 mo (± 33.68, 95%CI) and 55 mo (± 11.05, 95%CI), respectively. Univariate analysis revealed that lack of surgical excision was associated with decreased OS [hazard ratio (HR) 4.26, $P < 0.0001$] and that patients with localized disease had improved OS compared to both regional and distant disease (HR 3.07 and 6.96, respectively, $P < 0.0001$). Additionally, univariate analysis demonstrated that male sex, age over 50 at diagnosis, Grade III tumors, and increasing tumor size were associated with worsened OS ($P < 0.0006$). Univariate analysis of CSS similarly revealed that lack of surgical excision and Grade III carcinoma conferred decreased CSS (HR 4.37 and 5.44, respectively, $P < 0.0001$). Multivariate analysis confirmed that increasing age, in 10-year age bands, advanced tumor stage, increasing tumor size, Grade III carcinoma, male sex, and lack of surgical excision were associated with a statistically significant decrease in OS and CSS ($P < 0.04$). Of note, multivariate analysis revealed that the use of adjuvant radiation therapy was not associated with improved OS or CSS.

CONCLUSION

Multivariate analysis demonstrated increasing age, advanced tumor stage, increasing tumor size, Grade III carcinoma, male sex, and lack of surgical excision were associated with decreased OS and CSS ($P < 0.04$).

Key Words: Mucoepidermoid carcinoma; Salivary gland neoplasia; Surveillance, Epidemiology and End-Results; Head and neck cancer; Prognostic factors; Major salivary glands

Core Tip: Mucoepidermoid carcinoma (MEC) of the major salivary glands is a rare cancer with a limited number of studies with high statistical power. The purpose of this study was to identify prognostic factors effecting overall survival (OS) and cause-specific survival (CSS) of individuals diagnosed with MEC of the major salivary glands. By using de-identified information from the Surveillance, Epidemiology and End-Results Program, we concluded that younger age at diagnosis, female sex, smaller tumor size, lower tumor grade, localized tumor growth, and more recent year of diagnosis were positive predictors of statistically significant improvements in OS and CSS.

Citation: Taylor ZC, Kaya EA, Bunn JD, Guss ZD, Mitchell BJ, Fairbanks RK, Lamoreaux WT, Wagner AE, Peressini BJ, Lee CM. Overall and cause-specific survival for mucoepidermoid carcinoma of the major salivary glands: Analysis of 2210 patients. *World J Clin Oncol* 2020; 11(12): 1029-1044
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/1029.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.1029

INTRODUCTION

Salivary gland malignancies are very rare, accounting for less than 5% of all head and neck cancers[1]. Within the larger group of salivary gland neoplasms, there are two subclassifications; the major and minor salivary gland cancers. The major salivary glands are comprised of the parotid gland and submandibular glands. In contrast to most other head and neck cancers, which are characterized predominantly by

End Results (SEER) Database from the National Cancer Institute.

Informed consent statement: Informed consent was not obtained in this retrospective clinical research project as de-identified information was utilized from the Surveillance, Epidemiology, and End Results (SEER) Database from the National Cancer Institute.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this article.

Manuscript source: Unsolicited manuscript

Specialty type: Oncology

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: September 21, 2020
Peer-review started: September 21, 2020
First decision: October 21, 2020
Revised: November 5, 2020
Accepted: November 28, 2020
Article in press: November 28, 2020
Published online: December 24, 2020

P-Reviewer: Zahran M

S-Editor: Fan JR
L-Editor: A
P-Editor: Zhang YL

squamous cell carcinoma, the major salivary gland malignancies are categorized into a dozen or more histological subtypes, the most common of which is mucoepidermoid carcinoma[1-3].

Mucoepidermoid carcinoma (MEC) was first described by Stewart *et al*[4] in 1945 as salivary gland tissue that is comprised of epidermoid, mucous-secreting and intermediate cells. Since then, several grading systems have been developed in order to assign a histologic grade to the tumor upon pathologic evaluation and MECs are broken down into either low-, intermediate-, or high-grade malignancies depending on their level of invasion and differentiation[5-7]. This histopathological grading of the tumor is important as it is reportedly predictive of prognosis, where low-grade tumors have more favorable survival outcomes than high-grade tumors and intermediate-grade tumors fall in the middle[5,6,8-16].

Several studies have investigated potential risk factors for the development of MEC of the salivary glands. While smoking is a risk factor in a dose-dependent manner for all other major salivary gland cancer subtypes, it seems to be protective in MEC[17]. Furthermore, it has been discovered that prior radiation to the head or neck is a major risk factor for developing MEC in any of the salivary glands[5,18,19].

In contrast to most head and neck cancers in which TNM staging drives the primary treatment plan, the histopathological grading of MEC often directs the treatment regimen. Surgical resection, when feasible, is the cornerstone of therapy for MEC. Treatment options for mucoepidermoid carcinoma depend on grade of the tumor and resectability[7-9,15,20-23]. In most of these studies, the low-grade nature of Grade I tumors has allowed for surgical excision alone to be effective. Conversely, the high-grade tumors or tumors with positive surgical margins typically receive surgical excision and post-operative radiation[9,15,16,21,22,24,25]. This clear division of low-grade and high-grade with respect to treatment regimen has prompted some groups to attempt to characterize intermediate-grade neoplasms as more closely related to either the low- or high-grade tumors in order to drive treatment recommendations. However, there is disagreement amongst the academic community on this topic. Those that lump intermediate-grade in with low-grade affirm that there is no significant difference in clinical behavior or prognosis between the two grades[8,9,13,22,23], while others find that there is a significant difference in prognosis and intermediate-grade is closer in behavior to high-grade neoplasms[15,26].

Several other prognostic factors that have been studied at the institutional level include age, gender, degree of invasion, presence of positive surgical margins and the role of post-operative radiation therapy. Of note, both age and gender have presented themselves as independent factors that affect the overall prognosis of patients with MEC. Multiple groups have found that increasing age at diagnosis corresponds with worse prognosis across all tumor grades, although it is unclear what role other comorbidities play in this finding[5,7,14,23]. Additionally, males tend to have both higher grade neoplasms at diagnosis and worse overall survival[13-15,22,27,28]. Finally, post-operative radiation has been found to improve prognosis and extend overall survival in those patients with high-grade MEC or patients with positive margins following surgical excision, compared to surgery alone[8,9,13,20-22]. Importantly, these correlations have been made by evaluating small patient cohorts at individual institutions, owing to the rarity of MEC. Because of this, the statistical strength and ability to extrapolate to larger cohorts across the country is limited.

Our study aims to utilize data from the National Cancer Institute's Surveillance, Epidemiology and End-Results (SEER) Program to evaluate pretreatment clinical factors like age at diagnosis, decade of diagnosis, sex, race, tumor size, tumor stage, and tumor grade as well as treatment protocols and their effect on overall survival (OS) and cause-specific survival (CSS) for mucoepidermoid carcinoma of the major salivary glands.

MATERIALS AND METHODS

All data were acquired from the 1973-2016 database of the SEER program of the United States National Cancer Institute (NCI). The SEER database contains data from geographically specified United States locations that spans a population of approximately 30 million people. Registry data are submitted without personal identifiers; therefore, patient informed consent and ethics committee approval were not required to perform this analysis. The primary endpoints were OS and CSS. For this analysis we examined 2210 patients with a diagnosis of cancer of the major salivary glands and primary tumor histology of mucoepidermoid neoplasms. Our

inclusion criteria included patients treated from 1973 to 2016 whose de-identified tumor information was included in the SEER database, patients with MEC as the primary tumor histology, patients who had info on size of tumor, regional nodal involvement or metastatic disease, both sexes and all ages. The patients were then grouped by age at diagnosis, tumor stage, tumor size, tumor grade, patient race, patient gender, whether the patient received radiation, whether the patient received surgery, and diagnosis year.

Survival curves were estimated using the Kaplan-Meier method and used to compare age at diagnosis, tumor stage, tumor size, tumor grade, patient race, patient gender, whether the patient received radiation, whether the patient received surgery, and diagnosis year. Then, 95% confidence intervals for the median survival time of the groups were constructed. Approximate confidence intervals for the log hazard-ratio were calculated using the estimate of standard error (*se*):

se=\sqrt{\sum_{i=1}^{k}\frac{1}{e_{ij}}}

-where e_i is the extent of exposure to risk of death for group *i* of *k* at the *jth* distinct observed time for group *i* of *k* [Armitage P, Berry G. Statistical Methods in Medical Research (3rd edition). Blackwell 1994]. Log-rank tests were employed to determine if there is statistical evidence of differences between the survival curves of the groups. Finally, the Cox proportional hazard model was used in a multivariate analysis of the treatment groups, age groups, KPS groups, and primary tumor histology groups. All statistical analyses utilized StatsDirect Version 3.2.8 (StatsDirect Ltd., Altrincham, United Kingdom) and SigmaPlot Version 12.3 (SYSTAT Software, Inc., San Jose, CA). The statistical methods of this study were reviewed by Ben Peressini from DataWorks Northwest, LLC.

RESULTS

A total of 2210 patients with MEC of the major salivary glands met our inclusion criteria. There was not a sex preference as the prevalence of MEC for males and females was 1117 and 1093, respectively. Additionally, nearly 95% of patients in the study underwent surgery of some kind to have their tumor removed; however, only 46% of patients received radiation at any point in their treatment regimen. Median OS time for Grade I, II, and III/IV was 401 mo (± 48.25, 95%CI), 340 mo (± 33.68, 95%CI) and 55 mo (± 11.05, 95%CI), respectively (Table 1) Grade I correlates to low-grade MEC, grade II correlates to intermediate-grade MEC, and Grade III/IV correlates to high-grade MEC.

Upon univariate analysis, increasing age at diagnosis demonstrated a statistically significant decrease in OS ($P < 0.016$) (Table 1). A similar trend was seen upon analysis of tumor size, where increasing tumor size was associated with decreased OS ($P < 0.0006$). Not undergoing surgical excision of MEC appears to be a major predictor of OS [hazard ratio (HR) 4.26 ($P < 0.0001$)], as does having distant tumor involvement upon diagnosis [HR 6.96 ($P < 0.0001$)]. Of note, male sex was also associated with decreased OS [HR 1.76 ($P < 0.0001$)], with a median OS time of 187 mo (± 22.69, 95%CI) compared to the median OS time for females of 327 mo (± 31.14, 95%CI).

Multivariate analysis of overall survival confirmed many of the associations seen upon univariate analysis. Increasing age at diagnosis was once again associated with decreased OS ($P < 0.001$) as was increasing tumor size ($P < 0.001$) (Table 1). Both regional and distant tumor involvement showed a decrease in OS (HR 1.95 and 2.84, respectively, $P < 0.001$). Tumor grade was also an independent predictor of OS as Grade II and III/IV tumors demonstrated decreased OS (HR 1.3 and 2.1, respectively, $P < 0.04$) (Figure 1). Male sex (Figure 2) and lack of surgical excision once again conferred a significant decrease in OS (HR 1.26 and 2.09, $P < 0.001$). Notably, neither race nor receipt of adjuvant radiation demonstrated significant increases or decreases in OS on multivariate analysis.

Univariate analysis of cause-specific survival revealed that age over 50 at diagnosis was associated with a decrease in CSS ($P < 0.0001$) (Table 2). Very strong predictors of decreased CSS upon univariate analysis were regional and distant tumor involvement (HR 7.46 and 16.71, respectively, $P < 0.0001$), as well as Grade III/IV neoplasms (HR 15.48, $P < 0.0001$). Lack of surgery was also associated with decreased CSS (HR 4.37, $P < 0.0001$). Finally, as was seen upon analysis of OS, male sex was once again associated with decreased CSS (HR 2.38, $P < 0.0001$).

Multivariate analysis of CSS confirmed that age over 50 at diagnosis was associated with a decrease in CSS ($P < 0.001$) and that increasing tumor size conferred a decrease in CSS ($P < 0.04$) (Table 2). Regional and distant tumor involvement (Figure 3) as well

Table 1 Overall survival analysis of mucoepidermoid carcinoma of the major salivary glands

	n	Median survival	Univariate hazard ratio		Multivariate hazard ratio	
		95%CI	Estimate	95%CI	Estimate	95%CI
Age bands						
00-09	11	Cannot estimate	Cannot estimate		Cannot estimate	
10-19	86	Cannot estimate	0.12[a]	0.02-0.37	0.13[c]	0.06-0.32
20-29	174	Cannot estimate	0.16[a]	0.07-0.32	0.18[c]	0.12-0.26
30-39	275	Cannot estimate	0.62[b]	0.42-0.92	0.73[c]	0.68-0.78
40-49	319	401 ± 38.42	Reference		Reference	
50-59	431	248 ± 13.93	2.55[a]	1.93-3.39	2.51[c]	2.33-2.69
60-69	381	167 ± 26.25	5.00[a]	3.75-6.75	4.31[c]	3.28-5.67
70-79	336	70 ± 17.94	11.38[a]	8.25-15.95	7.52[c]	6.91-8.18
80+	197	35 ± 6.87	20.02[a]	13.67-29.92	12.24[c]	11.58-12.95
Stage						
Localized	1344	342 ± 26.24	Reference		Reference	
Regional	591	99 ± 19.59	3.07[a]	2.66-3.54	1.95[c]	1.95-1.96
Distant	143	29 ± 9.64	6.96[a]	5.51-8.75	2.84[c]	2.73-2.95
Unknown	132	118 ± 61.69	2.69[a]	1.86-3.80	1.6[b]	1.11-2.31
Primary tumor size (mm)						
0-10	209	Cannot estimate	Reference		Reference	
11-20	576	331 ± 59.73	1.95[c]	1.30-3.01	1.64[c]	1.39-1.94
21-30	355	248 ± 54.66	3.15[a]	2.08-4.91	2.07[c]	1.36-3.13
31-40	150	141 ± 57.38	4.63[a]	2.97-7.40	2.23[c]	1.98-2.52
41-50	57	46 ± 38.76	9.26[a]	5.56-15.59	2.66[c]	1.52-2.81
> 50	87	52 ± 36.21	9.14[a]	5.67-15.05	2.87[c]	2.63-3.13
Unknown/unspecific	776	220 ± 26.3	3.43[a]	2.35-5.18	2.09[c]	1.73-2.51
Grade						
I	403	401 ± 48.25	Reference		Reference	
II	850	340 ± 33.68	1.26	0.98-1.63	1.30[b]	1.02-1.67
III/IV	538	55 ± 11.05	5.44[a]	4.27-6.99	2.10[c]	1.98-2.23
Unknown	419	201 ± 39.44	2.49[a]	1.94-3.20	1.61[c]	1.52-1.70
Race						
American Indian/Alaska Native	16	Cannot estimate	0.47	0.13-1.20	1.64	0.61-4.45
Asian or Pacific Islander	206	308 ± 66.3	0.70[b]	0.53-0.91	0.93	0.71-1.21
Black	239	Cannot estimate	0.59[a]	0.45-0.76	1.00	0.78-1.29
Unknown	23	Cannot estimate	0.10[c]	0.00-0.54	0.31	0.04-2.26
White	1726	226 ± 21.22	Reference		Reference	
Sex						
Female	1093	327 ± 31.14	Reference		Reference	
Male	1117	187 ± 22.69	1.76[a]	1.54-2.01	1.26[b]	1.10-1.44
Radiation						
No/unknown	1200	340 ± 34.89	0.46[a]	0.40-0.53	1.07	0.70-1.63
Yes	1010	147 ± 23.39	Reference		Reference	

Sequence						
Not applicable	1260	327 ± 29.07	Reference		Reference	
Radiation after surgery	902	162 ± 25.62	1.82[a]	1.59-2.08	1.18	0.76-1.83
Radiation before surgery	48	162 ± 56.48	1.67[b]	1.12-2.40	1.17[c]	1.10-1.25
Surgery						
No	77	27 ± 11.81	4.26[a]	3.16-5.64	2.09[c]	1.40-3.10
Unknown	28	16 ± 10.37	4.43[a]	2.87-6.57	2.41[c]	1.43-4.05
Yes	2105	263 ± 23.24	Reference		Reference	
Diagnosis year						
1975-1995	960	221 ± 23.77	1.31[c]	1.13-1.52	1.38[c]	1.16-1.64
1996-2016	1250	Cannot estimate	Reference		Reference	
Surgery type						
Excision	2085	261 ± 23.23	Reference		Variable not used in multivariate analysis	
Limited surgical procedure/biopsy	20	Cannot estimate	1.01	0.52-1.96		
None	77	27 ± 11.81	4.28[a]	3.17-5.67		
Unknown	28	16 ± 10.37	4.44[a]	2.88-6.59		
Diagnosis year						
1975-1984	405	207 ± 31.31	1.77[a]	1.39-2.26	Variable not used in multivariate analysis	
1985-1994	497	230 ± 36.99	1.50[c]	1.18-1.91		
1995-2004	564	Cannot estimate	1.32[b]	1.04-1.68		
2005-2016	744	Cannot estimate	Reference			

[a]$P < 0.0001$.
[b]$P < 0.05$.
[c]$P < 0.001$.

as Grade III/IV tumors at diagnosis were associated with decreased CSS ($P < 0.001$), just as was seen upon univariate analysis. Both lack of surgery and male sex demonstrated decreased CSS (HR 2.17 and 1.36, respectively, $P < 0.01$). Finally, American Indian/Alaska Native race conferred decreased CSS (HR 4.29, $P < 0.001$), though there were only 16 patients in this subgroup making the conclusions difficult to extrapolate to a larger population.

DISCUSSION

Mucoepidermoid carcinoma accounts for the majority of the major salivary gland malignancies and represents just one of the many histological subtypes that are responsible for such malignancies[1-3].

Age

In this study, advanced age at diagnosis stood out as a very strong independent predictor of OS. Patients in the 50-59 years old age band had worse prognosis compared to younger age ranges (multivariate HR 2.51, $P < 0.001$) and this progressed in a stepwise fashion for each successive 10-year age band where patients who were 80 years or older had the worst OS (multivariate HR 12.24, $P < 0.001$). This relationship was mirrored in the multivariate analysis of CSS, where there was a decrease in CSS as patient age at diagnosis increased and patients who were greater than 80 years old at diagnosis had the worst CSS (multivariate HR 3.47, $P < 0.001$). These findings are in agreement with results from several other groups showing that age was a significant predictor of prognosis[5,7,12,14,23,27-29].

Table 2 Cause-specific survival analysis of mucoepidermoid carcinoma of the major salivary glands

	n	Median survival	Univariate hazard ratio		Multivariate hazard ratio	
		95%CI	Estimate	95%CI	Estimate	95%CI
Age bands						
00-09	11	Cannot estimate	Cannot estimate		Cannot estimate	
10-19	86	Cannot estimate	0.23[b]	0.03-0.90	0.28[b]	0.10-0.74
20-29	174	Cannot estimate	0.23[b]	0.06-0.67	0.29[c]	0.16--0.51
30-39	275	Cannot estimate	0.71	0.37-1.34	0.95	0.85-1.06
40-49	319	Cannot estimate	Reference		Reference	
50-59	431	Cannot estimate	2.50[a]	1.62-3.96	1.99[c]	1.30-3.06
60-69	381	Cannot estimate	3.34[a]	2.17-5.29	2.47[c]	2.18-2.80
70-79	336	Cannot estimate	5.41[a]	3.48-8.67	3.00[c]	2.63-3.43
80+	197	Cannot estimate	7.67[a]	4.69-12.92	3.47[c]	3.17-3.79
Stage						
Localized	1344	Cannot estimate	Reference			
Regional	591	Cannot estimate	7.46[a]	5.78-9.70	3.90[c]	3.77-4.04
Distant	143	41 ± 23.43	16.71[a]	11.95-23.34	5.79[c]	5.77-5.81
Unknown	132	Cannot estimate	6.27[a]	3.62-10.38	3.01[c]	1.79-5.05
Primary tumor size (mm)						
0-10	209	Cannot estimate	Reference		Reference	
11-20	576	Cannot estimate	1.87	0.86-4.62	1.4[b]	1.01-1.92
21-30	355	Cannot estimate	5.08[a]	2.41-12.34	2.13[c]	1.48-3.06
31-40	150	Cannot estimate	8.18[a]	3.75-20.31	2.27[b]	1.04-4.95
41-50	57	Cannot estimate	17.24[a]	7.48-44-63	3.19[c]	2.44-4.17
> 50	87	89 ± 108.69	18.24[a]	8.30-45.63	3.53[c]	2.58-4.83
Unknown/unspecific	776	Cannot estimate	6.25[a]	3.10-14.69	2.57[c]	1.73-3.82
Grade						
I	403	Cannot estimate	Reference		Reference	
II	850	Cannot estimate	1.75	0.98-3.33	1.56	0.88-2.76
III/IV	538	Cannot estimate	15.48[a]	9.17-28.16	4.35[c]	2.52-7.52
Unknown	419	Cannot estimate	7.02[a]	4.06-13.01	2.92[c]	1.67-5.10
Race						
American Indian/Alaska Native	16	Cannot estimate	1.24	0.33-3.20	4.29[c]	2.18-8.48
Asian or Pacific Islander	206	Cannot estimate	0.64[b]	0.41-0.96	0.79	0.52-1.19
Black	239	Cannot estimate	0.66[b]	0.44-0.95	1.06	0.94-1.19
Unknown	23	Cannot estimate	0.00[b]	0.00-0.90	Cannot estimate	
White	1726	Cannot estimate	Reference		Reference	
Sex						
Female	1093	Cannot estimate	Reference		Reference	
Male	1117	Cannot estimate	2.38[a]	1.92-2.96	1.36[b]	1.09-1.69
Radiation						
No/unknown	1200	Cannot estimate	0.27[a]	0.22-0.34	2.10	0.43-1.49
Yes	1010	Cannot estimate	Reference		Reference	

Sequence						
Not applicable	1260	Cannot estimate	Reference		Reference	
Radiation after surgery	902	Cannot estimate	2.66[a]	2.15-3.30	0.96	0.50-1.84
Radiation before surgery	48	Cannot estimate	2.79[c]	1.55-4.70	1.05	0.47-2.33
Surgery						
No	77	Cannot estimate	4.37[a]	2.89-6.38	2.17[b]	1.18-3.98
Unknown	28	74 ± 7.67	4.84[a]	2.54-8.44	1.62[c]	1.49-1.76
Yes	2105	Cannot estimate	Reference		Reference	
Diagnosis year						
1975-1995	960	Cannot estimate	1.40[b]	1.14-1.73	1.33[b]	1.03-1.72
1996-2016	1250	Cannot estimate	Reference		Reference	
Surgery type					Variable not used in multivariate analysis	
Excision	2085	Cannot estimate	Reference			
Limited surgical procedure/biopsy	20	Cannot estimate	1.50	0.48-3.55		
None	77	Cannot estimate	4.41[a]	2.92-6.44		
Unknown	28	74 ± 7.67	4.89[a]	2.57-8.53		
Diagnosis year					Variable not used in multivariate analysis	
1975-1984	405	Cannot estimate	2.09[a]	1.53-2.88		
1985-1994	497	Cannot estimate	1.47[b]	1.06-2.04		
1995-2004	564	Cannot estimate	1.44[b]	1.05-1.98		
2005-2016	744	Cannot estimate	Reference			

[a]$P < 0.0001$.
[b]$P < 0.05$.
[c]$P < 0.001$.

Sex

The role of sex as a predictive variable for determining MEC disease outcome has been explored on several different levels. Cheung *et al*[29] described improved 5-year survival rates for women compared to men in an analysis of all salivary gland malignancies. Several other studies of just MEC have evaluated and confirmed this improved survival for women[5,12-15,22,27,28]. In fact, several other groups explored this trend more in depth and noted that men presented with higher grade MEC upon diagnosis, providing a possible explanation for the favorable outcomes for women seen in other studies[7,12,15,22,27,29,30]. Our data showed that while there were nearly equal numbers of men and women diagnosed with MEC (1093 women and 1117 men), the median survival time was 1.75 times longer for women compared to men. Additionally, the multivariate analysis showed that men had a worse overall survival prognosis (multivariate HR 1.26, $P = 0.001$). Interestingly, Boukheris *et al*[1] showed an age-specific crossing pattern with respect to gender and incidence of MEC. When comparing both age and gender together, they discovered the incidence rate of MEC in men to be 72% that of women under the age of 50 ($P < 0.05$) [1]. However, this trend switched after the 50-year-old mark where the incidence rate of MEC in men was 157% that of women over the age of 50 ($P < 0.05$)[1].

Grade

Histopathologic grade of MEC has long been recognized as an independent predictor of prognosis. Even in 1970, Healey *et al*[6] described worsening 5-year overall survival rates for those with high-grade (Grade III) malignancies (31% OS for Grade III compared with 90% OS for Grade I). Since then, multiple groups have reaffirmed the negative impact of having a high-grade MEC malignancy on overall survival[5,8-11,13-16]. In fact, Seethala[31] asserts that there is no other salivary gland malignancy in which prognosis and treatment rely so heavily on histologic grading. Traditionally, low-grade tumors are treated with definitive surgery while high-grade MEC requires

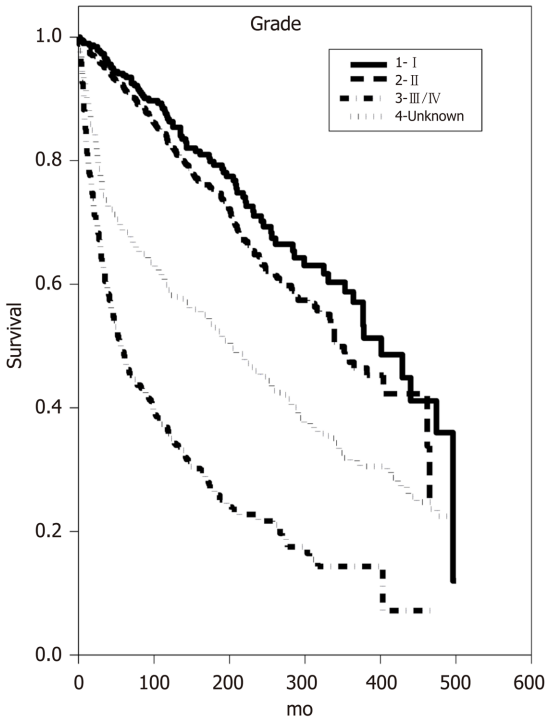

Figure 1 Kaplan-Meier overall survival plot of tumor grade at diagnosis.

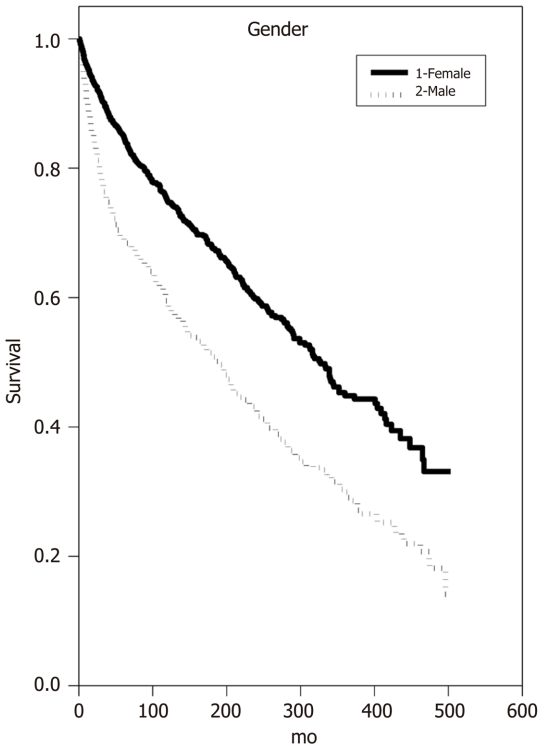

Figure 2 Kaplan-Meier overall survival plot of gender.

surgery and adjuvant radiation therapy. However, there is disagreement about how to treat patients with intermediate-grade MEC, due primarily to underlying disagreement about whether intermediate-grade malignancies behave more similarly to low-grade or high-grade neoplasms[26-28,32].

This differential classification of intermediate-grade tumors is due in part to the existence of several histologic grading systems which are used to varying extents by pathologists assigning a grade to the malignancies. In fact, it has been suggested that

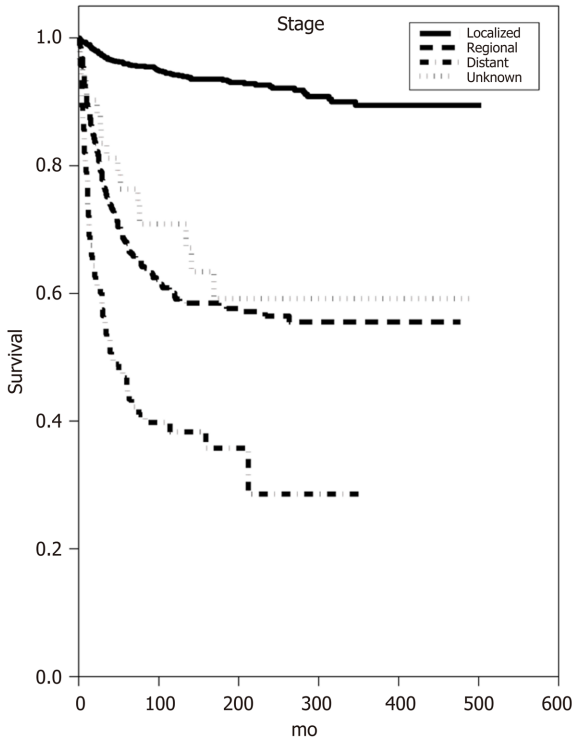

Figure 3 Kaplan-Meier cause-specific survival plot of tumor stage at diagnosis.

many pathologists refrain from using any of these grading criteria because they are cumbersome to use and there is a lack of consensus on which criteria is best[31,32]. Instead, pathologists use their own intuition in assigning a histologic grade, leading to further confusion about which tumors are truly low-grade, intermediate-grade or high-grade[31,32]. The four major grading criteria proposed for use for grading MEC of the major salivary glands include the modified Healey *et al*[6], Brandwein *et al*[5], Memorial Sloan-Kettering Cancer Center (MSKCC)[32] and Armed Forces Institute of Pathology (AFIP) criteria[7,30]. Both the AFIP and Brandwein models assign varying point values to the specific features that they observed as characteristic of more aggressive growth behavior and set ranges for what is considered low-grade, intermediate-grade, or high-grade[5,7,30]. Batsakis *et al*[33] described a subjective, three-tier grading system that took what Healey *et al*[6] proposed in 1970 and incorporated growth patterns and levels of cell differentiation into the criteria. The MSKCC system, proposed in 2014 to try and alleviate some of the confusion of the other three systems, similarly relies on a subjective analysis by the pathologist to determine whether the tumor specimen most closely aligns with their descriptions of low-, intermediate-, or high-grade MEC[32].

The AFIP grading system, though endorsed by the WHO[3], tends to downgrade the severity of MEC malignancies, meaning that it will classify more aggressive tumors as low-grade[31,32,34]. This has possible negative implications since treatment for low-grade tumors is strictly surgical excision which has proven to be insufficient for controlling high-grade MEC of the major salivary glands. On a similar note, the Brandwein system tends to upgrade the severity of malignancies, meaning that it will classify more indolent tumors as high-grade[32,34]. This too has possible negative implications for the patient who may undergo radical excision of the major salivary gland and surrounding structures and subsequent radiation for a tumor that could have been managed with local excision and less disfigurement. Despite this, some still recommend either the AFIP or Brandwein criteria because of ease of use, reproducibility, and the fact that a formalized system of some kind is better than no system at all, where the alternative is strictly subjective assessment[27,31].

The differential assignment of grade by each grading system was put on display as Qannam *et al*[34] used the varying criteria to classify MEC of a small patient subset. Histologic grading of 19 primary minor salivary gland tumors using the MSKCC, AFIP, modified Healey and Brandwein criterion only showed 32% agreement[34]. However, the level of disagreement was profound and most pronounced when looking at the distribution of malignancies that each grading system assigned as

intermediate-grade[34]. A similar histologic grading disagreement was seen when Katabi *et al*[32] applied the four grading systems to a population of 52 patients with MEC of the major salivary glands. Here, there was disagreement between the histologic grading systems in 23 (or 44%) of the cases[32].

Intermediate-grade MEC is arguably the most important grade to assign correctly since grade plays into treatment decisions so heavily. Importantly, some of the grading systems describe IMG MEC as more closely related to LG MEC than HG MEC, while some say the opposite. However, our findings are in line with the majority of studies, as our multivariate analysis demonstrated that the OS of those diagnosed with Grade II (IMG) MEC was more similar to the OS of those with Grade I (LG) MEC upon diagnosis (HR 1.3, $P < 0.04$) than it was to Grade III/IV (HG) MEC (HR 2.1, $P < 0.001$). Furthermore, the median OS time for Grade I, II, and III/IV was 401 mo (± 48.25, 95%CI), 340 mo (± 33.68, 95%CI) and 55 mo (± 11.05, 95%CI), respectively, once again showing that intermediate-grade MEC behaves more similarly to low-grade MEC.

Size

Larger MEC tumor size at diagnosis has uniformly conferred with worsening overall survival[7,11,12]. Our multivariate analysis of OS similarly demonstrated that increasing size of the primary tumor at the time of diagnosis corresponded to progressively worsening OS. Patients with tumors between 11-20 mm at diagnosis had worse OS than those with tumors between 0-10 mm (multivariate HR 1.64, $P < 0.001$) and this trend progressed for each successive 10mm size band where those with tumors greater than 50mm at diagnosis had the worst OS (multivariate HR 2.87, $P < 0.001$). Analysis of CSS also demonstrated decreased survival with increasing size of tumor at diagnosis where those with tumors between 0-10 mm had the best CSS, and those with tumors greater than 50 mm had the worst CSS (multivariate HR 3.53, $P < 0.001$).

Stage

As is seen in most other cancers throughout the body, more advanced MEC TNM staging at diagnosis is associated with worse overall and cause-specific survival. In 1975 and 1976, Spiro *et al*[35,36] made recommendations on ways to clinically stage cancers of the major salivary glands that included size, number, mobility, CN VII involvement and nodal status. Several years later, Spiro *et al*[12] looked at MEC of the salivary glands and found that while their assigned stage and histologic grade were very frequently in agreement, when there was a discrepancy (high grade, stage I or low grade, stage III), survival outcome was most impacted by stage and not histologic grade. This is contrary to Seethala's[31] assertion that histologic grading of MEC dictates prognosis and treatment plans. However, a possible explanation for this disagreement lies in the fact that Seethala's study, written in 2008, was using the more modern histologic grading systems of either AFIP, Brandwein, or modified Healey which all include some criteria that are normally part of staging criteria including angiolymphatic and perineural invasion. In other words, some factors that were historically part of staging criteria are now built into the commonly used grading criteria for MEC of the salivary glands leading to the difference in opinion between Spiro *et al*[35] and Seethala[31]. As such, it is very likely that the newer histologic grading being used at diagnosis is more important than clinical stage for the patient's overall prognosis and treatment plan moving forward.

That being said, tumor stage is still considered an independent predictor of disease outcome, where increasing T stage as well as nodal involvement corresponds to decreased OS and CSS[8,9,11-14,16,22,27,28,32,37-39]. In fact, the current National Comprehensive Cancer Network (NCCN) guidelines continue to primarily rely on tumor staging for treatment recommendations related to all salivary gland neoplasms with some consideration for tumor grade. In our study, we generalized the staging to include local (N0M0), regional (N1M0), and distant (NxM1) disease. Our data demonstrate that, perhaps as expected, localized MEC confers a better OS than either regional (multivariate HR 1.95, $P < 0.001$) or distant (multivariate HR 2.84, $P < 0.001$) tumor involvement. The relationship between stage and prognosis was even more pronounced when looking at CSS data where once again, localized MEC conferred better CSS than both regional (multivariate HR 3.9, $P < 0.001$) and distant (multivariate HR 5.79, $P < 0.001$) MEC involvement.

Treatment

Low-grade MEC of the major salivary glands has traditionally been treated with local excision of the tumor only. On the other hand, high-grade MEC is traditionally treated with wide local excision ± lymphadenectomy if lymph nodes are involved followed by

adjuvant radiation. The treatment of intermediate-grade MEC is less clear and this is due in part to the confusion of whether it is more closely related in behavior to low-grade or high-grade MEC. As addressed above, our data confirm that intermediate-grade typically has a more indolent disease course and survival plots are more similar to those of low-grade neoplasms. The less aggressive behavior of these tumors allows for local excision only unless they exhibit characteristics of high-grade malignancy, defined by the NCCN Head and Neck Cancer Guidelines of 2020 as close or positive surgical margins, perineural invasion, or angiolymphatic invasion. In these specific cases, the NCCN Guidelines recommend undergoing adjuvant radiation therapy.

Some have suggested that radiation therapy does not improve patient survival. While this may be true, there is a possible confound that not all groups correct for in their analysis, and that is that those receiving radiation therapy are likely diagnosed with high-grade MEC or have intermediate-grade MEC with some high-grade characteristics including positive surgical margins or extracapsular extension. These patients already have much lower overall survival and disease-free survival (DFS) rates. Nance *et al*[27]. controlled for histologic grade in his study of 50 patients with MEC of the salivary glands and was still able to demonstrate that radiation does not confer any survival benefit in patients with high-grade MEC, and actually showed worse DFS rates in those with intermediate-grade MEC that were treated with radiation compared to those that were not. Ferrell *et al*[39] also looked specifically at adjuvant radiation therapy following a primary resection for high- and low-grade MEC and showed improved OS for high-grade MEC and no statistically significant difference in OS compared to surgery alone for low-grade MEC. While our adjuvant radiation outcome data was not analyzed separately for each grade of tumor, the multivariate data did show that adjuvant radiation has no statistically significant difference in OS or CSS compared to surgery alone when looking at all grades of MEC. This is an area that deserves more attention as there are currently opposing views on the role of adjuvant radiation in the treatment plans for the different grades of MEC[27,39].

Another possible confound in the data on adjuvant radiation therapy is that newer technology has changed the safety profile of radiation therapy significantly. Prior to the major rollout of intensity-modulated radiation therapy in the late-90s, 3D conformal imaging was used. And prior to either of these methods, a simple 2D X-ray was all that was used to map a patient's organ location prior to therapy, leading to a significant amount of off-target radiation of healthy tissue. Now, with CT mapping and technology that delivers precise radiation doses to the cancerous tissue and permitted doses to the healthy surrounding tissue, the risk of off-target radiation damage is much lower. This is especially true of radiation for head and necks cancers in general, where one of the mainstays of treatment besides surgery has been radiation[40]. This trend in improved targeting of the tumor bed and protection of critical structures in accordance with the newer methods of radiation therapy could be accounted for in our multivariate analysis that shows both decreased OS (multivariate HR 1.38, $P < 0.001$) and CSS (multivariate HR 1.33, $P < 0.04$) in patients diagnosed and treated between 1975-1995 compared to those diagnosed and treated between 1996-2016. Another contributing factor to the improved OS and CSS is the past several decades is the improved safety of the surgical excision of tumors. Whether it be through an enhanced understanding of surgical technique at or around the salivary glands or fewer post-surgical complications as a result of facial nerve sparing, improvements in the mainstay of treatment for MEC have certainly had a positive impact on prognosis.

The SEER database does not collect information about chemotherapy use or dosing, so we are unable to comment directly on the benefits or drawbacks of such treatment for MEC of the major salivary glands. However, previous studies have made clear that chemotherapy has a poor ability to control MEC of the salivary glands and is even potentially detrimental to OS[14,39]. Rajasekaran *et al*[14] demonstrated a lower 5-year OS for surgery, chemotherapy and radiation combined when compared to surgery alone or surgery plus radiation for MEC of the parotid gland. Additionally, Ferrell *et al*[39] showed that surgery plus chemoradiation conferred worse OS than surgery alone when looking at all salivary gland cancers.

Race

There is no survival difference based on race, ethnicity, or socioeconomic status in any salivary gland malignancy, which is in contrast to other cancers of the head and neck that show an increased incidence and mortality for African Americans[29]. When looking at our multivariate analyses, we similarly did not see an overall survival difference based on race. There was a worse prognosis noted for American

Indian/Alaska Native patients when looking at cause-specific survival [multivariate hazard ratio of 4.29 ($P < 0.001$)], however the power of the conclusion drawn from that is not strong as only 16 patients identified as American Indian/Alaska Native.

Limitations

Since our data is from the SEER database, the limitations of our study are the same as those that are inherent to the database itself. There is a lack of a centralized pathology review to confirm histopathologic diagnoses, and therefore, histologic misclassification is a possibility. Additionally, there is a lack of information about which histologic grading system was used to grade the MEC malignancies of each patient, which is an important distinguishing factor for MEC of the major salivary glands. The SEER database also does not provide information about local control of disease which makes interpretation of the benefit of adjuvant radiation therapy difficult. Adjuvant radiation therapy is primarily used for local control of disease, however SEER only provides information about OS and CSS.

CONCLUSION

While mucoepidermoid carcinoma is the most common histological subtype of the major salivary glands, it is still a rare tumor with a paucity of studies providing conclusions with high statistical power. This study is one of the largest population-based studies of MEC of the major salivary glands focused on identifying prognostic factors effecting OS and CSS. Younger age at diagnosis, female sex, smaller tumor size, lower tumor grade, localized tumor growth, and more recent year of diagnosis were positive predictors of statistically significant improvements in OS and CSS. This study also focused on the role of adjuvant radiation for treatment of MEC of the major salivary glands. Multivariate analysis did not show any statistically significant improvement in OS or CSS with adjuvant radiation following surgery. However, we did not analyze the role of adjuvant radiation for each different histologic grade of MEC and there are currently dissenting opinions in the literature about whether or not adjuvant radiation therapy plays a role in high-grade MEC of the major salivary glands[27,39]. For this reason, we believe further research should focus on the role of adjuvant radiation for low-, intermediate- and high-grade MEC.

ARTICLE HIGHLIGHTS

Research background

While mucoepidermoid carcinoma (MEC) is a rare cancer, it is the most common histologic subtype of the major salivary glands. Despite this, there is a paucity of studies with high statistical power that provide conclusions on pretreatment and treatment related factors that affect survival. This study is one of the largest population-based studies of mucoepidermoid carcinoma of the major salivary glands focused on identifying prognostic factors effecting overall survival (OS) and cause-specific survival (CSS).

Research motivation

While mucoepidermoid carcinoma is a rare cancer, it is the most common histologic subtype of the major salivary glands. Despite this, there is a paucity of studies with high statistical power that provide conclusions on pretreatment and treatment related factors that affect survival. By identifying prognostic factors that affect both overall OS and CSS, we hope this study can help provide information to guide and inform treatment plans for patients diagnosed with MEC of the major salivary glands.

Research objectives

This study is one of the largest population-based studies of MEC of the major salivary glands and sought to identify prognostic factors influencing OS and CSS of patients with MEC of the major salivary glands.

Research methods

De-identified cancer registry data from the Surveillance, Epidemiology and End-Results (SEER) Database of the National Cancer Institute was used to investigate a

variety of factors that could influence survival of patients diagnosed with mucoepidermoid carcinoma of the major salivary glands. The primary endpoints were OS and CSS. Cox regression analysis was used to perform univariate and multivariate analyses of clinical variables such as age at diagnosis, diagnosis year, sex, race, tumor size, stage, grade, treatment with or without surgical excision, and adjuvant radiotherapy treatment.

Research results

A total of 2210 patients diagnosed with MEC of the major salivary glands met inclusion criteria. The clinical factors that were associated with statistically significant improvements in both OS and CSS include younger age at diagnosis, smaller tumor size, lower tumor grade, localized tumor growth, female sex, and more recent year of diagnosis. Importantly, no statistically significant improvement in OS or CSS was noted with adjuvant radiation therapy following surgery.

Research conclusions

This study identified a variety of factors that affect OS and CSS for patients with mucoepidermoid carcinoma of the major salivary glands. These factors can help inform and guide treatment planning for mucoepidermoid carcinoma of the major salivary glands. Additionally, this study provided commentary on the debate between cancer staging *vs* histologic grading being more predictive of clinical outcome as well as which histologic grading system should be utilized for these cancers, something that was possible due to the improved statistical power of this study.

Research perspectives

Further research is needed to better delineate the role of adjuvant radiation for low-, intermediate-, and high-grade MEC in order to better guide treatment planning. This study did not find a statistically significant improvement in OS or CSS for patients who received adjuvant radiation therapy, though we did not analyze the effect of radiation on OS and CSS for each histologic grade or tumor stage, nor did we analyze local control of disease from adjuvant radiation therapy due to the constraints of the SEER database. Furthermore, there are currently dissenting opinions about the role of adjuvant radiation for high-grade MEC of the major salivary glands.

ACKNOWLEDGEMENTS

The completion of this project would not have been possible without the support of my supervisor (Dr. Christopher Lee), my fellow medical school classmate (Erin Kaya), and the hard work of our biostatistician (Ben Peressini) as well as all the other surgeons and oncologists that provided both insight and editorial advice on this manuscript.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 1045-1063

DOI: 10.5306/wjco.v11.i12.1045

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Prospective Study

Assessment of burden and coping strategies among caregivers of cancer patients in sub-Saharan Africa

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Institutional review board statement: The study was reviewed and approved by the institutional review board of the University of Calabar Teaching Hospital, Calabar, Nigeria.

Informed consent statement: All study participants, provided written consent prior to study enrollment.

Conflict-of-interest statement: The authors of this manuscript have no

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Abstract

BACKGROUND

Cancer is a devastating and debilitating chronic disease that affects both patients and family members. Available evidence has confirmed that the care of chronically ill relatives by family members can be very challenging. This is because caregiving of cancer patients often presents a high level of burden on the caregivers. Consequently, this leads to a necessity to adopt coping mechanisms to cushion the effect of the burden experienced during caregiving.

AIM

To determine the burden experienced and coping strategies among caregivers of advanced cancer patients attending University of Calabar Teaching Hospital (UCTH), Cross River State, Nigeria.

METHODS

The study adopted a descriptive cross-sectional study design and the study population included informal family caregivers providing services to histologically diagnosed advanced cancer patients receiving treatment at the UCTH at the time of this survey. A researcher-developed structured questionnaire, a 22-item standardized validated Zarit Burden Interview (ZBI) and

conflicts of interest to disclose.

Data sharing statement: There are no additional data available.

Manuscript source: Unsolicited manuscript

Specialty type: Oncology

Country/Territory of origin: Nigeria

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 29, 2020
Peer-review started: May 29, 2020
First decision: September 18, 2020
Revised: September 29, 2020
Accepted: November 11, 2020
Article in press: November 11, 2020
Published online: December 24, 2020

P-Reviewer: Ganeshan D
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Wang LL

a modified 17-item Coping Orientation to Problems Experienced (COPE) Inventory were used to collect data from 250 eligible informal caregivers who were selected with regard to caregiver's characteristics, caregivers' level of burden and caregiver's coping strategies, respectively. Data gathered from the respondents were collated, coded and analyzed using Statistical Package for Social Sciences (SPSS version 24.0) software and Predictive Analytical Software (PAS version 19.0). Chi-square was used to test for association between categorical variables at the 0.05 level of significance. The results are presented in tables and charts.

RESULTS

The respondents consisted of more females 132 (62.86%) than males 78 (37.14%). The majority of respondents (46.2%) were aged between 31-50 years with a mean age of 35.9 ± 18.1 years. The assessment of burden level revealed that 97 caregivers (46.19%) experienced severe burden, 37 (17.62%) experienced trivial or no burden, while 76 (36.2%) perceived moderate burden. The coping strategies used by caregivers to ease the level of burden experienced during caregiving included; acceptance, reprioritization, appreciation, family, positive self-view and empathy. Also, it was documented that there was a strong association between caregivers' level of burden and coping strategies (P = 0.030). Findings also showed that age (P = 0.000), sex (P = 0.000), educational status (P = 0.000), functional ability (P = 0.000), duration of care (P = 0.000), desire to continue caregiving (P = 0.000) and type of cancer (P = 0.000) were statistically significantly associated with caregivers' coping strategies.

CONCLUSION

There is great recognition of the role of informal caregivers in improving the health of their relatives and family members who are chronically ill. It was recommended that support groups in collaboration with health care providers should organize a symposium for informal caregivers on the intricacies of caregiving in chronically ill patients. This would create a platform for experience sharing, information dissemination and health care professional-caregiver interaction to enhance positive caregiving outcomes.

Key Words: Caregivers' burden; Coping strategies; Cancer patients; Nigeria; Chronically ill

Core Tip: Home health care services are gradually becoming very important for providing continuous care to patients with terminal illness. This study provides an overall picture of the levels of burden experienced and coping strategies adopted by cancer caregivers in the study area. The severity of burden experienced and coping strategies adopted by cancer caregivers is important for oncology nurses in order to integrate caregivers' needs assessment into clinic admission routine aimed at directing the provision of evidence-based interventions to alleviate advanced cancer caregiving burden in sub–Saharan Africa.

Citation: Akpan-Idiok PA, Ehiemere IO, Asuquo EF, Chabo JAU, Osuchukwu EC. Assessment of burden and coping strategies among caregivers of cancer patients in sub-Saharan Africa. *World J Clin Oncol* 2020; 11(12): 1045-1063
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/1045.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.1045

INTRODUCTION

Cancer is a devastating and debilitating chronic disease that affects both the patient and family members. It is largely characterized by abnormal growth and spreads by

the movement of cells to other parts of the body *via* the blood and lymphatic system. In contrast to normal cells, ''apoptosis'' does not apply to cancer cells, as they continuously grow, proliferate and spread[1-3]. Currently, over 100 types of cancers have been identified. Cancer has a multifaceted etiology involving many factors which is largely influenced by a complex process known as carcinogenesis. Statistics have shown that over 50 million cancer deaths occur annually worldwide and 80% of these deaths occur in developing countries[4-5].

Cancer and cancer-related mortality are projected to increase by 50% (from 14 million to 21 million) and 60% (from 8 million to 13 million), respectively, in 2030[6]. Available statistics indicated that 32.6 million people were living with cancer during the 5 years of their study in Belgium, while in America, United Kingdom, China, South Africa and Nigeria 1.7 million, 1.3 million, 2.2 million, 2.56 million and 3.47 million persons were living with cancer, respectively[5,7,8]. In Nigeria, 53064 persons died of cancer in 2008[8-9]. Nigeria is also known to have the highest cancer mortality rate in Africa with an annual death toll of 10000 persons; with an incidence of 100000, 300000 and 500000 in 1990, 2010 and 2013, respectively[6,10] and 41000 cancer-related deaths were recorded in 2014 alone[11]. The upsurge in the incidence of cancer may pose serious challenges in caregiving with its attendant burden on the patients and caregivers.

Caregivers are any unpaid persons and include blood relatives, friends and housekeepers that provide a broad range of continuous assistance in performing activities of daily living (ADL) for cancer patients for at least two months in the hospital care setting, home or community. In this study, the term informal caregivers is used interchangeably with family caregivers. Caregiver burden is tailored towards describing the physical, social, financial and psychological impact of caregiving on the caregiver's life as perceived by the caregiver. Caregivers' burden in this study is assessed using the Zarit Standardized Scale[12]. Coping on the other hand is an emotion-focused *vs* problem-focused approach that addresses how informal caregivers respond and act both when experiencing burden of care and when the level of exposure to burden increases using diverse adaptive manipulations. The researchers' oncology anecdotal clinical interactions with advanced cancer patients and their family caregivers prompted the assessment of burden and coping strategies among advanced cancer caregivers in Nigeria.

Literature review

Concept of caregiver: The term "caregiver" is as old as Adam[13-14]. Caregivers are specialized assistants by virtue of their role. They provide unaided assistance to people with chronic ailments[15]. It has been documented that relatives are in a better position to provide care for their loved ones during the period of terminal illness (cancer crisis)[16]. This is mostly because cancer is not a respecter of persons, and results in destabilization and burden in the family. Therefore, caregiving entails assisting with activities of daily living in those with lower functional abilities.

Providing care to a seriously ill spouse, parent or other significant person can also restrict a caregiver's personal, psychological, social, circular and vocational opportunities, as well as create a financial burden[17-20]. The outcome of these strains can be supportive and productive or at the opposite extreme, highly stressful with physical health problems, psychological distress and increased caregiver burden. Of course, no significant difference in the magnitude of these forms of burden are perceived by cancer caregivers[21].

The concept of caregivers' burden: The American gerontologist, Zarit[22] first defined the burden of care as "the discomfort experienced by the principal caregiver of an older family member, including the caregiver's health, psychological well-being, finances, and social life". Since then, there is ample evidence on the burden of caring for the aged population. For instance, O'Neill *et al*[23] stated that, caregivers provide clinical and supportive care to cancer patients. Caregivers vary in the types of tasks they perform, the amount of time devoted to caregiving and living standards. Caregiving is not limited to elderly persons. Diseases at varying stages such as chronic and other debilitating conditions including cancer can require caregiving. However, different views and perspectives have emerged regarding the conceptualization, definition and measurement of burden. Caregiver burden is also perceived to be "a multidimensional bio-psychosocial reaction", "resulting from an imbalance of care demands, relative to caregiver's personal time, social roles, physical and emotional state, financial resources and formal care resources given, and other multiple roles they fulfill"[24]. O'Neill *et al*[23] classified caregiver distress as caregiver burden or caregiver depression while Fortinsky *et al*[25] stressed that caregiver distress results

from mood disturbance arising from the stress of providing care, which may manifest as a feeling of being easily bothered, fearful, isolated and lonely.

Generally, the conceptualization of burden has been deliberated in three perspectives. First, burden has been defined as "the extent of workload and measured in terms of the number and types of care tasks performed (*e.g.*, assistance with household chores, banking tasks or personal care tasks) and or the number of hours spent performing these tasks"[26]. Secondly, burden has also been defined as "the caregiver's judgment concerning the distress or difficulty associated with performing the care task"[20]. Thirdly, burden has been further defined as the "perceived impact of this workload on the caregiver's life"[27]. The variation within these definitions is that burden can be objective or subjective in terms of demand. The third definition of burden is used in this study.

The burden that the diagnosis and treatment of cancer impose on family caregivers appeared in the literature during the 1980s, following the use of diagnostic related groups beginning in 1983[28]. The category of burden bearers include; the patient, family members, the clinicians and medical research personnel, Government Organizations (*e.g.*, National Cancer Centers), spiritual leaders, and international organizations/national bodies (*e.g.*, Cancer Society of Nigeria)[3,29-30].

Family members of cancer patients express distress in exhibiting caregiving roles and this distress can be demonstrated as fear, burden, helplessness, depression, anxiety, weight loss, inability to concentrate, *etc.* In the Chinese culture, family caregiving is particularly dominant in terminally ill patients. For instance, the practice of familism and filial piety have been associated with the Confucian culture[31]. Thus, children should take care of the aged, sick or even dying parents in return for the parent's efforts in bringing them up. Also, Chinese/Taiwanese people prefer to die at home which poses significant challenges and adverse consequences for families. Caring for a cancer patient contributes to physical disease, psychiatric morbidity, and increased mortality[27].

Freedman[15] found that while men provide some level of care such as finance and other less burdensome tasks, women caregivers carry out high burden caregiving tasks such as dressing, toileting and bathing. Zarit[13] observed that women exhibit more affection, support, provide time consuming care and other caregiving responsibilities to their chronically ill patients better than their male counterparts. Men primarily support caregiving financially by delaying retirement especially for health conditions that require long-term care. However, a mixed method study carried out among advanced cancer patients reported that out of 30 patients, 80% had pain, 66.7% had vomiting, 73.3% had restlessness, 50% had dyspnea and 20% had cough[5]. These patients were unable to meet their needs by themselves and were often hospitalized for symptom management. The caregiver as the support person is responsible for providing physical, psychological, economic and social support. Actually, due to the dwindling human and material health resources in most health care systems, home health care services are essential to facilitate monitoring, symptom management and treatment of patients requiring long-term care. Therefore, there is a need to measure the burden and coping among advanced cancer family caregivers in Nigeria.

A descriptive and predictive study conducted in the Eastern United States on psychological distress, fatigue, burden of care, and quality of life in primary caregivers of patients with breast cancer undergoing autologous bone marrow transplantation (BMT) found that caregivers of patients with cancer suffer from diverse burdens such as fatigue, anxiety, and low quality of life, moderate to severe levels of burden, subjective and objective levels of burden[32]. A longitudinal study conducted in the United States assessed changes in symptom severity in caregivers of patients with advanced stage cancer and found that caregivers mostly experienced moderate and severe burden[33]. The study further reported that over 40% were at risk of distress and depression as a result of their caregiving role to patients with terminal illness. Hence, the study significantly proved that caregiving in cancer patients is risky and very burdensome.

Caregiver burden is a term used to describe the physical, social, financial and psychological impact of caregiving on the caregiver's life as perceived by the caregiver. Caregivers in this study were assessed using the Zarit Standardized Scale[12]. This scale comprises of: Physical - bodily structures, psychological - functioning, social - interactions, and financial - funds. Caregiver burden is a condition that affects many family caregivers globally[13]. It is the physical, emotional, social and financial problems experienced by a family member caring for physically and/or mentally/terminally ill patients[2,5,34]. A large body of literature supports the fact that the caregiver's physical, emotional, psychological, and social well-being can

significantly be affected by the burden experienced during caregiving. Consequently, health care providers need to understand the burdensome nature of caregiving and which coping mechanisms can best cushion the effect of the burden which is geared towards counselling, educating and supporting care receivers in Nigeria.

It has been shown that the longer the caregiving of patients with advanced cancer, the higher the level of caregiver burden reported. Besides the limitations of cancer caregiving, developing strategies to withstand cancer patient caregiving include the following: Provision of social support, positive self-view (psychological adjustment), and religious beliefs (spiritual growth and prayers), in order to meet the social needs of the patients and enhance positive health outcomes. The development of these coping strategies in cancer caregiving have been summarized in terms of changes in spirituality, attitude to life, interpersonal relationships and change in self-view[2,35].

Caregiving experience is burdensome when patients cannot cope with the symptoms they are experiencing. Family caregivers develop numerous symptoms during the caregiving process ranging from pain, nausea, vomiting, exhaustion, fatigue, sleeplessness and weight loss, dyspnea, depression, fatigue, cough, restlessness due to low socio-economic status as well as dwindling human and material health resources. Caregiving responsibilities fall on family members in Nigeria as advanced cancer patients may require optimal care and monitoring both at home and in the hospital setting. Families of advanced cancer patients also physically, socially, psychologically and spiritually experience significant distress during caregiving.

The physical, psychological, social, spiritual and financial impact of caring and coping among primary caregivers is considerable and often negative. Ample evidence has shown that caring for an advanced cancer patient may be associated with physical problems such weight loss, sleeplessness, fatigue and exhaustion. Also, psychological symptoms such as depression, anxiety, feeling of isolation and reduced self-esteem may be experienced. They are often confronted with social burden resulting in restriction of time, disturbances in routines, diminished opportunities for leisure activities and loss of income. Recent descriptive surveys and qualitative studies of caregivers' cancer care experiences in India and Nigeria depicts that 38.9% of caregivers of cancer patients reported symptoms of depression. 41% to 62% of the caregivers of advanced cancer patients experienced a high level of psychological burden compared to 19.2% of the general population. This high burden index was significantly associated with age and the patients' symptoms[2-3,34,36].

The enormous problems and coping strategies encountered by caregivers of cancer patients are unknown in cancer patients. Communication with health care providers might affect caregiver burden, and less research has focused on the burden and coping (if any) with cancer care giving among caregivers generally and those treated in the University of Calabar Teaching Hospital, Calabar in Cross River State specifically. This is the reason for this research.

Coping strategies/skills among advanced cancer caregivers: Folkman *et al*[37], Lazarus *et al*[38], Antony *et al*[39], Akpan-Idiok[3] and Rahmani *et al*[40] perceived ''coping'' as a process that explains how an individual (caregiver) responds during increased exposure to stress and when experiencing stressful stimuli (appraisal of burden). In the same studies, coping strategies were categorized as problem-focused and emotion-focused coping strategies. While emotion-focused coping strategies involve effortful strategies (interpretation of burden) that caregivers adopt to mitigate the adverse emotional outcomes instigated by stressful events, problem-focused coping strategies on the other hand, are aimed at ameliorating the negative impact of the burden using problem-solving mechanisms or eliminating the sources of stress by building up positive/negative coping such as adaptive or maladaptive coping strategies. In advanced cancer caregiving, caregivers use both adaptive and maladaptive coping strategies which can affect families' caregiving outcomes[41]. Rahmani *et al*[40] in their study also pinpointed that repudiation of patients/family members with terminal illness (*e.g.*, mental illness) was identified as a major predictor of caregivers' burden. As a result, such patients may be abandoned to psychiatric services. Furthermore, cultural roles, religious beliefs and social structure are strongly associated with family caregiving and the cancer disease process that involves the family system and acts as coping precursors among advanced cancer family caregivers. These forms of coping strategies based on whether they are harmful or helpful (*e.g.*, emotion-focused *vs* problem-focused coping; approach *vs* avoidance) are related to cultural context. Osundina *et al*[42] found no statistically significant relationship between burden and coping styles among schizophrenic family caregivers. Grover *et al*[4] also argued that caregivers' coping strategies can directly or indirectly influence patient health

outcomes.

Turnbull *et al*[43] documented that the caregivers' burden level was high and that the extent to which caregivers experience symptoms depends largely on their coping skills, energy level, health status, belief system and personality. Also, Sisk[20] observed that as the burden of caregiving increases, it disrupts daily activities, social relationships and negatively affects resources. According to the cancer palliative care module, "participating in a network of caring and reciprocal relationships with others and creating a sense of belonging and reason for living that transcends one's individual self or social support, has been found to be one of the most important coping mechanisms"[44]. The understudy of burden and the coping strategies employed by family caregivers in their caregiving roles can enhance needs assessment for designing family—centered interventions to ameliorate cancer caregiving burden in Nigeria. To meet the gaps, this study was directed by role and stress theories to answer the research questions: What are the perceived challenges that deter family members and relations from cancer caregiving? What are the perceived sustaining factors to cancer caregiving in Nigeria and in the University of Calabar Teaching Hospital, Calabar?

MATERIALS AND METHODS

Study area

The study area is the University of Calabar Teaching Hospital (UCTH) situated in the southern part of Nigeria. UCTH is a tertiary health institution that is poised to provide highly specialized health care services. It also serves as a research and training center for health care professionals. The hospital serves as a referral center to other health centers, clinics and health institutions where cancer patients are admitted and managed. The hospital is compartmentalized into major wards which include; medical, surgical, orthopedic, pediatrics, obstetrics and gynecology wards. Although there is no specific section for management of cancer patients in the hospital, the gynecological ward, female/male surgical ward and medical out-patient department (MOPD) have been designated to provide care to cancer patients.

Study design, study population and sample size

The study adopted a descriptive cross-sectional study as used by other authors to conduct similar studies[23-24]. The study population consisted of informal family caregivers providing services to histologically diagnosed cancer patients receiving treatment at UCTH at the time of the survey. As the population size was unknown, this study adopted the Power Analysis Calculation by Cohen[45] to deduce the required sample size. The power analysis was used to determine the minimum sample size for inferential statistical analysis (given that, the level of significance $\alpha = 0.05$; expected effect size = 0.95). Using the Sample size Power Analysis software (G. Power 3.1.5) the calculated sample size was 210. However, to account for attrition, wrongly filled and incomplete questionnaires, the sample size was increased by 16% to obtain an actual sample size of 250 informal family caregivers for the study. The current study is a follow-up from a previous key research on caregiver's perceptions of advanced cancer caregiving burden in Nigeria[2]. Eligible caregivers from the previous research who gave their consent to participate in the study were recruited. The inclusion criteria consisted of; all advanced cancer family caregivers aged 18 years and above who demonstrated enthusiasm to participate in the study, who resided within the study area and have provided care to the patient for two months or more. The current study describes family cancer caregivers' as unpaid persons (blood relatives, friends and house-keepers) aged 18 years and above who provide assistance to cancer patients for a minimum of two months in the study location[2].

Instruments used for data collection

The instruments used for data collection were a researcher-developed structured questionnaire, adopted 22-item standardized validated Zarit Burden Interview (ZBI) and 17-item adapted modified Coping Orientation to Problems Experienced (COPE) Inventory. The questionnaire consisted of 67 items divided into the following five sections: Section A: Socio-demographic, characteristics and duration of caregiving, Section B: Functional level of caregivers, Section C: Coping strategies of caregivers, Section D: Desire to continue with caregiving and Section E: Level of burden of caregivers. For functional ability of care receivers, a score of ≥ 50% indicates low

functional ability and vice versa for high functional ability (reliability coefficient = 0.87-0.93).

The modified ZBI scale is made up of 22 items which reflects how people sometimes feel when caring for other people. The ZBI scale is a 22-item questionnaire with each item rated from 0-88 (higher score denotes higher burden for a particular item). The total burden for a subject is the sum of the scores in all the items endorsed. The total score for the scale ranges from 0 to 88 on a five-point Likert scale. To measure the burden level of caregivers, the following scale was used; 0-20 represented little or no burden; 21-30 signified mild burden; 31-40 denoted moderate burden and 41-88 represented severe burden level. The psychometric properties of the ZBI scale include an acceptable inter-item reliability and convergent validity indicated by a Cronbach alpha of 0.79 and a correlation coefficient of 0.71 between caregiver global evaluation and scores was reported[46]. A test-retest reliability of 0.71 and internal consistency (Cronbach alpha = 0.91) was also reported[2-3,22,34].

The modified COPE Inventory was adopted to analyze the coping mechanism used by caregivers when confronted with the burden of caregiving. The inventory was designed using a four-point Likert scale. The COPE Inventory has been validated and widely used in Nigeria and shows evidence of factor replicability[47-50]. A validity and reliability test of the COPE inventory showed high internal consistency of 0.83 and 0.72, respectively.

Validity and reliability

The researcher adopted the face and content validity approach to establish the validity of the instrument as asserted by Polit *et al*[51] who stated that "the face validation of a standardized instrument is appropriate for any measuring scale". This was achieved by engaging two experts with similar research experience especially in relation to care for cancer patients for scrutiny, examination and useful inputs. Their inputs were noted and harnessed into the instruments before using it for data collection.

The researcher also adopted a test-retest method to establish the reliability of the instruments. The instruments were administered to 20 male and 20 female informal caregivers in Port Harcourt, River State, Nigeria on two different occasions with a two week interval. Thereafter, their responses were collated and analyzed using the Pearson Product Moment Correlation Coefficient to obtain a reliability score ranging from 0.85 to 0.96 across all items of the variables. However, Kerlinger[52] noted that a reliability coefficient of 0.50 and above is appropriate for any measuring scale, hence, the instruments in the current study were considered appropriate for use.

Method of data analysis

Data gathered from the respondents were collated, coded and analyzed using Statistical Package for Social Sciences (SPSS version 20.0) software and Predictive Analytical Software (PAS version 19.0). Descriptive statistics such as percentages, mean, and standard deviation were used to analyze the variables highlighted in the research objectives. Chi-square was used to test for association between categorical variables at the 0.05 level of significance. Results are presented in tables and charts.

Ethical consideration

Ethical approval was obtained from the UCTH Research Ethics Committee. Thereafter, written informed consent was obtained from the study participants after adequately informing them about the nature, purpose and significance of the study. The study participants were also assured of strict anonymity and confidentiality regarding the information they would provide. The study participants were informed that participation in this study was on a voluntary basis and they had the right to withdraw at any stage of the study without victimization or coercion.

RESULTS

Socio-demographic characteristics of the respondents

Of the 250 questionnaires distributed, 210 were completely filled and returned for analysis giving a response rate of 84%. The results which are presented in Table 1 show that 132 (62.9%) respondents were female and 78 (37.1%) were male. Almost half of the respondents 97 (46.2%) were aged between 31-50 years, 98 (46.7%) were married, 83 (39.6%) had secondary education, 81 (38.6%) were unemployed and almost two-thirds [132 (62.9%)] were the parents of caregivers.

Table 1 Socio-demographic characteristics of the respondents (*n* = 210)

Variables	*n* (%)
Gender	
Male	78 (37.1)
Female	132 (62.9)
Age (yr)	
≤ 30	79 (37.6)
31-50	97 (46.2)
51-70	34 (16.2)
mean ± SD	35.9 ± 18.1
Marital status	
Married	98 (46.7)
Single	57 (27.1)
Divorced	12 (5.7)
Widowed	43 (20.5)
Educational status	
No formal education	21 (10.0)
Primary	74 (35.2)
Secondary	83 (39.6)
Tertiary	32 (15.2)
Employment status	
Not employed	81 (38.6)
Artisan	10 (4.8)
Traders/business	21 (10.0)
Farmer	15 (7.1)
Contractors	4 (1.9)
Retired	50 (23.8)
Civil/public servant	19 (9.0)
Student/apprentice	10 (4.8)
Relationship to care receiver	
Parents	132 (62.9)
Spouse/partner	43 (20.5)
Sibling	21 (10.0)
Friend	10 (4.8)
Brethren	4 (1.9)

Akpan-Idiok *et al*[2]. SD: Standard deviation.

Caregivers' perceived level of caregiving to advanced cancer patients

The results presented in Figure 1 were analyzed using the Zarit Burden Scale analytical guideline and the respondents' scores were categorized as trivial or no burden (0-20), mild (21-30), moderate (31-40) and severe burden (41-88). The results showed that a significant proportion of the respondents [97 (46.2%)] experienced severe burden, 76 (36.2%) experienced moderate burden and 37 (17.6%) experienced trivial or no burden.

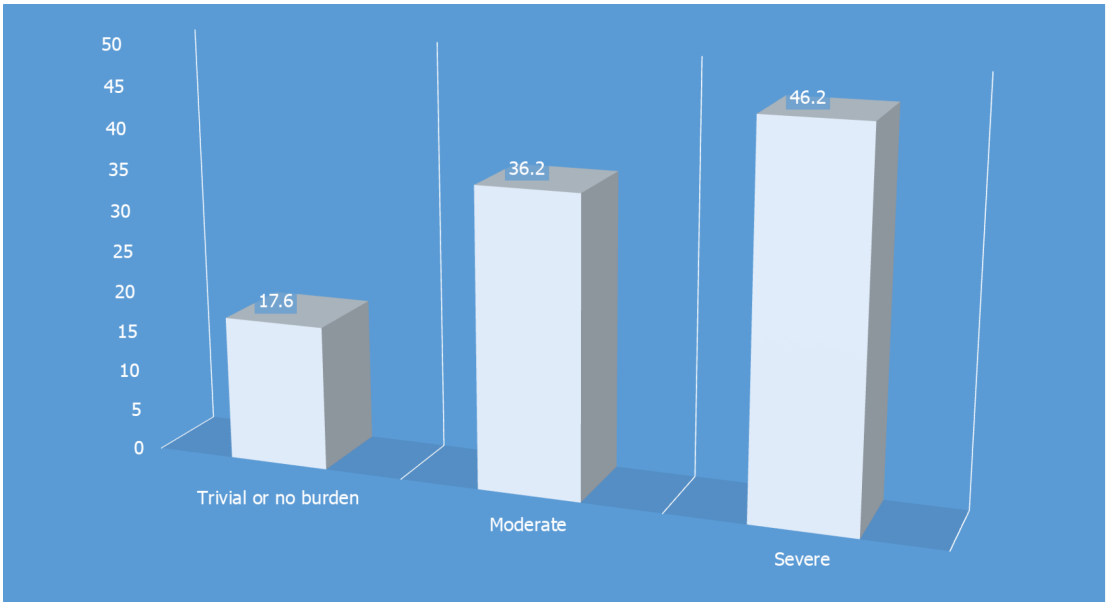

Figure 1 Burden level of caregivers.

Coping styles adopted by caregivers to care for advanced cancer patients

The coping styles highlighted in Table 2 were analyzed using the COPE inventory which is often used to assess the psycho-social characteristics of caregiving and other stressful events experienced by individuals (Osundina *et al*[42], 2017). The coping strategies were then categorized into two parts: Problem-focused coping strategies (acceptance, appreciation and reprioritization) and emotion-focused coping strategies (family, positive self-view and empathy) (Table 2). From the results, it was observed that higher means were reported for nearly all the assertions except for two which recorded lower mean values.

To measure the level of effectiveness of coping styles adopted by caregivers in providing care for advanced cancer patients, responses from the respondents were assessed based on their individualized mean score where a mean score between 0-2.99 denoted ineffective coping strategies while a mean score of ≥ 3.00 denoted effective coping strategies. The results in Figure 2 show that 185 (88.1%) caregivers indicated that the coping strategies used were effective in caregiving while 25 (11.9%) indicated that the coping strategies used was ineffective.

Relationship between caregivers' characteristics and coping strategies

The results presented in Table 3 show the relationship between caregivers' characteristics and effectiveness of coping strategies adopted. These results show that sex ($\chi^2 = 14.77$; $P = 0.000$), age ($\chi^2 = 17.79$; $P = 0.000$) and educational status ($\chi^2 = 48.45$; $P = 0.000$) were all statistically significantly associated with caregivers' coping strategies. This implies that age, sex and educational status have a significant influence on the level of effectiveness of coping strategies used by caregivers. From the table, it can be observed that middle-aged female caregivers with higher educational status attest to the fact that their choice of coping strategies was very effective compared to their counterparts.

Association between caregivers' perceived burden level and coping strategies

The results presented in Table 4 show the association between caregivers' perceived burden level and coping strategies. It can be seen that there is a strong association between caregivers' perceived burden level and coping strategies ($\chi^2 = 6.94$; $P = 0.030$). This implies that the more effective the coping strategies, the lesser the burden and *vice versa* as demonstrated in Table 4.

Relationship between functional level of the care receiver (cancer patient) and caregivers' coping strategies

Functional ability was measured with simple percentages using a 15-item questionnaire (physical status assessment tool) designed by the researcher. From the analysis, the results show that care receivers are highly dependent on caregivers in

Table 2 Coping styles adopted by caregivers to care for advanced cancer patients

Categories	Coping strategies sub-scale	Assertions	mean ± SD
Problem-focused coping strategies	Acceptance (changes in effort to accept things)	I have learnt how to adjust to things I cannot change	2.95 ± 1.00
		Helped me take things as they come	3.00 ± 1.09
		Shown me that all people need to be loved	3.24 ± 0.84
	Reprioritization (self-realization)	Helped me become more focused on priorities with a deeper sense of purpose of life	2.93 ± 1.03
		Lead me to be more accepting of things	3.25 ± 0.96
	Appreciation (changes in appreciation in life)	Lead me to meet people who have become some of my best friends	3.60 ± 0.73
		Helped me become more aware of the love and support available from other people	3.21 ± 0.91
		Brought my family closer together	3.29 ± 0.84
Emotion-focused coping strategies	Family (family unity)	Made me more sensitive to family issues	3.24 ± 0.65
		Helped me to deal better with stress and problems	3.33 ± 0.78
	Positive self-view (psychological coping skills)	Taught me to be patient	3.43 ± 0.85
		Helped me become a stronger person more able to cope effectively with future life challenges	3.24 ± 1.12
		Helped me realize who my real friends are	3.23 ± 1.05
	Empathy (increase in empathy for all human beings)	Made me more aware and concerned for the future of all human beings	3.29 ± 0.85
		Taught me that everyone has a purpose in life	3.31 ± 0.91
		Made me realize the importance of planning for my family's future	3.11 ± 1.76

Mean score of between 0-2.99 denotes ineffective coping strategies, mean score of ≥ 3.00 denotes effective coping strategies. SD: Standard deviation.

performing their routine daily activities except for grooming (brushing hair, teeth), taking medication, using the telephone and wandering which needs less supportive care (Table 5). It was further observed that 137 (65%) exhibited low functional ability while 73 (35.0%) showed high functional ability.

The results in Table 6 show that the relationship between functional ability and the caregivers coping strategies was statistically significant (χ^2 = 17.35; P = 0.000). This implies that coping strategies were more effective amongst caregivers providing care to patients with low functional ability (Table 6).

Relationship between duration of care and caregivers' coping strategies

The results presented in Table 7 show that the relationship between duration of care and caregivers' coping strategies was statistically significant (χ^2 = 17.72; P = 0.000). This analysis implies that the longer the duration of care, the higher the need to adopt more effective coping strategies.

Relationship between desire to continue caregiving and caregivers' coping strategies

The results presented in Table 8 show that the desire to continue caregiving was statistically significantly associated with caregivers' coping strategies (χ^2 = 21.19; P = 0.000). It was further observed that effective coping strategies serve as an impetus to continue providing care to cancer patients. The desire to continue with care was significantly dependent on the level of efficacy of the coping strategies used.

Test of association between type of cancer and caregivers' perceived burden level

The results presented in Table 9 show that types of cancer were statistically significantly associated with caregivers' burden level (χ^2 = 59.01; P = 0.000). It was

Table 3 Relationship between caregivers' characteristics and coping strategies

Variables	Coping strategies			χ^2 (*P* value)
	Effective (*n* = 185)	Ineffective (*n* = 25)	Total (*n* = 210)	
Sex				14.77 (0.000)[a]
Male	60 (76.9)	18 (23.1)	78 (100)	
Female	125 (95.0)	7 (5.0)	132 (100)	
Age (in years)				17.79 (0.000)[a]
≤ 30	70 (88.6)	9 (11.4)	79 (37.6)	
31-50	92 (94.8)	5 (5.2)	97 (46.2)	
51-70	23 (67.6)	11 (32.4)	34 (16.2)	
mean ± SD			35.9 ± 18.1	
Educational status				48.45 (0.000)[a]
No formal education	17 (80.9)	4 (19.1)	21 (10.0)	
Primary	70 (94.6)	4 (5.4)	74 (35.2)	
Secondary	81 (97.6)	2 (2.6)	83 (39.6)	
Tertiary	17 (53.1)	15 (46.9)	32 (15.2)	

[a]*P* < 0.05. SD: Standard deviation.

Table 4 Association between caregivers' perceived burden level and coping strategies

Variables	Coping strategies			χ^2 (*P* value)
Level of burden	Effective (*n* = 185)	Ineffective (*n* = 25)	Total (*n* = 210)	
				6.94 (0.030)[a]
Trivial or no burden	37 (100)	0 (0.0)	37 (100)	
Moderate burden	67 (88.1)	9 (11.9)	76 (100)	
Severe burden	81 (83.5)	16 (16.5)	97 (100)	

[a]*P* < 0.05.

further observed that caregivers experience severe burden mostly during caregiving of prostate [44 (72.1%)] and colorectal cancer patients [9 (60.0%)], while moderate burden was higher for those with breast cancer [44 (62.8%)] and cervical cancer [15 (34.8%)]. No burden was mostly reported for those with human immunodeficiency virus (HIV)-related cancers [5 (62.5%)].

Test of association between type of cancer and caregivers' coping strategies

The results presented in Table 10 show that types of cancer were not statistically significantly associated with caregivers' coping strategies ($\chi^2 = 7.00$; $P = 0.320$). It was further observed that caregivers' coping strategies were more effective for patients with breast cancer, Hodgkin's lymphoma and HIV-related cancer than other types of cancer.

DISCUSSION

In Nigeria, it has been reported that family members often serve as informal caregivers mostly at home to their relatives with chronic health conditions during the management, treatment and recovery process[2,42]. However, this role of caregiving consequently places a huge demand on the caregivers' social, financial and personal resources which becomes onerous. Hence, for continuous caregiving of cancer

Table 5 Functional status of care receivers

Functional ability	*n* (%)	
	Yes	No
Eating (need someone to feed him/her)	156 (74.3)	54 (25.7)
Bathing/showering	162 (77.1)	48 (22.9)
Dressing (choosing and wearing appropriate clothing)	157 (74.8)	53 (25.2)
Grooming (brushing hair, teeth)	23 (11.0)	187 (89.0)
Using toilet	151 (71.9)	5 9 (28.1)
Incontinence	172 (81.9)	38 (18.1)
Transferring from bed/chair/car	189 (90.0)	21 (10.0)
Preparing meals	182 (86.7)	28 (13.3)
Staying alone must be supervised	196 (93.3)	14 (6.7)
Taking medication	12 (5.7)	198 (94.3)
Managing money or finance	203 (96.7)	7 (3.3)
Performing household chores	163 (77.6)	47 (22.4)
Using the telephone	32 (15.2)	178 (84.8)
Mobility	142 (67.6)	68 (32.4)
Wandering or the potential to wander	40 (19.1)	170 (80.9)

Scores of ≥ 50 denotes low functional ability, scores of < 50 denotes high functional ability.

Table 6 Relationship between functional level of the care receiver (cancer patient) and caregivers' coping strategies

Variables	Coping strategies			χ^2 (*P* value)
Functional ability	Effective (*n* = 185)	Ineffective (*n* = 25)	Total (*n* = 210)	
				17.35 (0.000)[a]
Low functional ability	130 (94.9)	7 (5.1)	137 (100)	
High functional ability	55 (75.3)	18 (24.7)	73 (100)	

[a]*P* < 0.05.

Table 7 Relationship between duration of care and caregivers' coping strategies

Variables	Coping strategies			χ^2 (*P* value)
Duration of care (in mo)	Effective (*n* = 185)	Ineffective (*n* = 25)	Total (*n* = 210)	
				17.72 (0.000)[a]
1-5	32 (72.7)	12 (27.3)	44 (100)	
6-10	58 (85.3)	10 (14.7)	68 (100)	
≥ 11	95 (96.9)	3 (3.1)	98 (100)	

[a]*P* < 0.05.

patients, it has become imperative for caregivers to adopt suitable coping strategies that would serve as an impetus for optimal caregiving. The findings in the current study showed that nearly two-thirds of the study participants were female (Table 1). These results are in accordance with a similar study conducted by Akpan-Idiok *et al*[2], where female caregivers dominated in their study. Female dominance in caregiving is

Table 8 Relationship between desire to continue caregiving and caregivers' coping strategies

Variables	Coping strategies			χ^2 (*P* value)
Desire to continue caregiving	Effective (*n* = 185)	Ineffective (*n* = 25)	Total (*n* = 210)	
Not to continue	66 (75.9)	21 (24.1)	87 (100)	21.19 (0.000)[a]
To continue	119 (96.7)	4 (3.3)	123 (100)	

[a]*P* < 0.05.

Table 9 Association between type of cancer and caregivers' perceived burden level

Type of cancer cases	Burden level				χ^2 (*P* value)
	No burden (*n* = 37)	Moderate burden (*n* = 76)	Severe burden (*n* = 97)	Total (*n* = 210)	
					59.01 (0.000)[a]
Breast cancer	14 (20.0)	44 (62.8)	12 (17.1)	70 (100)	
Prostate cancer	7 (11.5)	10 (16.4)	44 (72.1)	61 (100)	
Cervical cancer	5 (11.6)	15 (34.8)	23 (53.5)	43 (100)	
Colorectal cancer	3 (20.0)	3 (20.0)	9 (60.0)	15 (100)	
Hodgkin's lymphoma	2 (25.0)	2 (25.0)	4 (50.0)	8 (100)	
HIV-related cancers (Kaposi sarcoma, non-Hodgkin lymphoma, *etc.*)	5 (62.5)	1 (12.5)	2 (25.0)	8 (100)	
Other types	1 (20.0)	1 (20.0)	3 (60.0)	5 (100)	

[a]*P* < 0.05. HIV: Human immunodeficiency virus.

Table 10 Association between type of cancer and caregivers' coping strategies

Type of cancer cases	Coping strategies			χ^2 (*P* value)
	Effective (*n* = 185)	Ineffective (*n* = 25)	Total (*n* = 210)	
				7.00 (0.320)
Breast cancer	66 (94.3)	4 (5.7)	70 (100)	
Prostate cancer	52 (85.2)	9 (14.8)	61 (100)	
Cervical cancer	37 (86.0)	6 (14.0)	43 (100)	
Colorectal cancer	13 (86.7)	2 (13.3)	15 (100)	
Hodgkin's lymphoma	7 (87.5)	1 (12.5)	8 (100)	
HIV-related cancers (Kaposi sarcoma, non-Hodgkin lymphoma, *etc.*)	7 (87.5)	1 (12.5)	8 (100)	
Other types	3 (60.0)	2 (40.0)	5 (100)	

HIV: Human immunodeficiency virus.

linked to the fact that they are mostly in charge of indoor activities especially with regard to providing care and support to family members/relatives in all aspects, whereas males tend to lead in out-door activities (*e.g.*, providing financial resources). Historically, it can also be argued that women have a natural gift for caregiving than their male counterparts[32,53]. Almost 50% of the respondents were married and young. These results is in accordance with other studies that confirmed that most caregivers to patients with chronic health problems are middle aged[12,31,34]. Given *et al*[24] asserted that

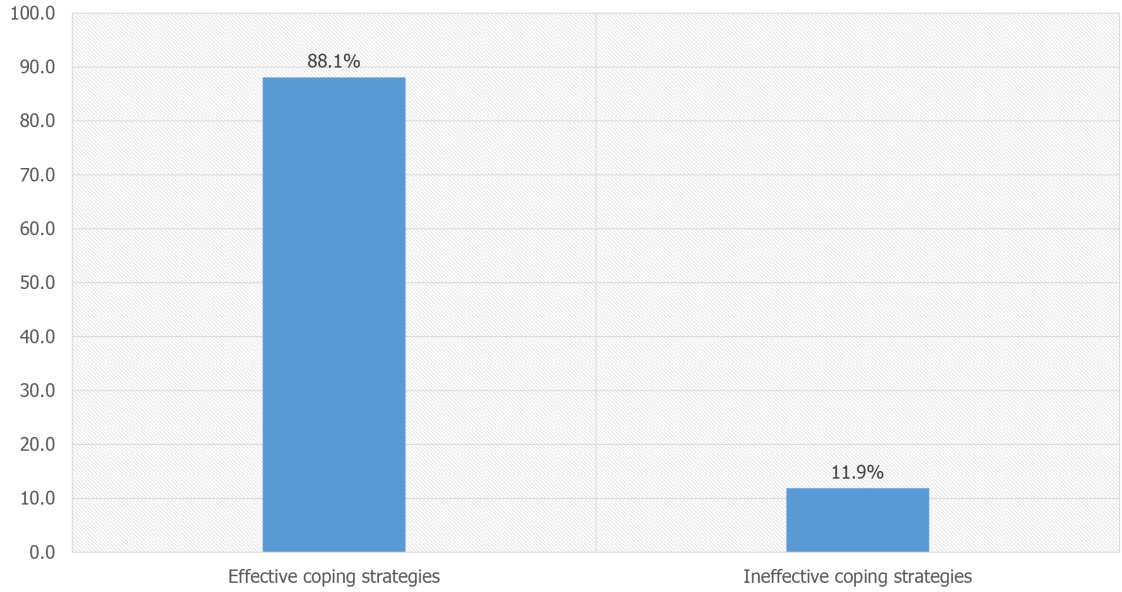

Figure 2 Effectiveness of caregivers' coping strategies.

since most cancer patients are aged 40 years and above, it is appropriate that younger and active persons care for them. Also, experience in providing emotional and psychological support to family members with ill-health may also account for the high number of caregivers who are married. From the results in Table 1, parents of caregivers were the largest category of care receivers. This is not surprising as cancer affects mostly older adults. As a result, their children and other relatives care for them. This finding is congruent with other studies which reported that care receivers were mainly parents and a partner/spouse[33,54].

The findings in the current study also showed that nearly 50% of the respondents [97 (46.2%)] experienced severe burden, while another 113 (53.8%) experienced moderate or no burden (Figure 1). These results were similar to those reported in other studies where most caregivers experienced severe burden[32,55]. This implies that most caregivers bear all the responsibilities of caring for their patients (which in most cases are their parents) and as such their personal, financial and social support places a huge burden on them. This is different for others who experience a moderate or trivial burden where responsibilities may be shared amongst other family members. This means that there is access to all forms of human and material resources to provide optimum care for cancer patients**.** It was observed that there is a strong association between caregivers' perceived burden level and coping strategies. This implies that the level of burden experienced by caregivers is significantly dependent on the coping strategies adopted. As shown in Table 4, caregivers with effective coping strategies can diminish their level of burden. This finding contradicts a Nigerian study where the relationship between level of burden and caregivers' coping strategies was not statistically significant[42].

Coping strategies adopted by caregivers, as presented in Table 2, include both problem-focused coping strategies (acceptance, appreciation and reprioritization) and emotion-focused coping strategies (family, positive self-view and empathy). Analysis showed that over two-thirds of caregivers [185 (88.1%)] indicated that the coping strategies used were effective (Figure 2). The efficacy of the caregivers' coping strategies may largely be determined by their impact on reducing the level of burden experienced during caregiving. Thus, the more effective the coping strategies, the lesser the burden. These results were similarly documented by Osundina *et al*[42] where a number of coping styles were identified including appreciation, emotional support, acceptance, planning, suppression, mental disengagement, religious coping, *etc.* Coping strategies are designed to motivate and encourage caregivers in providing care to cancer patients despite the challenges they often encounter.

The relationship between caregivers' characteristics (age, sex and educational status) was significantly associated with the caregivers' coping strategies. As shown in Table 3, it was also observed that middle-aged female caregivers with higher educational status tend to have more effective coping strategies compared to their counterparts. In Nigeria, middle-aged individuals (31-50 years) are considered the

most economically active group compared to other age groups. As such, they often demonstrate the capacity to deal with other forms of burden experienced during caregiving with an expedient coping mechanism. This explains why caregivers aged 31-50 years deal with the burden of caregiving better than other age groups as reported in other studies[2,34]. The results also showed that females demonstrated better coping strategies than their male counterparts. This is principally linked to the fact that about two-thirds of the respondents were female. Besides the current study, ample evidence has also confirmed that informal caregivers are mostly female and experience higher levels of burden compared to their male counterparts[2,3,46,56,57,60]. This is primarily because females are delegated to perform cultural subservient roles irrespective of age. As a result, they experience high levels of burden which require the adoption of effective coping strategies to continue providing care to cancer patients. It was also observed that caregivers with higher educational status adopted more effective coping strategies than their counterparts. The demonstration of adequate knowledge and skills in coping with the burden experienced during caregiving may be why caregivers with effective coping strategies were mostly those with higher educational status. As opined by Akpan-Idiok *et al*[14], caregivers with higher educational status are equipped with a broader repertoire of coping strategies geared towards solving problems rather than assessing the onerous nature of caregiving.

With regard to functional ability, the results showed that about two-thirds of the care receivers [137 (65%)] had low functional ability. As such, caregivers are susceptible to a higher burden during caregiving. This was also observed in other studies where functional impairment significantly contributed to the burden level of caregivers[24,27,39,54,58]. This explains why they demonstrated better coping strategies compared to other caregivers. In the current study, it was also documented that the relationship between functional ability and caregivers' coping strategies was statistically significant (P = 0.000) (Table 6). This implies that care receivers with low functional ability present a high level of burden to caregivers; thus, adopting expedient coping strategies would guarantee continuous caregiving by these caregivers.

The results presented in Table 7 show that the relationship between duration of care and caregivers' coping strategies was statistically significant (P = 0.000). This implies that the longer the duration of care, the higher the need to adopt more effective coping strategies. This is because, longer duration of care demonstrated a strong correlation with higher burden level as confirmed in previous studies[34,39,58]. Hence, the more time spent on caregiving, the higher the burden and the higher the need for effective coping strategies. The results also documented that the desire to continue caregiving was statistically significantly associated with caregivers' coping strategies (P = 0.000). It was further observed that effective coping strategies serve as an impetus to continue providing care to cancer patients. The desire to continue in care may largely be dependent on the level of efficacy of coping strategies used. With regard to the types of cancer and caregivers' burden level, caregiving in prostate and colorectal cancer patients resulted in a much greater burden than other types of cancer (Table 9). This may be linked to the extent of discomfort, stage of cancer and health status of the patients. This implies that the severity of caregiver' burden level can be assessed by the type of cancer involved.

CONCLUSION

There is great recognition of the role of informal caregivers in improving the health of their relatives and family members who are chronically ill. Findings in the current study identified coping strategies used by caregivers to ease the level of burden experienced during caregiving and these mechanisms include; acceptance, reprioritization, appreciation, family, positive self-view and empathy. Also, it was documented that there is a strong association between caregivers' level of burden and coping strategies (P = 0.030). It was also observed that age, sex, educational status, functional ability, duration of care and desire to continue caregiving were statistically significantly associated with caregivers' coping strategies. Based on the above findings, it was recommended that support groups in collaboration with health care providers should organize a symposium for informal caregivers on the intricacies of caregiving to chronically ill patients. This would create a platform for experience sharing, information dissemination and health care professional-caregiver interaction. To mitigate the burden of caregiving, it was also recommended that policy makers enact policies that would ensure that chronically ill patients have access to material

and financial support and should be the collaborative responsibilities of the government, non-governmental organizations and other support groups. Further studies on caregiver's burden level and coping strategies among patients with comorbidities should also be carried out.

ARTICLE HIGHLIGHTS

Research background

Nigeria is known to have the highest cancer mortality rate in Africa with an annual death toll of 10000 persons; with a cancer incidence of 100000, 300000 and 500000 in 1990, 2010 and 2013, respectively, and 41000 cancer-related deaths were recorded in 2014 alone. The upsurge in the incidence of cancer may pose serious challenges in caregiving with its attendant burden on the patients and caregivers. The physical, psychological, social, spiritual and financial impact of caregiving is considerable and often negative. Ample evidence has shown that caring for an advanced cancer patient may be associated with physical problems such as weight loss, sleeplessness, fatigue and exhaustion. Also, psychological symptoms such as depression, anxiety, feeling of isolation and reduced self-esteem may be experienced. They often cause a social burden resulting in restriction of time, disturbances in routines, diminished opportunities for leisure activities and loss of income. Recent descriptive surveys and qualitative studies of caregivers' cancer care experiences in India and Nigeria show that 38.9% of caregivers of cancer patients reported symptoms of depression. 41% to 62% of caregivers of advanced cancer patients experienced a high level of psychological burden compared to 19.2% of the general population.

Research motivation

Cancer is a devastating and debilitating chronic disease that affects both the patient and family members. Available evidence has confirmed that the care of chronically ill relatives by family members can be very challenging. This is because caregiving of cancer patients often presents a high level of burden on the caregivers. Consequently, this requires the adoption of coping mechanisms to cushion the effect of the burden experienced during caregiving.

Research objectives

To determine the burden experienced and coping strategies among caregivers of advanced cancer patients attending University of Calabar Teaching Hospital (UCTH), Cross River State, Nigeria.

Research methods

The study adopted a descriptive cross-sectional study design and the study population consisted of informal family caregivers providing services to histologically diagnosed advanced cancer patients receiving treatment at the UCTH as at the time of the survey. A researcher-developed structured questionnaire, a 22-item standardized validated Zarit Burden Interview (ZBI) and a modified 17-item Coping Orientation to Problems Experienced (COPE) Inventory were used to collect data from 250 eligible informal caregivers who were selected with regard to caregiver's characteristics, caregivers' level of burden and caregivers' coping strategies, respectively. Data gathered from the respondents were collated, coded and analyzed using Statistical Package for Social Sciences (SPSS version 20.0) software and Predictive Analytical Software (PAS version 19.0). Chi-square was used to test for associations between categorical variables at the 0.05 level of significance. Results are presented in tables and charts.

Research results

Assessment of burden level revealed that a reasonable proportion of the caregivers [97 (46.19%)] experienced severe burden, and 37 (17.62%) experienced trivial or no burden, while 76 (36.2%) perceived moderate burden. The results showed that the coping strategies used by caregivers to ease the level of burden experienced during caregiving included; acceptance, reprioritization, appreciation, family, positive self-view and empathy. It was also found that there was a strong association between caregivers' level of burden and coping strategies (P = 0.030).

Research conclusions

There was a strong association between socio-demographic characteristics (age, education, functional ability, desire to continue caregiving, types of cancer) and caregivers' coping strategies

Research perspectives

Further studies on caregiver's burden level and coping strategies in patients with comorbidities should also be carried out.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 1064-1069

DOI: 10.5306/wjco.v11.i12.1064

ISSN 2218-4333 (online)

CASE REPORT

Latent brain infection with *Moraxella osloensis* as a possible cause of cerebral gliomatosis type 2: A case report

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Author contributions: Strojnik T, Kavalar R, Rupnik M, Robnik SL, Popovic M and Gornik-Kramberger K drafted the manuscript, assisted with data analysis, and performed statistical analysis; Strojnik T and Velnar T participated in the design and the oversight of the study; all authors read and approved the final manuscript.

Informed consent statement: The patient provided informed consent.

Conflict-of-interest statement: The authors declare no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and

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Abstract

BACKGROUND

The gram-negative aerobic bacterium *Moraxella osloensis* is an opportunistic pathogen in brain tissues.

CASE SUMMARY

The gram-negative aerobic bacterium *Moraxella osloensis* was isolated from a patient's brain tissue during a stereotactic biopsy.

CONCLUSION

This is the first report of a brain tissue infection with *Moraxella osloensis* possibly causing brain gliomatosis.

Key Words: *Moraxella osloensis*; Brain infection; Cerebral gliomatosis; Stereotactic brain biopsy; Case report

Manuscript source: Invited manuscript

Specialty type: Oncology

Country/Territory of origin: Slovenia

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 31, 2020
Peer-review started: March 31, 2020
First decision: September 24, 2020
Revised: October 10, 2020
Accepted: November 4, 2020
Article in press: November 4, 2020
Published online: December 24, 2020

P-Reviewer: Vyshka G
S-Editor: Chen XF
L-Editor: Webster JR
P-Editor: Wang LL

Core Tip: The gram-negative aerobic bacterium *Moraxella osloensis* is an opportunistic pathogen and was isolated from a patient's brain tissue during a stereotactic biopsy. This is the first report of a brain tissue infection with *Moraxella osloensis*, possibly causing brain gliomatosis.

Citation: Strojnik T, Kavalar R, Gornik-Kramberger K, Rupnik M, Robnik SL, Popovic M, Velnar T. Latent brain infection with *Moraxella osloensis* as a possible cause of cerebral gliomatosis type 2: A case report. *World J Clin Oncol* 2020; 11(12): 1064-1069
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/1064.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.1064

INTRODUCTION

Despite the recent advances in neuroimaging of the brain, an accurate diagnosis of focal brain lesions requires tissue sampling and histological verification in order to determine treatment modalities in neuro-oncology. Stereotactic biopsy is the gold standard for neuropathological diagnosis that guides the choice of management and avoids the risks of blind treatment. It is particularly reliable for diagnosing those lesions that cannot be removed through open surgery due to their location, depth and number, such as deeply located cerebral lesions, multifocal tumors and lesions located in eloquent areas[1,2].

Bacterial isolates from brain tissue are extremely rare[3]. The gram-negative aerobic bacterium *Moraxella osloensis* is considered an opportunistic human pathogen. Although this particular bacterium is very rarely encountered in clinical practice, there have been individual case reports of endophthalmitis, endocarditis, osteomyelitis, pneumonia, central venous catheter infection, as well as bacteraemia caused by *Moraxella osloensis*, including three patients with meningitis[4-8]. However, it is not known whether this microbe may also be involved in tumorigeneses of brain tissue. The mechanism for such oncogenic transformation in *Moraxella osloensis* infections is not completely understood and it is supposed that the pathogenesis may be similar to that of oncogenic viruses or, alternatively, as a result of a long chronic low-grade infection that eventually results in uncontrolled growth[7]. We report a patient with gliomatosis cerebri and *Moraxella osloensis* isolated from the brain tissue. To our knowledge, this is the first documented case of brain infection with this agent, which might be the reason for the brain gliomatotic alterations.

CASE PRESENTATION

Chief complaints

A 74-year old lady was admitted to the Neurological Clinic of the University Medical Centre Ljubljana with a 3-mo history of gait disturbance, urinary incontinence, cognitive decline and mood changes.

History of present illness

The patient reported gait disturbance, urinary incontinence, cognitive decline and mood changes for the last three months.

History of past illness

No past illnesses were documented.

Personal and family history

Personal and family history was unremarkable, except for arterial hypertension.

Physical examination

On admission, the neurological examination revealed left hemiparesis with positive plantar response on the left. She walked with difficulty. The mental state examination found both an attention deficit and memory deficit. The lady was slow, uninterested and lacked spontaneity. Neuropsychological tests indicated frontal lobe syndrome.

Laboratory examinations

Microbiological cultures of the peripheral blood and cerebrospinal fluid were negative. Specific analysis of cerebrospinal fluid and blood excluded infection with *Borrelia burgdorferi* and *Treponema pallidum*. The chest radiograph was normal. Systemic diseases and primary neoplasms elsewhere were ruled out and eventually, the patient was discharged.

After two months, she was referred to the Department of Neurosurgery of the University Medical Centre Maribor. On admission, she was immobile, slow and uninterested. The neurological examination revealed left central facial palsy and left hemiparesis. Repeated magnetic resonance imaging (MRI) was similar to the first scan.

Routine blood chemistry tests were also performed and all the results were within the reference range, as were the sedimentation rate and hematological tests. The laboratory tests showed normal levels of thyroid-stimulating hormone, B12 and folic acid. The cerebrospinal fluid was clear with a normal protein concentration (protein, 0.28 g/L; lactate, 1.8 mmol/L; glucose, 3.7 mmol/L; 1 lymphocyte/μL).

Imaging examinations

Neuroradiological investigations revealed multifocal brain lesions. Computed tomography (CT) shown bilateral hypodense and poorly defined subcortical brain alterations. Initial MRI, obtained seven days after admission, demonstrated some small focal areas of high intensity on T2-weighted imaging and on fluid attenuation inversion recovery sequences, located in the periventricular region of both frontal lobes. No contrast enhancement was evident (Figure 1A). Cerebral perfusion scintigraphy revealed only minimal changes in brain perfusion in the frontal region, which could have coincided with frontotemporal dementia.

FINAL DIAGNOSIS

The autopsy revealed massive pulmonary thromboembolism on both sides. The post mortem examination of the central nervous system showed thrombosis of the left middle cerebral artery with a consequent acute hemorrhagic left hemispheric brain infarction and thickened corpus callosum. Microscopic analysis revealed widespread neoplastic astrocytic growth, infiltrating the brain tissue and affecting many areas, including the area of previous biopsy, left thalamus, whole corpus callosum and both gyri cinguli as well as the left occipital, right parietal and both temporal lobes. In the splenium of the corpus callosum, there was microscopic tumor growth of glioblastoma, consistent with cerebral gliomatosis type 2 (Figure 1B-E).

TREATMENT

The patient underwent a stereotactic biopsy for histological verification of the changes in the right periventricular region. The modified Riechert Stereotactic System (MHT, Freiburg, Germany) and a workstation for multi-planar trajectory planning (Amira, Visage Imaging; Berlin, Germany) were used. The biopsy samples were obtained stepwise along the trajectory through the entire lesion - serial biopsy specimens. The cytopathologist in the operating room immediately evaluated the alternate tissue samples using a smear preparation with methylene blue staining, and reported possible gliomatosis. The tissue fragments for microbiological investigations were immediately transferred from the biopsy forceps into culture medium (BacT/ALERT FA; Biomerieux Durham, United Kingdom) and sent to the microbiological laboratory. The identification was performed with VITEK 2 (Bio Mereus; Craponne, France). Sequencing of the amplified 16S rRNA gene confirmed the identification. The amplification was performed using primers and conditions described by Bianciotto *et al*[9] and sequencing was carried out by MWG BIOTECH (Ebersberg, Germany). The sequence showed 99% identity to *Moraxella osloensis* in the NCBI database (NCBI/BLAST: http://blast.ncbi.nlm.nih.gov/Blast.cgi) and 98.6% identity to *Moraxella osloensis* in the curated database Ribosomal Database Project (http://rdp.cme.msu.edu/seqmatch/seqmatch_intro.jsp) (Table 1). Similar identity scores were also obtained for *Enhydrobacter aerosaccus*. Due to reported errors in *Enhydrobacter* sequences, a low number of *Enhydrobacter* hits as compared to Moraxella hits and phenotypic identification results, the final reported identification of this strain was *Moraxella osloensis*. The bacterial strain is still available in the archive of the

Table 1 An overview of closest matches of patient isolates 16S rDNA with sequences in two databases (GenBank and Ribosomal Database Project)

Identification	GenBank		RDP	
	GenBank numbers	% of identity	RDP numbers	% of identity
Moraxella osloensis	AB643592.1	99%	S000386983, S000425263, S002227306, S003316307	98.6%
Moraxella species	AB905490.1, KC119125.1	99%	S003750534, S004078352	98.6%
Enhydrobacter species	FR823402.1	99%	S002223560, S002408247	98.6%

RDP: Ribosomal Database Project.

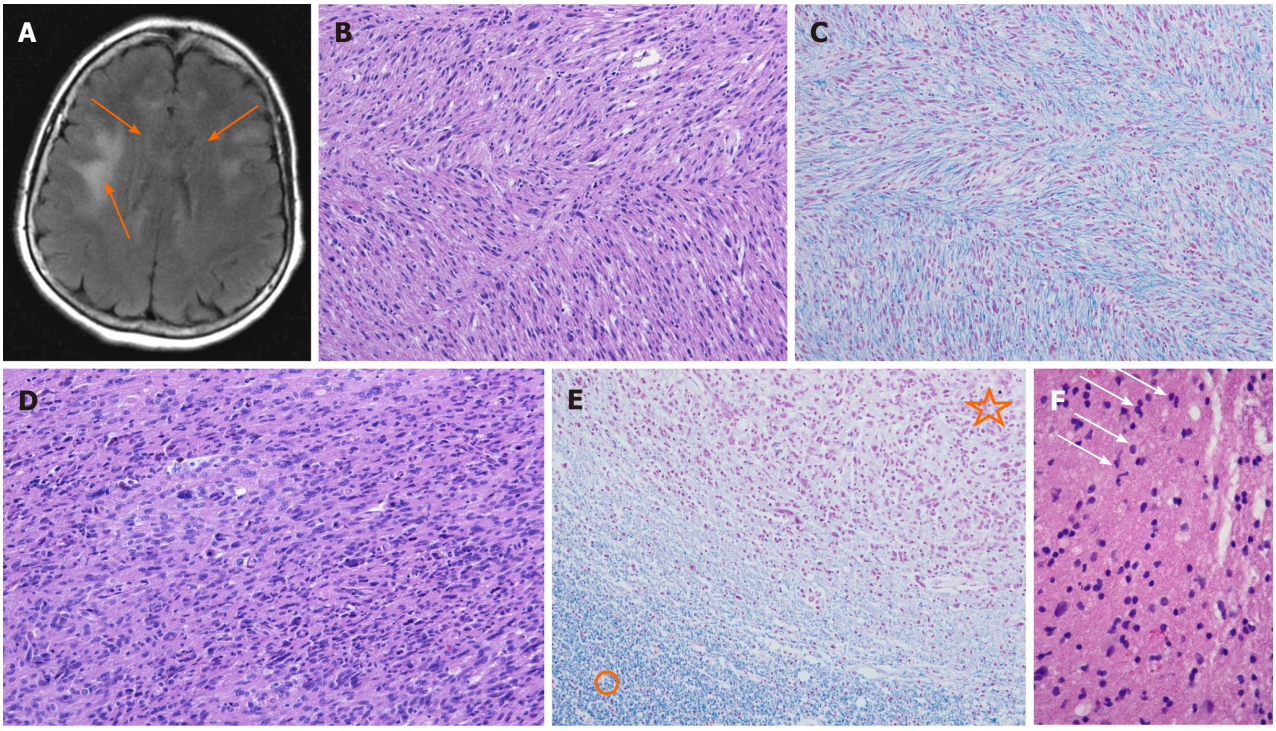

Figure 1 Magnetic resonance imaging, T2-weighted sequence, stereotactic brain biopsy, and post-mortem brain changes in the patient.
A: Magnetic resonance imaging revealed some focal areas of high intensity in the white matter of both frontal lobes (arrows) on T2-weighted sequence; B and C: Microscopic feature of cerebral gliomatosis in the genu of the corpus callosum: Hypercellular white matter with tumor cells in between the myelinated fibers [hematoxylin and eosin (H/E) staining and Klüver-Barrera staining, respectively]; D: Microscopic feature of malignant glioma in the splenium of the corpus callosum: Hypercellular tumor composed of polymorphic and some multinucleated tumor cells with brisk mitotic activity (H/E); E: There were no myelinated nerve fibers inside the tumor mass (upper part, star) compared to the adjacent white matter (lower part, circle) (Klüver-Barrera); F: Hypercellular white matter with slightly polymorphic nuclei (arrows) suspected for infiltrating neoplastic glial cells.

microbiological laboratory. The remaining tissue fragments were fixed in formaldehyde and sent to the pathology laboratory for analysis. A post-biopsy CT scan was performed to exclude complications and to verify accurate target sampling.

The patient's clinical condition was unchanged during hospitalization. After a week, she was transferred to the neurological clinic.

The histological analysis of samples obtained by serial stereotactic biopsy failed to provide a definitive diagnosis (Figure 1F). The pathologist found gliomatosis, intermingled with some neoplastic astrocytes. Three weeks later, we received the microbiological test results of the brain tissue samples, which detected *Moraxella osloensis*. An antimicrobial susceptibility test performed using the disk diffusion method showed that the isolate was susceptible to a variety of antimicrobial agents such as ampicillin, cefaclor, cefuroxime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, chloramphenicol, tetracycline, imipenem, azithromycin and rifampicin.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient was in poor clinical condition after the stereotactic biopsy due to continuous neurological deterioration. She received palliative medical care in the neurological department and six weeks after the biopsy she died.

DISCUSSION

A specific histological diagnosis is crucial in order to select the best therapeutic option. In this case report, we presented a patient with a progressive frontal lobe syndrome. After extensive diagnostic evaluation, multiple lesions detected by MRI remained the only discernible evidence of her illness. The differential diagnosis based on CT and MRI findings included, among others, gliomatosis cerebri, progressive multifocal leukoencephalopathy and lymphoma. Surprisingly, microbiological analysis of the brain samples revealed infection with *Moraxella osloensis*, which was completely unexpected. The samples were obtained under sterile conditions during the stereotactic biopsy and it was very unlikely that the samples were contaminated during the course of sampling and analysis. The infection with *Moraxella osloensis* was probably clinically silent at first in our patient, due to the low virulence of this organism or perhaps due to the antibiotic therapy for urinary tract infection. It was unclear where the organism had spread from. The incidence of surgical site infection at our hospital is lower than reported in many comparable studies[10].

The post-mortem neuropathological examination revealed cerebral gliomatosis affecting various areas of both cerebral hemispheres and the corpus callosum. We suppose that the patient suffered a latent brain infection with *Moraxella osloensis*, which could have had a possible oncogenic effect on the development of cerebral gliomatosis, or more likely, unfavorably altered the course of the disease. Different microorganisms have long been suspected to play a role in development of brain tumors[10-12]. Another possibility could be that a latent bacterial infection may have modulated the immune responses in the brain tumor defense[12,13]. However, some chronic bacterial infections are thought to be associated with amyloid depositions in Alzheimer's disease, as well[13]. A PubMed search yielded some published cases of *Moraxella osloensis* meningitis[3,5]. To our knowledge, this is the first report of brain tissue infection with this microorganism. Bacteria may initiate a cascade of events, leading to chronic inflammation and amyloid deposition or even participate in tumorigenesis. An early diagnosis of encephalitis is critical for effective treatment. In addition to histological analysis, we suggest performing microbiological analysis more often during stereotactic biopsy for multiple brain lesions. However, we are aware that the association between bacterial infection and gliomatosis cerebri could be purely coincidental. In order to rule out a possible causal relationship between microbial infection and cerebral gliomatosis, further studies are needed.

CONCLUSION

This is the first report of a brain tissue infection with *Moraxella osloensis*, which may initiate a cascade of events, leading to chronic inflammation, amyloid deposition or even tumorigenesis. Early diagnosis of encephalitis is vital for effective treatment. In addition to histological examination, microbiological analysis of stereotactic biopsy samples is imperative.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 1070-1075

DOI: 10.5306/wjco.v11.i12.1070

ISSN 2218-4333 (online)

CASE REPORT

Preoperative rectal tumor embolization as an adjunctive tool for bloodless abdominoperineal excision: A case report

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Abstract

BACKGROUND

Abdominoperineal excision (APE)-related hemorrhage can be challenging due to difficult access to pelvic organs and the risk of massive blood loss. The objective of the present study was to demonstrate the use of preoperative embolization (PE) as a strategy for blood preservation in a patient with a large low rectal tumor with a high risk of bleeding, scheduled for APE.

CASE SUMMARY

A 56-year-old man presented to our institution with a one-year history of anal bleeding and rectal tenesmus. The patient was diagnosed with bulky adenocarcinoma limited to the rectum. As the patient refused any clinical treatment, surgery without previous neoadjuvant chemoradiation was indicated. The patient underwent a tumor embolization procedure, two days before surgery performed *via* the right common femoral artery. The tumor was successfully devascularized and no major bleeding was noted during APE. Postoperative recovery was uneventful and a one-year follow-up showed no signs of recurrence.

CONCLUSION

Therapeutic tumor embolization may play a role in bloodless surgeries and

increase surgical and oncologic prognoses. We describe a patient with a bulky low rectal tumor who successfully underwent preoperative embolization and bloodless abdominoperineal resection.

Key Words: Rectal neoplasms; Proctectomy; Bloodless medical and surgical procedures; Embolization, therapeutic; Colorectal surgery; Case report

Core Tip: Abdominoperineal excision (APE) remains a major surgery with considerable morbidity. Half of patients undergoing APE have some type of postoperative complication, and bleeding requiring transfusion of blood products is the main morbidity of the procedure. Preoperative embolization as a strategy for blood preservation in a giant rectal hemangioma has been successfully described.

Citation: Feitosa MR, de Freitas LF, Filho AB, Nakiri GS, Abud DG, Landell LM, Brunaldi MO, da Rocha JJR, Feres O, Parra RS. Preoperative rectal tumor embolization as an adjunctive tool for bloodless abdominoperineal excision: A case report. *World J Clin Oncol* 2020; 11(12): 1070-1075
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/1070.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.1070

INTRODUCTION

An abdominoperineal excision (APE) consists on a combined abdominal and perineal resection of the anorectum and may be performed in benign conditions and malignancies. In low rectal cancer, advances in chemoradiotherapy and surgical devices have warranted a decrease in APE rates. Nevertheless, in those cases with anal sphincter involvement, the operation may undoubtedly be an alternative for oncologic control[1].

Despite the evolution of colorectal surgery, such as the development of laparoscopic access and robotic surgery, proctectomy remains a major surgery with considerable morbidity[2]. Approximately half of patients undergoing APE have some type of postoperative complication, and bleeding requiring transfusion of blood products is the main morbidity of the procedure[3].

APE-related hemorrhage can be challenging due to difficult access to pelvic organs and the risk of massive blood loss (> 1000 mL of blood)[4]. Furthermore, blood loss and blood transfusions have been associated with worse oncologic and postoperative outcomes in non-metastatic colorectal cancer. This effect is not completely understood but immunomodulatory signals leading to immunosuppression may be involved in adverse events[5].

The concept of bloodless surgery involves a series of perioperative strategies to prevent transfusion of blood products[6]. Recent studies have shown promising results in patients who have adopted this strategy, in bloodless centers[7]. Of note, the positive effect on surgical results depends on the adoption of adequate blood conservation methods[6]. The objective of the present study was to demonstrate the use of preoperative embolization (PE) as a strategy for blood preservation in a patient with a large low rectal tumor with a high risk of bleeding, scheduled for APE.

CASE PRESENTATION

Chief complaints

The patient was a 56-year-old man who suffered from anal bleeding and rectal tenesmus.

History of present illness

He presented to our institution with a one-year history of anal bleeding and rectal

related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Informed consent statement: All authors carefully protected the patient's anonymity. The patient signed an informed consent allowing the publication of this case report and any other related publication.

Conflict-of-interest statement: The authors report no conflict of interest.

CARE Checklist (2016) statement: We have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Manuscript source: Invited manuscript

Specialty type: Oncology

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: July 16, 2020
Peer-review started: July 16, 2020
First decision: August 7, 2020
Revised: August 20, 2020
Accepted: October 20, 2020
Article in press: October 20, 2020

Published online: December 24, 2020

P-Reviewer: Yoon YS
S-Editor: Fan JR
L-Editor: Webster JR
P-Editor: Wang LL

tenesmus. Worsening of symptoms was progressive. The patient also reported anorectal pain and weigh loss (15% of body weight in the same period).

History of past illness

No underlying diseases were reported by the patient.

Physical examination

Physical examination was normal, except for a rectal mass starting 1 cm from the anal border, circumferential and obstructive.

Laboratory examinations

Laboratory tests were normal, except for a hemoglobin level of 9.4 g/dL. Carcinoembryonic antigen level was 3.34 ng/mL.

Imaging examinations

Colonoscopy was incomplete due to the bulky rectal mass. Tumor biopsy revealed a rectal adenocarcinoma. Abdominal and thoracic contrast-enhanced computed tomography scans showed extensive parietal thickening of the rectum, with an extension of 17.5 cm without signs of locoregional and distant metastasis (Figure 1).

FINAL DIAGNOSIS

The patient was diagnosed with bulky adenocarcinoma limited to the rectum. As he refused any clinical treatment, surgery without previous neoadjuvant chemoradiation was indicated.

TREATMENT

The patient also refused blood transfusion due to religious belief. To decrease bleeding during surgery, the patient underwent a tumor embolization procedure, two days before surgery performed *via* the right common femoral artery. Devascularization was performed with regular micra tris-acryl gelatin microspheres (500 μm) until partial reduction of vascular flow in the tumor topography. Metal coils were also released in the main trunk of the rectal arteries with subsequent administration of acrylic glue (25% n-butyl-cyanoacrylate). Angiographic control evidenced occlusion of the main branch and preservation of collateral circulation of the rectum and part of the tumor topography by small adjacent rectal branches (Figure 2). Regarding the surgical procedure, due to the absence of an adequate anal margin, we opted for an APE with total mesorectum excision and terminal colostomy in the upper left quadrant of the abdomen. A large rectal tumor occupying the entire pelvis was diagnosed, and there was no involvement of other abdominal organs (Figure 3). There was no blood transfusion during the operation. Pre- and postoperative hemoglobin levels were 9.4 and 9.1 g/dL, respectively. Analysis of the surgical specimen showed an adenocarcinoma of the rectum and anal canal, 15 cm in longitudinal length and invasion of the muscularis propria. A total of 54 disease-free lymph nodes were retrieved. There was no angiolymphatic and perineural invasion; however, extensive tumor necrosis was observed (Figure 4).

OUTCOME AND FOLLOW-UP

Surgical margins were free of neoplasia and tumor staging was classified as pT2pN0cM0. The patient was discharged on the 7th postoperative day due to a metabolic ileus clinically managed. Adjuvant chemotherapy was not performed and no synchronous colonic neoplasms were diagnosed during the colonoscopy performed three months after surgery. Clinical evaluation 12 mo after surgery, showed no evidence of cancer recurrence.

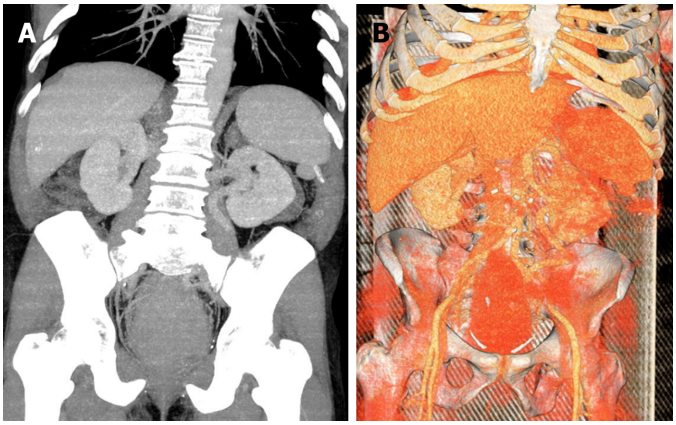

Figure 1 Computed tomography scans with vascular reconstruction. A: A bulky rectal tumor with B: Marked hypervascularization.

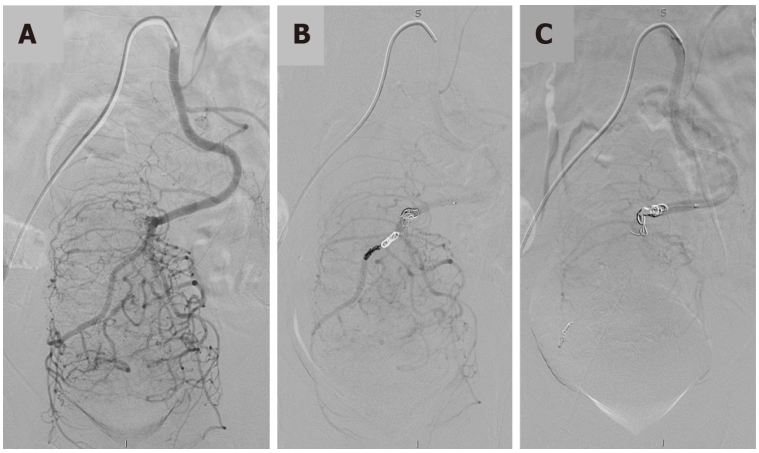

Figure 2 Preoperative embolization. A: Digital subtraction angiography (DSA) of the inferior mesenteric artery identifying the enlarged superior rectal artery with prominent branches supplying the rectal tumor; B: DSA of the inferior mesenteric artery after 300-500 micra tris-acryl gelatin microspheres distal embolization into the superior rectal artery and partial occlusion of its main branch with controlled detachable platinum coils; C: Final DSA control of the inferior mesenteric artery after injection of N-butyl-2 cyanoacrylate with ethiodol 1:4 at the bifurcation of the right and left branches of the superior rectal artery, showing a significant reduction in distal arterial supply.

DISCUSSION

Under normal conditions, the evaluation of blood supply in the distal rectum and mesorectum shows a predominance of blood vessels within the rectal wall[8]. In rectal cancer patients contrast-enhanced endoscopic ultrasound imaging usually reveals well vascularized masses with inhomogeneous enhancement of the contrast resulting from necrotic areas[9]. In the reported case, although atypical, a hypervascularized mass, with a predominance of blood vessels in the mesorectum was observed, as demonstrated by imaging exams. This hypervascularization is a hallmark of cancer and may be associated with the worst oncologic outcomes and with surgical complications (accidents during dissection and greater blood loss)[10].

The most common measures of blood conservation in oncologic patients have been discussed elsewhere and can be grouped according to the period in which they are started[6]. In APE patients, preoperative measures include treatment of anemia, suspension of substances that interfere with coagulation and careful procedure. Intraoperatively, it is important to minimize surgical trauma and to identify the proper surgical plane to perform a fine total mesorectal excision. Also, there is potential for autologous blood salvage and autologous normovolemic hemodilution. Postoperatively, lower levels of hemoglobin should be tolerated whenever possible and laboratory testing should be reduced to a minimum[6].

PE as a strategy to reduce intraoperative blood loss is a concept that has been developed for several anatomical territories. In pelvic tumors, devascularization rates greater than 75% can be obtained[11]. In our experience, PE was safe and successfully reduced intraoperative bleeding in a patient with a giant cavernous hemangioma of

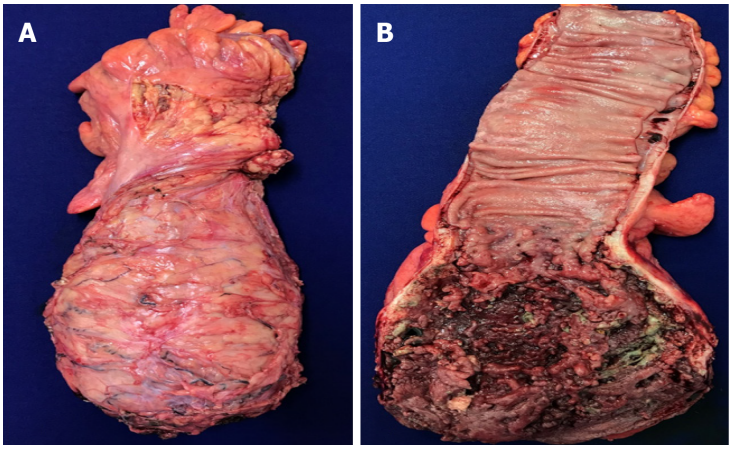

Figure 3 Surgical specimen after abdominal perineal resection. A: Total mesorectal excision; B: Extensive tumor necrosis can be observed after opening the surgical specimen.

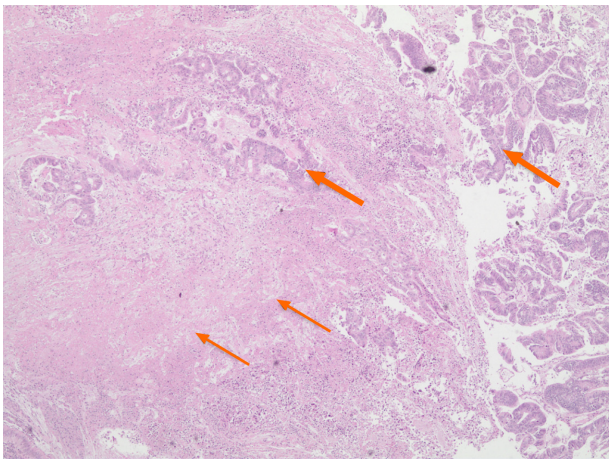

Figure 4 Rectal adenocarcinoma (thick arrows) showing extensive tumor necrosis (thin arrows). Hematoxylin and Eosin stain, × 40 magnification.

the rectum[12]. Although relatively simple and safe, PE can lead to significant tumor necrosis and a higher risk of bleeding, therefore, surgical resection of the tumor mass must be performed early. At our institution, we perform the definitive operation within 48 h after PE.

To the best of our knowledge, PE of bulky rectal tumors with modern techniques has not been described; however the rationale sounds reasonable, since a correlation between devascularization and less blood loss has been observed in other hypervascular tumors such as in renal masses[13]. In our experience, preoperative embolization of locally advanced rectal tumors reduces the blood content within bulky masses and can be used as an effective and safe adjunct to blood conservation. However, prospective and randomized studies are necessary to reveal the causal relationship between PE and reduced blood loss in bulky rectal masses.

CONCLUSION

Based on our experience and on a literature review we believe that preoperative embolization of rectal cancer may be an adjunctive tool in bloodless rectal surgeries.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2020 December 24; 11(12): 1076-1083

DOI: 10.5306/wjco.v11.i12.1076

ISSN 2218-4333 (online)

CASE REPORT

Endometrial clear cell carcinoma invading the right oviduct with a cooccurring ipsilateral oviduct adenomatoid tumor: A case report

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Author contributions: Hu ZX contributed to pathological diagnosis, collecting the patient's medical records and pathological pictures, and writing the first draft of the paper; Tan MH contributed to pathological diagnosis and data management; Li QZ performed the surgery; Xu JL performed B-ultrasound examination; Chen W contributed to gross specimen picture arrangement; Xie ZH contributed to taking the pathological biopsy and taking photos; Zhou YJ contributed to H&E staining; Liang Q contributed to immunohistochemical staining; An JH contributed to translation and submission of the paper; Shen H contributed to study design, data analysis, conclusion extraction, and guiding paper writing, modification, and finalization.

Informed consent statement: The patient provided informed written

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Abstract

BACKGROUND

To investigate the clinicopathological features of endometrial clear cell carcinoma that has invaded the right oviduct with a cooccurring ipsilateral oviduct adenomatoid tumor.

CASE SUMMARY

A case of endometrial clear cell carcinoma invading the right oviduct with a cooccurring ipsilateral oviduct adenomatoid tumor was collected and analyzed using pathomorphology and immunohistochemistry. Endometrial clear cell carcinoma cells were distributed in a solid nest, papillary, shoe nail-like, and glandular tube-like distribution. There was infiltrative growth, and tumor cells had clear cytoplasm and obvious nuclear heteromorphism. The cancer tissue was necrotic and mitotic. The cancer tissue invaded the right oviduct. The ipsilateral oviduct also had an adenomatoid tumor. The adenomatoid tumor was arranged in microcapsules lined with flat or cubic cells that were surrounded by smooth muscle tissue. The adenomatoid tumor cells were round in shape.

CONCLUSION
Clear cell carcinoma of the endometrium can invade the oviduct and occur simultaneously with tubal adenomatoid tumors. Upon pathological diagnosis, one should pay close attention to distinguishing whether an endometrial clear cell carcinoma is invading the oviduct or whether it is accompanied by an adenomatoid tumor of the oviduct. Immunohistochemistry is helpful to differentiate these two disease entities. Endometrial clear cell carcinomas express Napsin-A and P16 and are negative for estrogen receptor and progesterone receptor. The presence of endometrial clear cell carcinoma does not affect the expression of CK and calretinin in adenomatoid tumors.

Key Words: Endometrium; Clear cell carcinoma; Oviduct; Adenomatoid tumors; Differential diagnosis; Case report

Core Tip: In pathological diagnosis, when investigating invasion of the oviduct, one should pay close attention to distinguishing whether the endometrial clear cell carcinoma invades the oviduct or whether it is accompanied by an oviduct adenomatoid tumor. The significance of this investigation is to determine whether the endometrial adenocarcinoma has tubal metastasis. This is critical for the confirmation of T3a in tumor-node-metastasis staging.

Citation: Hu ZX, Tan MH, Li QZ, Xu JL, Chen W, Xie ZH, Zhou YJ, Liang Q, An JH, Shen H. Endometrial clear cell carcinoma invading the right oviduct with a cooccurring ipsilateral oviduct adenomatoid tumor: A case report. *World J Clin Oncol* 2020; 11(12): 1076-1083
URL: https://www.wjgnet.com/2218-4333/full/v11/i12/1076.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i12.1076

INTRODUCTION

Clear cell carcinoma of the endometrium is a special pathological type of endometrial carcinoma which accounts for only 3.5% of all endometrial carcinomas[1]. Clear cell carcinoma of the endometrium is highly invasive and is associated with a poor prognosis. Adenomatoid tumors are rare benign tumors that mainly occur in the reproductive systems of both men and women[2]. In women they are common in the uterus and rarely occur in the oviduct. The coexistence of endometrial clear cell carcinoma and oviduct adenomatoid tumor is even rarer. Here we present a case of endometrial clear cell carcinoma invading the right oviduct with a cooccurring ipsilateral adenomatoid tumor which was collected at The First People's Hospital of Zhaoqing. Pathological morphology and immunohistochemical analysis were performed to provide reference for clinical pathological diagnosis and differential diagnosis.

CASE PRESENTATION

Chief complaints

The patient presented with irregular vaginal bleeding for 2 years and vaginal discharge for 1 year. Additionally, her menstrual period was prolonged and disordered, and her menstrual volume was large. Occasionally during menstruation there were blood clots and flocculent tissues.

History of present illness

In April 2020, curettage was performed in another hospital and the pathology report of the resected tissue suggested endometrial carcinoma of the uterine cavity. The tumor was predicted to be a type II endometrial carcinoma and surgical treatment was recommended.

consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Manuscript source: Unsolicited manuscript

Specialty type: Oncology

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: August 21, 2020
Peer-review started: August 21, 2020
First decision: September 13, 2020
Revised: September 27, 2020
Accepted: October 15, 2020
Article in press: October 15, 2020
Published online: December 24, 2020

P-Reviewer: Viswanath Y
S-Editor: Huang P
L-Editor: Wang TQ
P-Editor: Zhang YL

History of past illness

For further diagnosis and treatment, the patient was admitted to The First People's Hospital of Zhaoqing in June 2020. The patient underwent bilateral tubal ligation in 2004.

Physical examination

A gynecological examination concluded that the vulva was normal, the vagina was unobstructed, there was a low volume of thin secretions, the cervix was slightly inflamed, there was no hypertrophy of the cervix and no lifting pain or coloring, the uterine body was in the posterior position, the uterus was enlarged and tough to the equivalent of 2 mo of pregnancy, the activity of cervix was general, there was no tenderness in the abdomen, and no mass was palpable in bilateral appendages.

Laboratory examinations

Routine blood tests showed a low hemoglobin level at 69 g/L and high levels of tumor associated antigens CA125 and CA15-3, which were 76.2 U/mL and 28.28 U/mL, respectively.

Imaging examinations

Gynecological color Doppler ultrasound showed solid lesions in the uterus and mixed lesions between the right ovary and right uterine horn. The lesions were approximately 44 mm × 27 mm in size, had an unclear boundary with the right ovary, had an uneven echo distribution, and had no change in posterior echo. The patient was treated by total abdominal hysterectomy, bilateral adnexectomy, pelvic lymph node dissection, and pelvic adhesion lysis (Figure 1).

FINAL DIAGNOSIS

There were three main pathological diagnostic observations: (1) The cancerous tissue was a mixed endometrial adenocarcinoma. The cancer tissue infiltrated the deep muscle layer of the uterus, and invaded the right oviduct and the ipsilateral oviduct. The mixed endometrial adenocarcinoma was accompanied by an adenomatous tumor; (2) No tumors were found in the cervix, left oviduct, or bilateral ovaries; and (3) No cancer metastasis was found in bilateral pelvic lymph nodes.

TREATMENT

The patient presented with irregular vaginal bleeding, excessive vaginal discharge, moderate anemia, and increased tumor associated antigen expression. A B-mode ultrasound scan revealed solid intrauterine lesions and mixed lesions between the right ovary and the right cornu uteri. The pathological investigation of the tumor biopsy confirmed the presence of uterine cavity type II endometrial carcinoma and indicated that surgical intervention was required.

OUTCOME AND FOLLOW-UP

The patient recovered well after operation, and no complications occurred during the follow-up of 3 mo.

DISCUSSION

Endometrial clear cell carcinoma is a rare malignant tumor. It is a type II endometrial cancer that is highly invasive and prone to metastasis, has high recurrence and mortality rates, and has a poor prognosis[3,4]. The main clinical symptom is irregular vaginal bleeding. This patient presented with irregular vaginal bleeding and discharge. Investigative blood tests showed moderate anemia and elevated tumor-associated antigens CA125 and CA15-3. B-mode ultrasound showed multiple lesions consistent with malignant endometrial tumors which had pathological abnormalities. This was confirmed by immunohistochemical staining. Cancer tissue invaded the right

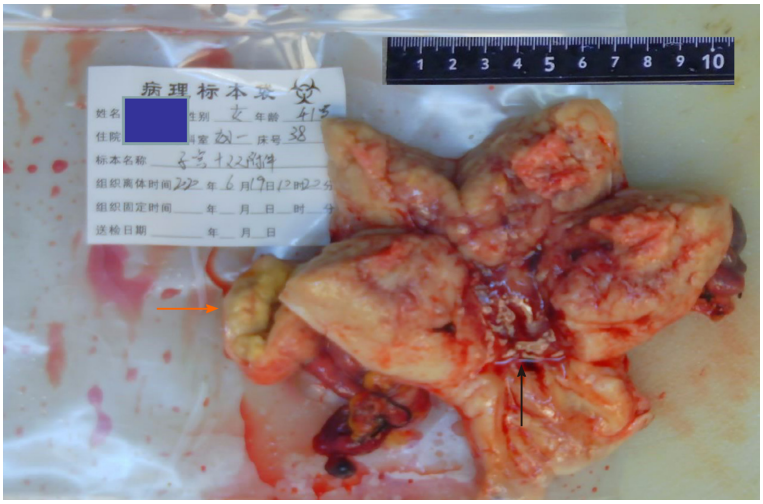

Figure 1 Cauliflower mass in the uterine cavity (black arrow) and right oviduct mass (orange arrow).

oviduct, indicating that metastasis has occurred. A high proportion of tumor cells expressed Ki-67, indicating that the tumor had a high proliferation index and that the tumor was growing fast. In this case, the morphology of the endometrial clear cell carcinoma was complex. We report nest-like, solid, papillary, shoe nail-like and glandular tube-like infiltration into the deep myometrium. The cytoplasm of the cancer cells was clear or eosinophilic and the nucleoli were obvious. Necrosis and mitosis were also obvious. Mucus secretion was observed in some glandular cavities. We also observed interstitial fiber hyperplasia that is consistent with the histopathological morphology of endometrial clear cell carcinoma reported in the literature[5] (Figure 2).

In order to make informed decisions on the best future therapeutic regimes, the tumor tissue needs to be differentiated from endometrioid carcinoma, serous carcinoma, and metastatic clear cell renal cell carcinoma (ccRCC). Here we identified a type II endometrioid carcinoma. Type II endometrioid carcinoma is often histologically tubular and cribriform, whereas papillary histology is rare. In this case, stromal cells were absent and the tumor was surrounded by complex hyperplasia of the endometrium which lacked the characteristic transparent cytoplasm of clear cell carcinoma. Occasionally in endometrial carcinoma, subnuclear vacuoles similar to secretory endometrium may appear. These express CK, CK7, vimentin, ER, PR, and P16, but do not express the endometrial marker Napsin A. Here we report an endometrial carcinoma with the typical morphology of clear cell carcinoma. This case expresses CK, CK7, P16, and Napsin A, but does not express vimentin, ER, or PR. This confirms the presence of endometrial clear cell carcinoma[6]. Ping *et al*[7] and others have shown that there are three expression patterns of Napsin A in endometrial clear cell carcinoma: Punctate, focal, and diffuse. In this case, we observed punctate expression of Napsin A, which supports the diagnosis of clear cell carcinoma. ER and PR are robust differential diagnostic markers which distinguish between clear cell carcinoma and endometrioid carcinoma. The lack of ER and PR expression in this case excluded the possibility of endometrioid carcinoma. Microscopically, serous carcinoma typically forms a nipple-like structure but can also be arranged in glandular tube or solid structures. The nipple has three forms: A large and wide nipple, small nipples clustered around a large nipple, or an intraductal nipple. Intraductal nipple is characterized by obvious atypia of tumor cells, high nuclear grade, serous cytoplasm, and eosinophilic cytoplasm, and some may have sand bodies. Additionally, immunohistochemical staining indicates that serous carcinoma is strongly positive for p53 and P16[8] (Figure 3).

Serous carcinoma was ruled out in this patient due to transparent cytoplasm of the tumor cells, morphological characteristics that did not resemble serous carcinoma, normal P53 expression, mottled positive expression of P16, and Napsin A positive cells. Additionally, there was an absence of Wilms' tumor 1 (*WT-1*), a tumor suppressor gene that is widely expressed in ovarian serous carcinoma and less than 20%-30% in endometrial serous carcinomas[9]. The lack of *WT-1* expression in this case further eliminates the diagnosis of serous carcinoma.

Metastatic ccRCC is associated with similar symptoms to a renal tumor, such as a hematuria. Imaging examination of ccRCC can find renal space-occupying lesions.

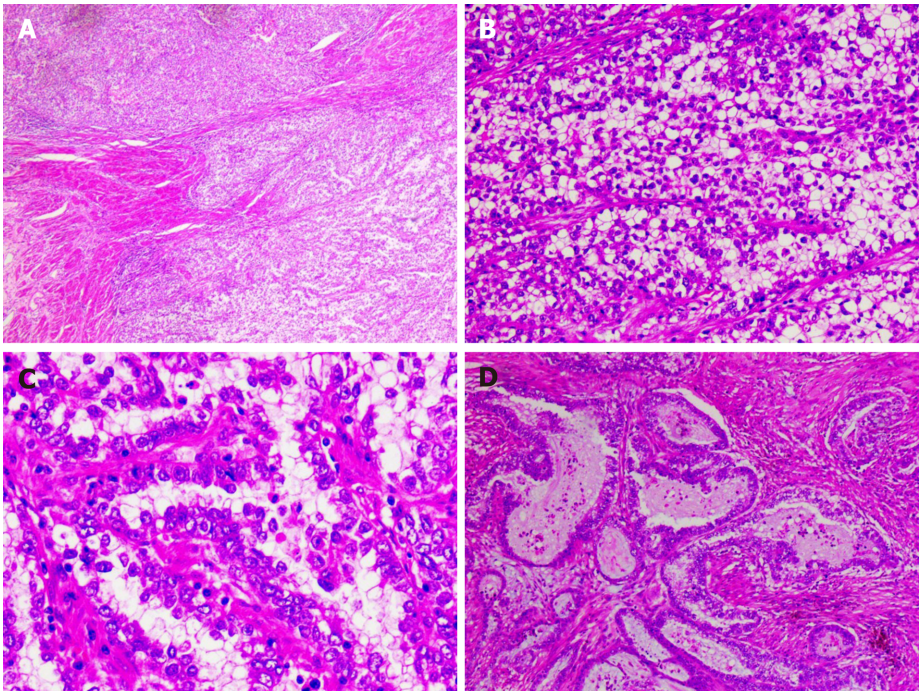

Figure 2 Histology of the uterine tumor (hematoxylin and eosin staining). A: The cancer tissue showed nest-like and solid infiltration into the myometrium; B: The cytoplasm of tumor cells was clear; C: Tumor cells were papillary and had a stud-like arrangement; D: Tumor cells were arranged in a glandular tube. Mucus was present in the gland cavity.

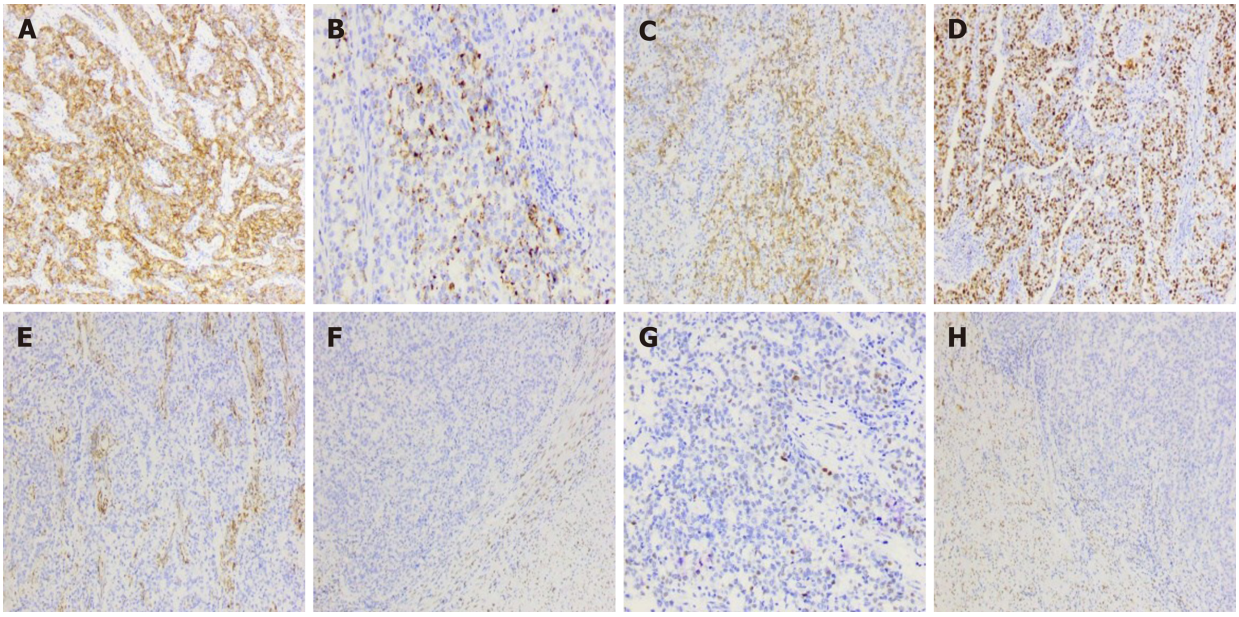

Figure 3 Immunohistochemical staining of the intrauterine tumor. A: Positivity for CK7; B: Positivity for Napsin-A; C: Positivity for P16; D: High Ki-67 index; E: Negativity for vimentin; F: Negativity for ER; G: Wild type p53; H: Negativity for Wilms' tumor 1.

Common metastatic sites are the lung, bone, liver, and brain. Morphologically, in addition to clear cells, blood sinus-like structures can also be observed. ccRCC tumors express CD10 and vimentin and have a low Ki-67 index.

In this patient, vimentin was not expressed whereas Ki-67 was highly expressed; we therefore excluded metastatic ccRCC. Furthermore, CA125 was localized to the margin of the cavity, which supports the diagnosis of a primary uterine tumor. However, the possibility of a mixed endometrial carcinoma could not be ruled out.

Adenomatous tumors are benign tumors that are exclusive to the reproductive system. They can occur in the uterus, oviducts, ovaries, and ovarian crowns[10]. It is now clear that adenomatoid tumors originate from mesothelial cells[11,12]. The

pathological diagnosis of an adenomatoid tumor is mainly based on the characteristics of tumor cells, such as lacunar, adenoid, vascular, or cystic structure, intraluminal mucus, anaplastic and mitotic features, lined with flat or cubic cells. Immunohistochemical staining of adenomatous tumors shows strong expression of CK and calretinin. To ensure the best clinical management, it is important that they are differentiated from angioleiomyoma, lymphangioma, leiomyolipoma, adenocarcinoma, and signet ring cell carcinoma[13].

In this patient, the adenomatous tumor occurred in the oviduct with a typical morphology. The immunohistochemical staining for CK and calretinin showed strong positive expression, which supported the diagnosis of an adenomatoid tumor (Figure 4). This patient underwent a tubal ligation in 2004. Whether this procedure potentially induced the development of the adenomatoid tumor needs to be further investigated. An adenomatoid tumor and endometrial clear cell carcinoma coexisted in this case (Figure 5). There was a clear boundary between the adenomatoid tumor and endometrial clear cell carcinoma. There was no clear cell carcinoma component within the adenomatoid tumor, indicating that it was more difficult to invade than normal uterine smooth muscle tissue. The expression of CK and calretinin in cancer tissues suggested that the two tumors had different origins and were not the same tumor, however further investigation is needed to confirm this.

CONCLUSION

In summary, we have shown that endometrial clear cell carcinoma, a tumor that can invade the oviduct, can cooccur with oviduct adenomatoid tumors. Endometrial clear cell carcinoma is Napsin A and P16 positive, and ER and PR negative. Furthermore, the presence of endometrial clear cell carcinoma does not affect the expression of CK and calretinin in an adenomatoid tumor. In pathological diagnosis, when investigating invasion of the oviduct, one should pay close attention to distinguishing whether the endometrial clear cell carcinoma invades the oviduct or whether it is accompanied by an oviduct adenomatoid tumor. The significance of this investigation is to determine whether the endometrial adenocarcinoma has tubal metastasis. This is critical for the confirmation of T3a in tumor-node-metastasis staging.

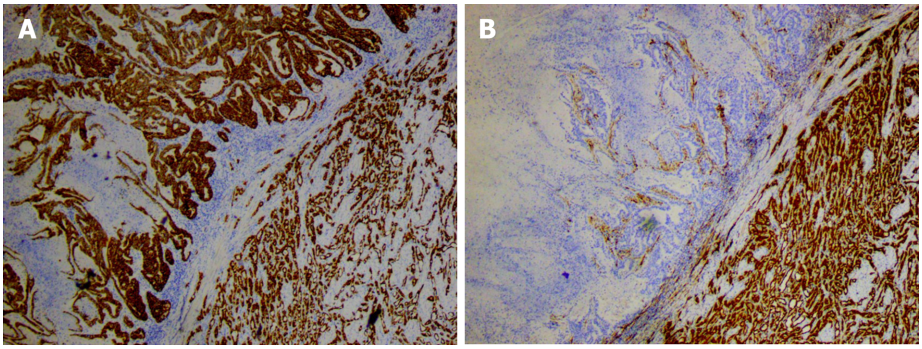

Figure 4 Immunohistochemical staining of the oviduct tumor. A: The tumor tissue and adenomatoid tumor were CK positive; B: The tumor tissue was calretinin negative and adenomatoid tumor was calretinin positive.

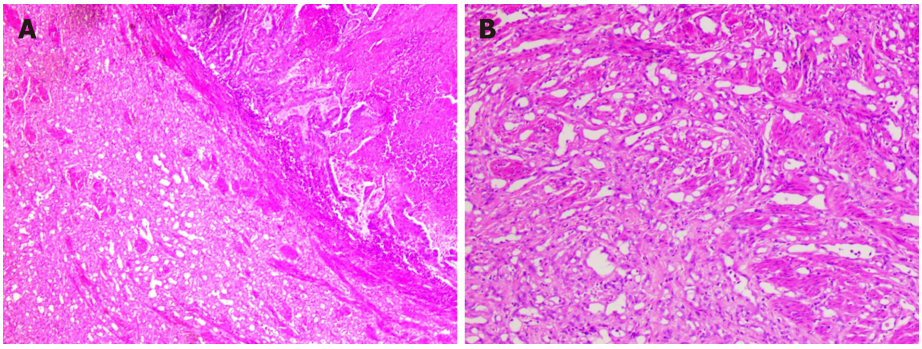

Figure 5 Histology of the oviduct mass (hematoxylin and eosin staining). A: Cancer tissue coexisted with adenomatoid tumor area; B: Microcapsule-like structure of adenomatoid tumor area.

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