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EDITORIAL

Challenges in the diagnosis and treatment of gestational trophoblastic neoplasia worldwide

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Abstract

Gestational trophoblastic neoplasia (GTN) is a rare tumor that originates from pregnancy that includes invasive mole, choriocarcinoma (CCA), placental site trophoblastic tumor and epithelioid trophoblastic tumor (PSTT/ETT). GTN presents different degrees of proliferation, invasion and dissemination, but, if treated in reference centers, has high cure rates, even in multi-metastatic cases. The diagnosis of GTN following a hydatidiform molar pregnancy is made according to the International Federation of Gynecology and Obstetrics (FIGO) 2000 criteria: four or more plateaued human chorionic gonadotropin (hCG) concentrations over three weeks; rise in hCG for three consecutive weekly measurements over at least a period of 2 weeks or more; and an elevated but falling hCG concentrations six or more months after molar evacuation. However, the latter reason for treatment is no longer used by many centers. In addition, GTN is diagnosed with a pathological diagnosis of CCA or PSTT/ETT. For staging after a molar pregnancy, FIGO recommends pelvic-transvaginal Doppler ultrasound and chest X-ray. In cases of pulmonary metastases with more than 1

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cm, the screening should be complemented with chest computed tomography and brain magnetic resonance image. Single agent chemotherapy, usually Methotrexate (MTX) or Actinomycin-D (Act-D), can cure about 70% of patients with FIGO/World Health Organization (WHO) prognosis risk score ≤ 6 (low risk), reserving multiple agent chemotherapy, such as EMA/CO (Etoposide, MTX, Act-D, Cyclophosphamide and Oncovin) for cases with FIGO/WHO prognosis risk score ≥ 7 (high risk) that is often metastatic. Best overall cure rates for low and high risk disease is close to 100% and > 95%, respectively. The management of PSTT/ETT differs and cure rates tend to be a bit lower. The early diagnosis of this disease and the appropriate treatment avoid maternal death, allow the healing and maintenance of the reproductive potential of these women.

Key words: Gestational trophoblastic neoplasia; Chemotherapy; Chorionic gonadotropin; Invasive mole; Choriocarcinoma; Placental site trophoblastic tumor; Epithelioid trophoblastic tumor

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Core tip: Gestational trophoblastic neoplasia is a cancer that originates from placental tissue, with potential for invasion and widespread metastasis. It secretes human chorionic gonadotrophin, which serves as a highly useful biomarker that contributes to the diagnosis, monitoring of therapeutic response, subsequent early detection of relapse and assessment of cure. Once the diagnosis is made, staging and International Federation of Gynecology and Obstetrics/World Health Organization prognostic risk score should be obtained, to initiate the treatment of choice – chemotherapy, which allows high cure rates, especially if the treatment occurs in Reference Centers, which has specialized staff in the treatment of this neoplasm.

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INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is a rare tumor that originates from pregnancy and, if treated in reference centers, has high cure rates, even in cases of multi-metastatic neoplasia[1,2]. GTN includes the following histopathological forms: Invasive mole (IM), choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT), encompassing lesions that originate in the chorionic villi and the extravillous trophoblast, with different degrees of proliferation, invasion and dissemination[3]. About 50% of all cases of GTN occur after hydatidiform mole, 25% after abortions or ectopic pregnancies and 25%, after term or preterm deliveries. However, PSTT and ETT can arise after term deliveries or non-molar pregnancies in 95% of the cases[4].

Although GTN is a highly metastatic and lethal neoplasia, its natural history was modified in the 1950s, when Li *et al*[5] introduced Methotrexate (MTX) as an effective antineoplastic treatment to promote the systematic cure of women with non-metastatic disease. Further advances, combined multiple drugs, notably those with etoposide and cisplatin, allowed high remission rates, even in cases of disseminated neoplasia[6,7].

With the establishment of chemotherapy in the treatment of GTN, the systematization of the diagnosis and GTN staging proposed by the International Federation of Gynecology and Obstetrics (FIGO), held at the Washington meeting in 2000, represented a great advance in the treatment of women with GTN[8]. The FIGO 2000 guideline not only standardized the GTN classification, but also proposed well-established diagnostic and therapeutic criteria and standardized the risk factors for chemoresistance, highlighting patients who would benefit from initial treatment with a single agent or, on the contrary, signaling patients who should be initially treated

with multiple agent chemotherapy[8]. However, it is important to note that the FIGO 2000 criteria should not be applied to the management of PSTT/ETT which be-have quite differently from the other forms of GTN.

After more than 15 years of the FIGO 2000 guideline implementation for the diagnosis and treatment of GTN, many questions arose as real challenges for the treatment of women with GTN[9]. The purpose of this editorial will be to discuss the situations that still limit the best treatment of GTN, as well as to reflect on alternatives to improve the treatment of women with this condition worldwide.

BASIC OF GTD PATHOLOGY

The commonest forms of GTD are complete and partial molar pregnancies. Their cytogenetic origin derives from an abnormal fertilization. In cases of complete hydatidiform mole, the oocyte loses its DNA, being fertilized by 1 spermatozoa with diploid genetic load, or by 2 haploid spermatozoa - generating a diploid parthenogenetic zygote. In the cases of partial hydatidiform mole, the oocyte has conserved its DNA, being fertilized by 1 spermatozoa with diploid genetic load, or by 2 haploid spermatozoa - generating an zygote with a diandrical triploidy. Women with complete hydatidiform mole may develop postmolar GTN about 20%-25%, while only 1%-5% of women with partial hydatidiform mole will present malignant lesions.

The presence of chorionic villi in the myometrium, with or without vascular invasion, characterizes the IM, the most common form of GTN. Usually its diagnosis is obtained through the uterine histopathology obtained by hysterectomy.

CCA is the most malignant and metastatic form of GTN. Although it's primary lesion usually presents with great uterine invasion, in about 30% of the cases it crosses with distant metastases, notably in the lungs, liver and brain, by hematogenous dissemination.

Among the non-villous lesions that make up a GTN, PSTT and ETT are derived from the intermediate trophoblast. These clinical forms exhibit lower levels of hCG relative to invasive spring and CCA. In addition, the therapeutic response of PSTT and ETT to chemotherapy alone is limited, requiring hysterectomy to maximize cure rates.

HOT TOPICS ON GTN DIAGNOSIS AND STAGING

The FIGO 2000 guideline established the diagnostic criteria for GTN that would determine the immediate onset of chemotherapy[8]: (1) Four or more plateaued hCG concentrations over three weeks; (2) Increase of hCG concentrations for three or more consecutive measurements for at least two weeks; (3) If there is a histologic diagnosis of choriocarcinoma; and (4) Elevated hCG concentrations for six months or longer.

It should be highlighted that the fundamental pillar of the GTN diagnosis is the hormonal surveillance of serum hCG, the biological and tumor marker of this disease. However, two situations pointed out by FIGO 2000 guideline are currently being questioned. The first relates to whether chemotherapy needs to always be initiated for women with a histopathological diagnosis of CCA. The second concerns if chemotherapy is really needed for patients whose hCG remains raised but falling beyond the 6 mo after uterine evacuation of a molar pregnancy.

Prior literature unanimously suggests immediate onset of chemotherapy for patients with metastatic CCA or with elevated rising hCG. However, there are not infrequent cases of patients who arrive at referral centers with histological diagnosis of CCA and who have declining or even normal levels of hCG, without evidence of metastatic disease. This situation can happen because the histopathological diagnosis of CCA is not always given quickly and/or because the disease was completely resected at the time of diagnosis. A Brazilian retrospective cohort study that followed 47 women with a histopathological diagnosis of CCA managed expectantly, observed that only 44.7% received chemotherapy due to plateauing or rising hCG level after an initial follow up of 2-3 wk[10]. It is noteworthy that the expectant management initially adopted for patients with histological diagnosis of CCA when compared to patients immediately treated with chemotherapy did not worsen the prognosis of these patients, besides no cases of relapse or death were found in this population studied[10].

Regarding the FIGO 2000 recommendation to initiate chemotherapy for patients during postmolar follow-up with hCG raised but falling after 6 mo of uterine evacuation, FIGO itself is controversial, once retracted this opinion in 2012[11], but then resumed the recommendation in the FIGO Cancer Report in 2015[12]. Although this

situation is uncommon, affecting about 1% of the women in the post-molar follow-up, expectant management has about 80% spontaneous remission, without the need for chemotherapy[13-15]. These results are more favorable, the lower the hCG levels. No woman developed relapsed disease and overall survival was 100%[13-15]. It is likely that the new FIGO Cancer Report due out in 2018 will recommend that automatic chemotherapy should not be started in this group of women and that continued hCG surveillance is reasonable.

Delaying the onset of chemotherapy, as recommended by the FIGO criteria, could lead to the occurrence of tumor chemoresistance or even metastatic disease and the need for multiple agent chemotherapy[15]. However, the data available shows continued surveillance avoids exposing women unnecessarily to potential toxicities of chemotherapy without increase the risk of resistance or more aggressive treatment later, if necessary[13-15]. In settings where patients with nonmetastatic CCA or with a raised but falling hCG beyond 6 mo from uterine can only be followed with periodic measurements of hCG and evaluation of metastatic disease, since the vast majority of these women will present spontaneous remission[15].

Despite the nearly universal acceptance of the FIGO 2000 criteria to initiate chemotherapy for patients with GTN[8], there is still a set of recommendations initially outlined by the Charing Cross Trophoblastic Disease Center (London, United Kingdom), which were adopted by the European Organization for the Treatment of Trophoblastic Disease (EOTTD)[3,16]. Although plateau or elevated hCG remains the most important diagnostic criteria for GTN, many countries worldwide consider immediate indication for chemotherapy serum hCG concentration of ≥ 20000 IU/L four weeks or more after uterine evacuation, due to the increased chance of such patients developing GTN and/or uterine perforation. Despite the United Kingdom recommendations[3,16], this indication for chemotherapy has not been adopted by FIGO[8].

A Brazilian study confirmed the increased risk for developing postmolar GTN in patients with an hCG ≥ 20000 IU/L four weeks after evacuation, about 80%[17]. However, this study did not report any uterine perforation or to an increase in the aggressiveness of chemotherapy when comparing the groups of women immediately treated with those in which an initial expectant treatment was adopted. In fact, maintaining hormonal surveillance among women with hCG levels higher than 20000 IU/L in the fourth week after molar evacuation would prevent unnecessary chemotherapy in 20% of women[17]. However, the study population was small and further validation work in a larger population would be desirable.

Once the clinical diagnosis of GTN has been made following a histopathological diagnosis of a molar pregnancy, repeat biopsies to confirm malignant progression are unnecessary and nearly always contraindicated because of the risk of promoting life-threatening hemorrhage. Indeed, as samples are usually taken from the uterus in women of reproductive age who can expect to be cured by chemotherapy, a biopsy might result in a hysterectomy or loss of life which is reprehensible[18]. Moreover, biopsies of metastatic sites where bleeding cannot be controlled such as the lungs and abdominal/pelvic organs may precipitate severe hemorrhage, resulting in death[18]. In addition, it should be always considered that the diagnosis of GTN, in almost all cases, is hormonal - by the evaluation of the hCG behavior[19].

Before initiating chemotherapy, staging of GTN is critical. And here are two differences that must be stressed. While in the United States, initial staging with brain and abdomen-pelvis magnetic resonance imaging (MRI), and chest computed tomography (CT) is recommended[20], FIGO/EOTTD recommends that only pelvic-transvaginal Doppler ultrasound and chest X-ray should be initially requested in patients with post-molar GTN. In cases of doubts regarding the normality of the chest X-ray or in the case of metastases with more than 1cm, the screening of metastases with chest CT and brain MRI should be complemented[3,8]. The major problem of using CT rather than chest X-ray for assessing the presence of pulmonary metastases following a molar pregnancy is the risk of including micrometastases < 1 cm. This will upstage and or increase the prognostic score for patients leading to more women starting on multi-agent chemotherapy than necessary. Indeed, several studies have shown that CT defined chest micro-metastasis as opposed to chest X-ray defined pulmonary metastases does not affect outcomes and should not influence staging/scoring or the selection of chemotherapy[21,22].

The role of positron emission tomography (PET), associated or not to CT in the evaluation of metastatic GTN, has not yet been well established[22]. The available information points out that the PET does not add anything to the GTN staging when compared to conventional imaging work-up that is less expensive and more widely available. PET may help to evaluate metastases in unusual sites or to differentiate active metastatic nodules from necrotic and/or hemorrhagic tissue following chemotherapy and in cases of chemoresistance or relapse, notably in patients with

PSTT or ETT, for guiding surgical intervention[22,23]. Both false positive and negative results can occur with FDG-PET imaging so careful co-evaluation with other imaging modalities is desirable[24].

PERSPECTIVES OF THE TREATMENT ON GTN

Before discussing GTN treatment in detail, we will initially consider the use of prophylactic chemotherapy for cases of hydatidiform mole thought to be at high risk of developing GTN. The criteria for diagnosing such high risk moles varies and includes very high hCG at the time of evacuation and women who are unable to comply with an hCG surveillance programme following the molar evacuation. Although there is a clear reduction in the risk of development of postmolar GTN[25], the use of prophylactic chemotherapy may increase patients' morbidity (by the side effects of cytotoxic drugs), the risk of chemoresistance, and medical care costs, for the treatment of a neoplasm fully curable without the use of prophylactic chemotherapy[26]. While there is no clear scientific evidence about the benefits of using prophylactic chemotherapy for cases of high-risk hydatidiform mole, we agree that it is time to stop recommending prophylactic chemotherapy for these women[27].

Similarly, prophylactic hysterectomy for the treatment of high-risk hydatidiform mole, or even as primary GTN treatment, should only be considered in women that completed childbearing[28]. However, what we have observed in several settings across the world is that women frequently underwent hysterectomy as their main treatment for a suspected molar pregnancy. Apart from preventing such women from getting pregnant in the future, many fail to then adhere to hCG surveillance because they think they are cured after surgery[18]. This is a serious problem as a significant number will still end up needing chemotherapy due to growth of micrometastases outside the uterus. These patients will be diagnosed late if they are not on hCG surveillance and so worsen their prognosis.

It has also been pointed out that second curettage for some patients diagnosed with GTN can avoid the need for starting chemotherapy. Although the outcomes are controversial and the studies are either small, non-randomised[29] or retrospective in design[30,31], a reduction in the need for chemotherapy was observed between 9%-40% of the patients undergoing a second curettage. Nevertheless, whilst the efficacy of this procedure remains unclear, the benefit appears to be greatest only in patients with non-metastatic GTN and levels of hCG below 5000 IU/L[29-31].

The choice of chemotherapy treatment is based on the combination of the anatomic staging with the World Health Organization (WHO) scoring system based on risk factors[8] (Table 1). According to this scoring system, tumors are divided into two categories: Low-risk GTN, if the score is equal to or lower than 6; and high-risk, if the score is equal to or greater than 7. The score is associated with the risk of developing chemoresistance, and thus guides the choice of first line chemotherapy[8].

Low-risk GTN should be first treated with a single agent, either MTX or Actinomycin-D (ActD)[32,33]. Although a Cochrane review points to a superiority of Act-D over MTX[34], what we observe is that there are numerous chemotherapy regimens for either MTX (50 mg fixed dose or 50 mg/m^2 or 1 mg/kg on days 1, 3, 5, 7, with or without folinic acid rescue, 0.4 mg/kg D1-5, 30-50 mg/m^2 once weekly), and for Act-D (10-13 mcg/kg D1-5, 1.25 mg/m^2 biweekly), making it impossible, with the data available, to actually evaluate the best initial treatment for low-risk GTN[32-34].

Although cases of low-risk GTN are widely cured with single agent chemotherapy[8,32,33], it has been observed that patients with GTN and with a FIGO score of 5-6 only have about a 35% chance of cure with MTX regimen. This indicates that these patients form an "intermediate-risk group", for whom the MTX regimen might be considered to be relatively unlikely to achieve a cure[35]. For these patients, one could either start on a more aggressive chemotherapy regimen, or develop a new assessment which could be added to the existing scoring system to enable improved patient stratification to single verses multi-agent therapy. Recent work suggests that the uterine artery pulsatility index[36], might help to identify patients resistant to MTX treatment. However, it is still unclear how to incorporate the pulsatility index into the FIGO scoring system.

Indeed, there is an international scientific effort to validate the FIGO/WHO prognostic risk score[37]. Studies have shown that of the eight patients who had a pre-treatment hCG exceeding 10000 IU/L and 100000 IU/L, interval exceeding 7 mo since previous pregnancy and tumor size of over 5 cm were identified as being predictive of single-agent resistance[38]. Another perspective shows that no patient with pre-treatment hCG level higher than 400000 IU/L achieve remission under single agent chemotherapy treatment, regardless of the prognostic risk score[39].

Table 1 International Federation of Gynecology and Obstetrics/World Health Organization staging and classification of gestational trophoblastic disease

GTN: FIGO staging and classification (Washington, 2000)				
FIGO anatomic staging				
Stage I: Disease confined to the uterus				
Stage II: GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)				
Stage III: GTN extends to the lungs, with or without known genital tract involvement				
Stage IV: All other metastatic sites				
Modified WHO prognostic scoring system as adapted by FIGO				
Prognostic factors	**Score**			
	0	**1**	**2**	**4**
Age	< 40	≥ 40	-	-
Antecedent gestation	Mole	Abortion	Term	-
Interval (mo)	< 4	4-6	7-12	> 12
Pretreatment serum hCG (IU/L)	$< 10^3$	10^3 to $< 10^4$	10^4 to $< 10^5$	$> 10^5$
Largest tumor size (including uterus)	< 3	3 to 4	≥ 5	-
Site of metastases	Lung	spleen, kidney	gastro intestinal tract	brain, liver
Number of metastases	-	1-4	5-8	> 8
Previous failed chemotherapy	-	-	single drug	2 or more drugs

Interval (in months) between the end of antecedent gestation (when known) and symptom onset. FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; GTN: Gestational trophoblastic neoplasia; hCG: Human chorionic gonadotropin.

Less commonly, patients reach referral centers for treatment with high-risk GTN and disseminated disease. These patients were usually treated with the regimen of choice for high-risk GTN[3,8,32]: EMA/CO (combining Etoposide, MTX, Act-D, Cyclophosphamide and Oncovin). Initial reports indicated a survival rate of about 86% with deaths occurring either early within 4 wk of admission due mainly to bleeding or metabolic upset from tumor lysis in patients with very advanced disease or late from drug resistant disease. In addition, some deaths were due to non-gestational tumors that histopathologically mimicked GTN[40]. To avoid these early deaths, high risk GTN patients with a FIGO score ≥ 13, with or without a higher number of metastases (> 6) and higher hCG (> 1000000 IU/L), seem to benefit from the use of induction low-dose Etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 (EP; days 1 and 2 every 7 d) for one to three cycles until well enough to start EMA/CO[40].

Although more than 90% of patients with GTN are cured with chemotherapy regimens based on Etoposide and Cisplatin[3,8,32], there are some patients with chemoresistant neoplasia who present a major therapeutic challenge. In such cases, one must try to obtain tumor tissue to determine the genetic origin of CCA (gestational verses non-gestational) and to rule out the possibility of PSTT/ETT (where treatment necessarily includes surgery)[3,8,32]. Indeed, the management of PSTT/ETT is quite different reflecting its distinct biological behavior. The disease is slower growing, produces less hCG, remains confined to the uterus for longer, is more likely to involve local lymph nodes and is a little more resistant to chemotherapy than CCA[41]. It is now appreciated that all types of preceding pregnancy can give rise to PSTT/ETT and that the key poor prognostic factor is an interval more than 4 years from the last known or causative pregnancy[42]. Moreover, recent work has revealed that 10%-15% of women with atypical placental site nodules (APSN) may either have a co-existent or subsequently develop a PSTT/ETT so APSN can no longer be ignored[43]. Patients with histologically confirmed PSTT/ETT confined to the uterus are best managed with hysterectomy whilst those with metastatic disease will need combination agent chemotherapy followed by resection of residual disease sites. Patients with an interval more than 4 years from the causative pregnancy are unlikely to be cured with regular platinum and etoposide based chemotherapy regimens such as EP/EMA plus surgery and so should be considered for experimental systemic therapies regardless of stage[42]. Some GTN patients including those with PSTT/ETT who have disease with some sensitivity to platinum and etoposide may still be salvaged with high dose chemotherapy but other more effective and less toxic alternatives are needed[3]. In studying the immuno-expression of these tissues, it has been found that PD-L1 and its receptor PD-1 are strongly expressed by GTN, suggesting the ligand is involved in tumor-immune evasion[44]. Indeed, a few cases of

multi drug-resistant GTN including PSTT/ETT have recently shown complete responses to the anti-PD-1 agent Pembrolizumab with several women off treatment and well for 6-24 mo[45]. Therefore, it is tempting to speculate that such checkpoint immunotherapies may provide a new effective salvage treatment for women with GTN failing existing therapies and that this might replace the need for high dose chemotherapy.

Despite the great improvement observed in the treatment of women with GTN, especially in the methods of disease monitoring, more accurate metastasis screening and more effective treatments, even in multimetastatic cases, we believe that the most important key for survival of women affected by this disease is their treatment in Reference Centers. Brewer was the first to report that both the morbidity and mortality of patients with GTN was nine times lower at a center staffed by physicians experienced in the management of this neoplasia than with the "occasional" physician treating this entity[46]. Moreover, the UK experience of centralized care within a national health system has provided an exemplar of what can be achieved with the UK specialized centers reporting the highest cure rates globally[47]. The Brazilian experience now also clearly shows that when these patients are followed in Reference Centers they demonstrate lower metastasis rate, lower median time interval between molar evacuation and chemotherapy onset shorter than those initially treated outside the Reference Centers[48].

Between advances[49-51] and challenges[52], the truth is that GTN is still an unknown disease of many physicians in the world. When the obstetrician is unable to recognize this anomaly of pregnancy, postponing its diagnosis[53,54]; when the gynecologist does not understand the importance of hormonal vigilance and strict contraception during this period[55,56]; when the oncologist indicates unnecessary surgeries to treat women with GTN or uses incorrect chemotherapy regimens, our women with GTN will suffer, sometimes losing their uterus or even their lives. Figure 1 briefly illustrates the entire treatment of GTD.

It is important to highlight that GTN can arise from any pregnancy form (abortion, ectopic, term/preterm, and, of course after hydatidiform mole), and that it should be ruled out in cases of metastatic neoplasia in women during the menacme, with unknown primary site, especially if the clinical history reveals a recent gestational history. Finally, it is important to remember, that a simple hCG test may help provide the diagnosis of this neoplasia, monitor the treatment, confirm the cure and detect relapse early to enable effective salvage therapy.

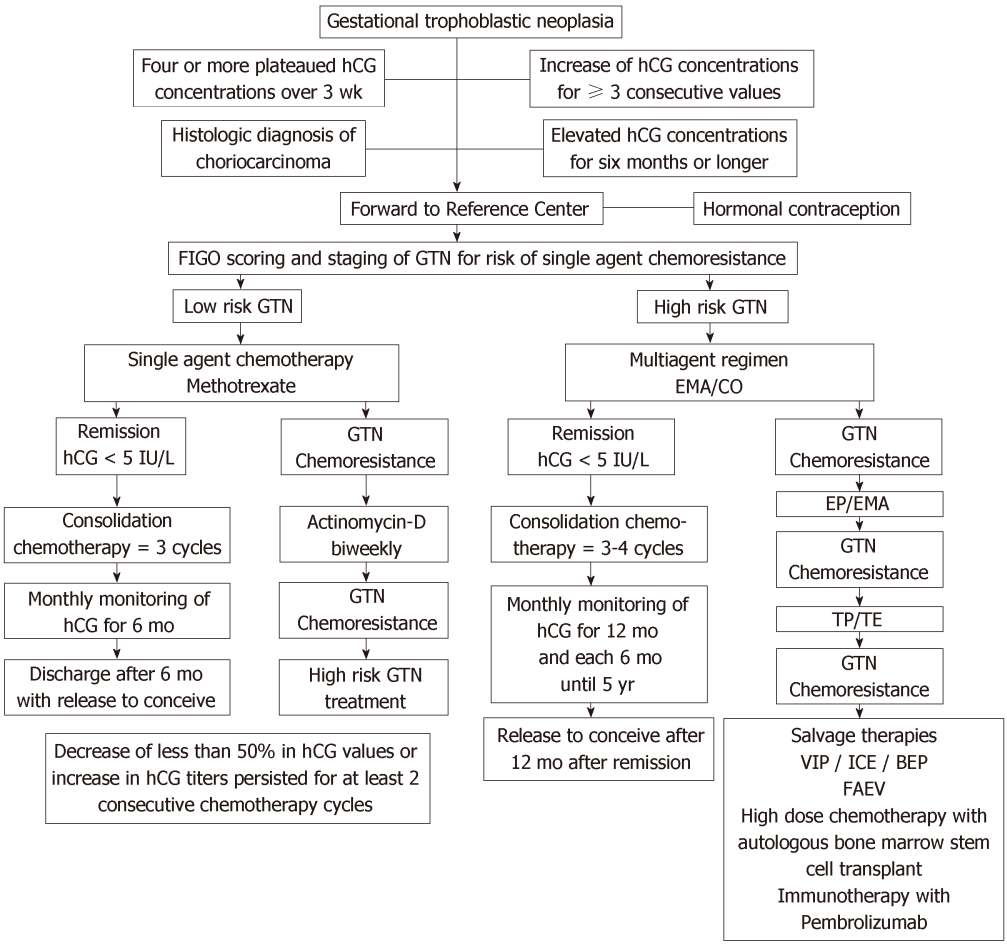

Figure 1 Algorithm summarizing the modern treatment of gestational trophoblastic neoplasia. GTN: Gestational trophoblastic neoplasia; hCG: Human chorionic gonadotropin.

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MINIREVIEWS

Oligometastases in prostate cancer: Ablative treatment

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Abstract

Technological advances in radiotherapy have led to the introduction of techniques such as stereotactic body radiation therapy (SBRT), allowing the administration of ablative doses. The hypothesis that oligometastatic disease may be cured through local eradication therapies has led to the increasing use of SBRT in patients with this type of disease. At the same time, scientific advances are being made to allow the confirmation of clinically suspected oligometastatic status at molecular level. There is growing interest in identifying patients with oligometastatic prostate cancer (PCa) who may benefit from curative intent metastasis-directed therapy, including SBRT. The aim is to complement, replace or delay the introduction of hormone therapy or other systemic therapies. The present review aims to compile the evidence from the main ongoing studies and results on SBRT in relation to oligometastatic PCa; examine aspects where gaps in knowledge or a lack of consensus persist (*e.g.*, optimum schemes, response assessment, identification and diagnosis of oligometastatic patients); and document the lack of first-level evidence supporting the use of such techniques.

Key words: Oligometastases; Metastasis-directed therapy; Stereotactic body radiation therapy; Stereotactic ablative radiotherapy; Prostate cancer

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Core tip: The hypothesis that oligometastatic disease may be cured with local eradication therapies has led to the growing use in prostate cancer (PCa) of treatments targeted to metastasis, including stereotactic body radiation therapy (SBRT). Such therapy intends to complement, replace or delay the introduction of systemic therapy. The present review aims to compile the evidence from the main ongoing studies and results on SBRT in relation to oligometastatic PCa, and examines aspects where gaps in knowledge persist, *e.g.*, optimum schemes, response assessment, and identification and diagnosis of oligometastatic patients.

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INTRODUCTION

The hypothesis that local therapies may cure metastatic disease arose from the description by Hellman and Weichselbaum[1] in 1995 of the so-called oligometastatic state. Based on their clinical experience, these authors described an intermediate state of distant spread, reflecting disease with a low, slow and late metastatic spreading capacity. There is progressively increasing confirmation of the correlation between the clinical behavior and molecular characteristics of oligometastatic patients[2]. The metastatic process is becoming increasingly well known. Based on the identification of cellular clones in metastatic tissue biopsies, it has been seen that dissemination to form new metastases is a frequent phenomenon, and that metastatic spread does not always originate from the primary tumor[3]. This has given rise to the idea that the early elimination of metastases can avoid subsequent disseminations[4,5]. Such knowledge of the metastatic cascade has contributed to the interest in performing ablative local therapies targeted to all the metastatic sites amenable to eradication.

Prostate cancer (PCa) metastasizes mainly to bone and lymph nodes. Visceral involvement is infrequent. Eradication treatment of visceral metastases is mainly surgical. While that of lymph node metastases is variable and conditioned to many factors, use is indistinctly made of surgery as well as stereotactic body radiation therapy (SBRT) and conventional external beam radiation therapy (cEBRT), mainly for the elective irradiation of certain lymph node chains. This need to associate several local treatment options has led to emergence of the concept of metastasis-directed therapy (MDT) in oligometastatic patients.

PCa is characterized by a long natural course, and in most cases is initially hormone-sensitive. Thus, in oligometastatic patients there are at least three scenarios involving different therapeutic approaches: oligometastases synchronous to the primary tumor; oligorecurrences; and oligoprogression situations, which conceptually constitute castration-resistant patients.

As a locally ablative tool, SBRT has been little studied in the first of the aforementioned scenario, though it plays a relevant role in oligorecurrences and oligoprogression.

The treatment of these patients remains a challenge. Multiple systemic treatment options are available, and the introduction of an ablative local treatment option increases the complexity and controversy of optimum treatment timing.

The present review aims to compile the main results published in the literature and examines aspects where gaps in knowledge persist in the use of SBRT, *e.g.*, the optimum schemes, response assessment, and the identification and diagnosis of oligometastatic patients.

OLIGOMETASTATIC DISEASE

The definition of oligometastatic disease comprises at least three controversial points: the identification of oligometastatic behavior; which patients should be included under the concept of oligometastasis; and the optimum imaging techniques allowing its detection.

Identification of oligometastatic state and concept of oligometastasis

In the last consensus document on advanced PCa published in 2017, a total of 10% of those surveyed claimed not to believe in the existence of an oligometastatic state.

Identifying oligometastatic patients is crucial both in order to offer local treatment with curative intent and to optimize resource utilization and avoid needless iatrogenic problems[6]. On the other hand, patients with a tendency towards polymetastatic disease will not benefit from MDT, and the intensification of systemic therapy should be contemplated in such cases.

PCa is characterized by a broad spectrum of clinical aggressiveness. A number of biomarkers are under study, including plasma cell-free nucleic acids (*e.g.*, cell-free

DNA and circulating tumor cells), with a view to establishing their usefulness in treatment monitoring and for establishing a prognosis. However, none of them have been shown to be able to identify those patients that will exhibit oligometastatic behavior.

In bone metastases of castration-resistant PCa (mCRPC), aberrations of DNA repair genes, BRCA1, BRCA2 and ATM have been identified more frequently than in primary tumors[7]. Some studies suggest that oligometastatic progression may be regulated at least in part by epigenetic alterations and potentially by microRNA[2]. MicroRNA is RNA composed of 19-22 nucleotides that regulates gene expression. A study of tumor samples from oligometastatic patients subjected to radiotherapy found that those individuals who did not develop polymetastases exhibited a different microRNA profile, including the microRNA-200 family.

A number of genic platforms have been marketed that are able to predict which PCa patients are likely to develop metastases after primary treatment. An oligometastatic molecular fingerprint therefore will probably soon become available. Until then, these platforms, together with clinical parameters such as advanced age, the Gleason score and a rapid prostate-specific antigen (PSA) doubling time are our only tools for predicting oligometastatic behavior[8]. Another point of controversy is the number of metastases to be included under the term "oligometastasis". Based on the published series, there is a tendency to include up to 5 metastases in one or several organs under the term oligometastasis[9].

The hypothesis of a differential behavior of PCa between patients with few metastases and those with generalized lymph node metastases was proposed by Singh *et al*[10] in 2004. These authors found that patients with 5 or fewer metastatic lesions had longer overall survival (OS) than patients with more than 5 metastatic lesions (73% *vs* 45% at 5 years and 36% *vs* 18% at 10 years), as well as longer metastasis-free survival.

Another sometimes neglected term that needs to be used because it contextualizes the clinical situation is "oligorecurrence" as defined by Niibe *et al*[11] in 2010 to identify oligometastatic patients with a controlled primary tumor.

The number of metastases to be included under the term oligometastasis is even more crucial in the case of lymph node metastatic spread, where the quantification of either isolated nodes or lymph node areas increases screening variability. The solution to this dilemma is to define an oligometastatic patient as an individual in which all the tumor locations are amenable to MDT with radical intent.

Diagnosis of (oligo)metastatic disease

The number of metastases detected, and consequently classification as oligometastatic disease, depends on the method used for detection. The most recent European Association of Urology (EAU) guidelines recommend at least one cross-sectional abdominopelvic imaging study [computed tomography (CT) or magnetic resonance imaging (MRI)] in conjunction with a bone scan (BS) for the screening of metastases in intermediate- and high-risk primary PCa[12]. After biochemical relapse (BCR), and given the low detection rate, BS and abdominopelvic CT are only recommended in patients with serum PSA > 10 ng/mL or a PSA doubling time < 6 mo. In addition, multiparametric MRI may be useful in the event of BCR after prostate radiotherapy to assess local rescue possibilities[13]. However, these conventional imaging modalities have low sensitivity in detecting small-volume disease and may underestimate the disease burden.

Advances in molecular and biological imaging directly targeting tumor cells have resulted in greater efficacy in detecting PCa. In recurrent PCa, choline positron emission tomography-computed tomography (choline PET/CT) is the preferred restaging technique, with a pooled sensitivity and specificity of > 85%[14]. Unfortunately, these figures probably decrease in the context of lymph node metastases[15], and sensitivity in application to micrometastatic disease is low. Choline PET/CT has demonstrated superiority in detecting local relapse and bone metastases versus whole-body MRI (including diffusion-weighted imaging), though with similar accuracy in detecting lymph node metastases[16]. The two techniques are presently regarded as complementary diagnostic options rather than alternatives[17].

A new radiotracer targeting prostate-specific membrane antigen (PSMA) has recently been developed and has demonstrated potentially higher detection rates than the conventional imaging modalities. PSMA is a protein expressed on dysplastic prostate cells, with expression levels 100-1000 times higher than in normal cells. These expression levels increase even further in higher disease stages and grades[18]. Recent meta-analyses show 68Ga-PSMA PET to offer excellent diagnostic performance in primary and secondary staging, due to its ability to detect lesions even in the presence of very low serum PSA levels[19]. As an example, in the meta-analysis published by von Eyben *et al*[19], the pooled detection rate was 50% even in a subgroup of studies

evaluating patients who showed BCR with PSA levels of 0.2-0.49 ng/mL. The technique has been shown to modify the treatment proposal in approximately one-half of the patients[20]. The most recent EAU guidelines therefore recommend PET/CT using PSMA together with choline in patients with BCR and low serum PSA levels (< 1 ng/mL). The use of androgen deprivation therapy (ADT) may affect interpretation of the PSMA-PET explorations, since the expression of PSMA on the part of prostate cells increases with androgen receptor inhibition and may result in increased sensitivity of PSMA-PET after the administration of ADT. The new imaging techniques, and in particular PSMA-PET scans, may play an important role in the diagnosis of limited metastatic disease. Such techniques should be used, when available, in patients considered candidates for SBRT, in order to better define the extent of the disease and screen patients suitable for MDT[21,22].

SCENARIOS IN OLIGOMETASTATIC PCa

Three scenarios can be found in oligometastatic PCa: (1) *De novo* oligometastatic disease, corresponding to patients diagnosed with synchronous metastases; (2) Oligorecurrent disease, corresponding to the appearance of metachronous metastases after local control of the primary tumor (with either surgery or radiotherapy), in which the metastases are usually detected from images requested after the occurrence of BCR; and (3) Oligoprogressive disease, corresponding to metastatic patients with systemic treatment, who at some point show progression of a limited number of metastases. These patients are subjected to ADT, either alone or combined with other systemic drugs, and therefore may be classified as castration-resistant cases (Figure 1).

Synchronous - de novo metastases

Local ablative treatment of oligometastatic disease with curative intent does not make sense if radical treatment of the primary tumor is not applied at the same time. Radical treatment of this group of patients includes a combination of surgery, cEBRT, SBRT and systemic therapy.

Retrospective studies suggest a survival benefit from prostatectomy or radical cEBRT in patients with metastatic PCa. Clinical trials evaluating MDT, including SBRT, in the metastatic disease setting are ongoing.

Oligorecurrent or metachronic metastases

The current basis for the treatment of metastatic hormone-sensitive PCa is systemic therapy, starting with ADT[23] with or without docetaxel[24], and more recently abiraterone acetate[25]. There is some controversy as to whether these aggressive drug combinations should be used for oligorecurrences, given their greater side effects compared with ADT in monotherapy[13]. Both initial observation with delayed ADT and immediate ADT are even considered as standard of care (SOC).

ADT has important side effects, and it is being evaluated whether SBRT in this group of oligorecurrent patients may serve to delay the start of hormone therapy. Two prospective studies[20,26] have shown SBRT as MDT to be able to prolong ADT-free survival (ADT-FS). However, we do not know whether the prolongation of this period will have an impact on OS.

It is somewhat contradictory that currently the addition of SBRT in oligometastatic PCa allows a delay in ADT while on the other hand research is being made or advocated to intensify therapy with the addition of drugs such as docetaxel and abiraterone to ADT - with the resulting increase in side effects. We need to identify prognostic factors with a view to screening patients who will benefit from such aggressive therapy, and to identify those in whom MDT with SBRT can postpone the introduction of ADT until disease progression. Studies comparing these two regimens and their impact upon OS are needed, since the quality of life repercussions are obvious.

The detractors of delaying the introduction of ADT in oligorecurrent disease point to the persistent difficulty of detecting metastases, and underscore that untreated metastatic disease remains despite the introduction of MDT.

Oligoprogression (oligoprogressive disease)

Oligoprogressive disease includes patients with oligometastatic progression following systemic therapy. Although the latter constitutes the basis of treatment for metastatic cancers, the effect is usually temporary, with the subsequent development of resistant clones and disease progression.

In the event of mCRPC, multiple systemic therapies improve survival. These include the chemotherapeutic agents docetaxel and cabazitaxel, androgen-targeting agents such as abiraterone and enzalutamide, a vaccine (sipuleucelT), and a radio-

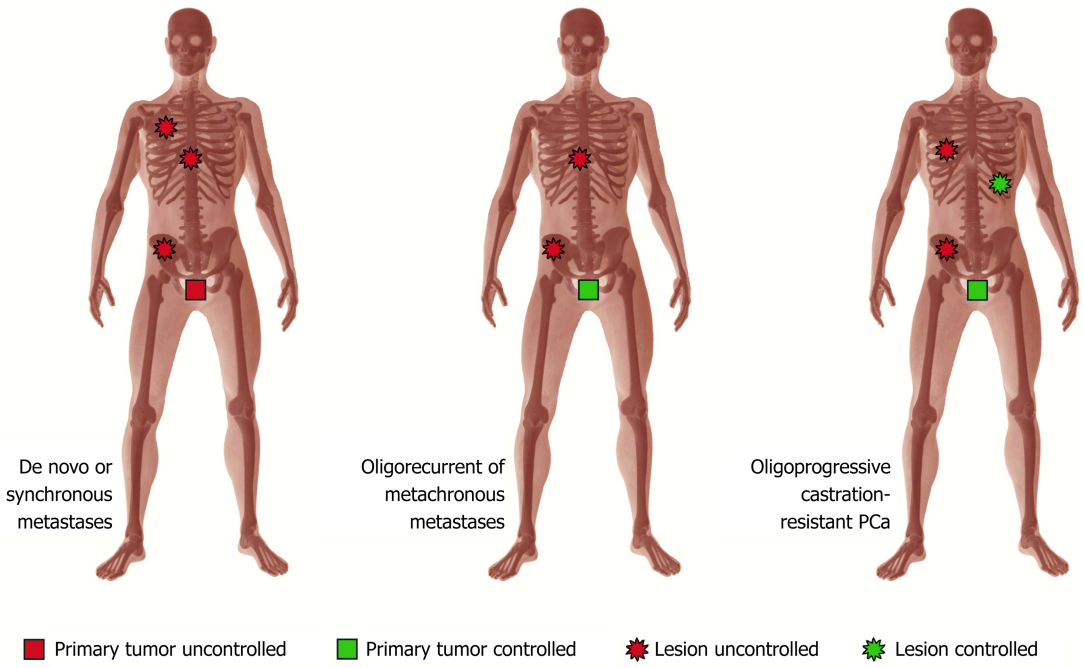

Figure 1 Scenarios in oligometastatic prostate cancer.

drug (radium-223)[13]. However, mCRPC remains an incurable disease associated with a life expectancy of 2-3 years.

In the event of oligoprogression, SBRT associated to systemic treatment has been shown to delay the start of a second hormonal line. Since each of these agents affords a mean increase in OS of 3-5 mo, it has been postulated that combining SBRT in the event of oligoprogression may prolong patient survival.

MDT

According to the hypothesis of Hellman and Weichselbaum[1], the application of ablation treatments to all tumor sites in oligorecurrent patients could cure oligometastatic disease. Based on cohort studies, the resection or ablation of oligometastatic disease has become standard therapy for other tumors such as colorectal cancer and renal cell carcinoma[27].

Prostate cancer mainly spreads to bone and lymph nodes, with few visceral metastases. The ablative treatment options for these locations are fundamentally surgery, cEBRT and SBRT. Most studies involve a combination of these treatment modalities. As a result, and in order to establish the contribution of local treatment considered globally, these therapies have been grouped under an emergent concept called MDT.

SBRT as MDT

SBRT or stereotactic ablative radiotherapy (SABR) is an external radiotherapy technique that delivers ablative doses [biologically effective dose (BED) > 100 Gy] in a few fractions (1-8 fractions). A high dose is administered with each fraction, and there is a large dose gradient between the tumor and the healthy tissues. This is a high precision technique that requires guided imaging systems and strict immobilization in accordance with the treated site. The terms SBRT and SABR are firmly rooted in clinical nomenclature and are difficult to replace. They prove confusing, however, since they do not truly reflect the technique performed, which actually should be referred to as extreme imaging guided hypofractionation. The technique is performed on an outpatient basis and involves only a few sessions, with no acute toxicity. It is also convenient for the patient and has no impact upon quality of life.

Radiotherapy technique and SBRT schemes as MDT in oligometastatic PCa

There is no consensus on the definition of SBRT volumes in application to bone oligometastases. The largest series published to date[28] included 106 metastases in 81 patients, of which 32% had PCa. The gross tumor volume was defined as the lesion evidenced on CT and/or MRI images. They added a clinical target volume of 5 mm over the surrounding tissue and generated the planning target volume (PTV) with an expansion of 2-5 mm.

Table 1 shows the schemes used in the main series published to date. The schemes are heterogeneous, with a predominance of those using one or three fractions, with a dosing range of 20 Gy/1 fraction to 50 Gy/5 fractions. Ost *et al*[29] reported significantly higher local control rates with BED > 100 Gy. Muldermans *et al*[30], in their multivariate analysis, found only the SBRT dose to be significantly correlated to local control (LC). Lesions treated with 16 Gy had a LC rate of 58%, while those receiving ≥ 18 Gy had LC rate of 95% at two years ($P < 0.001$). No patient treated with ≥ 18 Gy in a single fraction or with any fractionated scheme experienced local failure.

Muacevic *et al*[31], in the same way as Siva *et al*[26] in the POPSTART study, concluded that a single fraction of 20 Gy over the bone lesion or affected lymph node proves effective and safe.

Given the diversity of schemes, at the consensus meeting of the Spanish Society of Radiation Oncology (SEOR)[32] it was agreed to use either 6 fractions of 7.5 Gy or three fractions of 10 Gy for lymph node SBRT, according to medical criterion and depending on the tolerance of the surrounding structures.

In lymph node oligometastases, the irradiation technique, as well as the treatment volumes used, range from SBRT only at macroscopic disease relapse[20,33-36] to irradiation of the entire chain in which the affected lymph node is located, or even irradiation of all the pelvic chains with boost targeted to the affected lymph nodes[37]. The optimum irradiation volume is not clear. Because of the high risk of subclinical disease in pelvic lymph nodes beyond what PET is able to detect[38] and the consequent risk of relapse in the adjacent lymph nodes[34], the recommendations of the Australian and New Zealand Radiation Oncology Genito-Urinary group of 2018 advocated irradiation of all the pelvic lymph nodes at risk[21].

It should be remembered that surgical resection is the SOC for lymph node relapse in patients with a controlled primary tumor, provided the disease is amenable to complete resection, with or without ADT[21].

Response assessment /definition of local control

Most metastases treated with SBRT in PCa are bone metastases. A limiting factor in all SBRT studies involving bone metastases is the lack of a standard and objective method for measuring treatment response or failure. Such evaluation remains a challenge and should be based on a combination of the changes in the images referred to the location of the PTV, the PSA kinetics, and the variations in associated symptoms. Various radiological changes in CT images have been described after SBRT, including remineralization of lytic bone metastases, demineralization of sclerotic bone metastases, progression and response in different lesions. Studies relating the radiological changes to clinical outcomes are not available. Except in situations with measurable tumor spread to soft tissues, the Response Evaluation Criteria In Solid Tumors (RECIST 1.1)[39] do not offer consistent response criteria and are therefore of little value. Functional imaging and the PERCIST (Positron Emission tomography Response Criteria In Solid Tumors) have also been used, defining LC as no increase in uptake (11 choline PET, PSMA) or the absence of lesion growth as determined by MRI. The response in the case of bone metastases is usually investigator-dependent, which makes it difficult to compare the different therapeutic schemes and thus the efficacy of treatment. In the case of vertebral SBRT, such uncertainty has led to the development of a consensus sponsored by the SPINO group[40], where among other conclusions MRI has been classified as the optimum imaging test for assessing response to SBRT in the spine, and response has been defined as the absence of progression.

Most of the published series included LC among their endpoints. The concept of LC comprised lesions classified as stable disease, and partial response or complete response, *i.e.*, the absence of progression. Consistent response criteria need to be developed to compare the results and evaluate the efficacy of new treatment approaches such as SBRT, similar to those established by the Neuro-Oncology group (SPINO) for the evaluation of response in spinal metastases[40].

SBRT RESULTS

A summary of different published studies is presented in table format (Tables 1 and 2). There is a predominance of retrospective studies that analyze SBRT jointly in bone and lymph node metastases. Few series analyze the two types of metastases separately. The primary endpoints assessed are LC, toxicity, the imaging method used for diagnosis, ADT-FS, progression-free survival (PFS), and OS on a point basis.

Local control

Local control is commonly defined as the absence of progression in PTV based on

Table 1 Summary of selected publications reporting stereotactic body radiation therapy for mixed and bones oligometastatic prostate cancer

Ref.	Study type	No. patients/lesions	No. of metastases	Imaging method	Site of metastases	SBRT schedules	LC	PFS
Mixed								
Jereczek-Fossa *et al*[56]	R	34/38	Single pelvic LN and/or single distant lesion	CT, BS, Choline PET	Bone, LN, local recurrence	30-36 Gy/3-5 fr	88% (16.9 mo)	42.6% (30 mo)
Ahmed *et al*[49]	P	17/21	≤ 5	Choline PET/CT, MRI, CT	Bone, LN, Liver	Median dose 20 Gy (8-24 Gy/1-3 fr), 50 Gy/5 fr (LN), 60 Gy/3 fr (Liver)	100% (6 mo)	74% (6 mo), 40% (1 yr)
Berkovic *et al*[45]	R	24/29	≤ 3	BS, 18F-FDG PET/TC, Choline PET/TC	Bone, LN	Median dose 50 Gy (40-50)/8-10 fr	100% (2 yr)	72% (1 yr), 42% (2 yr)
Decaestecker *et al*[34]	P	50/70	≤ 3	18F-FDG PET/TC, Choline PET/TC	Bone, LN, Viscera	50 Gy/10 fr, 30 Gy/3 fr	100% (2 yr)	64% (1 yr), 35% (2 yr)
Pasqualetti *et al*[57]	P	29/45	≤ 3	Choline PET/CT	Bone, LN	24 Gy/1 fr, 27 Gy/3 fr	Median 11.5 mo	NR
Muldermans *et al*[30]	R	66/81	< 5	Choline PET/CT, MRI, CT, BS	Bone, LN, Liver	Median dose 16 Gy (16-24)/1 fr, 30 Gy/3 fr, 50 Gy/5 fr	82% (2 yr)	45% (2 yr)
Bouman-Wammes *et al*[48]	R	43/54	≤ 4	Choline PET/CT	Bone, LN	30 Gy/3 fr, 45 Gy/3 fr, 35 Gy/5 fr	NR	Median 31.5 mo
Triggiani *et al*[47]	R	OR: 100/139, OP: 41/70	≤ 3	OR: Choline PET, CT and BS, OP: Choline PET, CT/scintigraphy	Bone, LN	BED 116 (80–216.6) Gy	OR: 92.8% (2 yr), OP: 90.2% (2 yr)	OR: 43% (2 yr), OP: 22% (2 yr)
Pasqualetti *et al*[46]	P	51/78	≤ 5	Choline PET/CT	Bone, LN	24 Gy/1 fr, 27 Gy/3 fr	98.7% (1 yr), 97.4% (2 yr)	NR
Ost *et al*[20] (STOMP)	P	Surveillance: 31/65, MDT: 31/51	≤ 3	Choline PET/CT	Extracranial	N = 25 SBRT 30 Gy/3 fr	Median FU (3 yr), MDT: 100%, Surveillance: 19.3%	NR
Siva *et al*[26] (POPSTART)	P	33 /50	≤ 3	CT/BS /18F-NaF PET	Bone, LN	20 Gy/1 fr	97% (1 yr), 93% (2 yr)	58% (1 yr), 39% (2 yr)
Conde *et al*[50]	P	67 (100)	≤ 4	Choline PET/CT, NMR Diffusion	Bone, LN	45 Gy/6 fr, 30 Gy/3 fr	100% (Median FU 9 mo)	Median 21 mo, OR: 22.9 mo, OP: 8.7 mo
Bone								
Muacevic *et al*[31]	P	40/64	≤ 2	Choline PET/CT	Bone	Mean dose 20.2 Gy (16.5-22 Gy)/1 fr	95.5% (2 yr)	NR
Habl *et al*[58]	R	15/20	≤ 5	Choline PET/CT, 68Ga-PSMA-PET	Bone	25-35 Gy/5 fr	100% (2 yr)	Median 7.3 mo
Fanetti *et al*[59]	R	55/77	≤ 5	Choline-PET/CT, MRI, CT, 68Ga-PSMA-PET/CT	Bone	24 Gy/3 fr (+ frequent)	83% (1 yr)	56% (1 yr)

BED: Biologically effective dose; BS: Bone scan; CT: Computed tomography; 18F-FDG: [18F]-fluorodeoxyglucose; 68Ga-PSMA: 68-Ga-Prostate-Specific Membrane Antigen; LC: Local control; LN: Lymph node; MDT: Metastasis-directed therapy; MRI: Magnetic resonance imaging; 18F-NaF: 18F Sodium Fluoride; NMR: Nuclear magnetic resonance; NR: Not reported; OP: Oligoprogressive; OR: Oligorecurrent; PET/CT: Positron emission tomography with coregistered computed tomography; P: Prospective; PFS: Progression free survival; R: Retrospective.

Table 2 Summary of selected publications reporting stereotactic body radiation therapy for lymph nodes oligometastatic prostate cancer

Ref.	Study type	No. Patients / lesions	No. of metastases	Imaging method	Site of metastases	SBRT schedules	LC	PFS
Lymph node								
Casamassima *et al*[33]	R	25/25	NR	Cholina PET/CT	LN	N = 18: 30 Gy/3 fr	90% (3 yr)	Median 24 mo
Detti *et al*[36]	R	30/39	NR	Cholina PET/CT	LN	24-36 Gy/1-5 fr	100% (1 yr)	NR
Ponti *et al*[60]	R	16/18	≤ 2	Cholina PET/CT	LN	12-35 Gy/1-5 fr	94% (2 yr)	NR
Ost *et al*[29]	R	72/89	≤ 3	18F-FDG, Cholina PET/CT,MRI	LN	At least 5 Gy/fr with BED at least 80 Gy	95.8% (3 yr)	Median 21 mo 34% (3 yr) 13% (5 yr)
Ingrosso *et al*[61]	R	40/47	NR	Cholina PET/CT	LN	35-40 Gy/5 fr (+ frequent)	98% (mean FU 30 mo)	NR
Jereczek-Fossa *et al*[62]	R	94/124	≤ 5	Cholina PET/CT/CT/ MRI	LN	24-30 Gy/3 fr (+ frequent)	84% (2 yr)	30% (2 yr)

BED: Biologically effective dose; CT: Computed tomography; 18F-FDG: [18F]-fluorodeoxyglucose; LC: Local control; LN: Lymph node; MRI: Magnetic resonance imaging; NR: Not reported; PET/CT: Positron emission tomography with coregistered computed tomography; PFS: Progression free survival; R: Retrospective; SBRT: Stereotactic body radiation therapy.

serial images. Tables 1 and 2 show the reported LC rates to range from 82%-100% at two years. This is consistent with a systematic review of SBRT in the treatment of oligometastatic PCa, which reported LC rates of > 90% and isolated cases of severe toxicity[41]. These high LC rates have been described for both bone and lymph node metastases. A relevant proportion of patients (25%-38%)[26,34] progress and remain amenable to ablative SBRT. However, after lymph node SBRT, new lymph node relapses frequently occur outside the treated field, accounting for 67% of all relapse cases over a median follow-up of two years[34]. SBRT may be used in selected patients, though they should be informed of the high risk of recurrence, which may prove more difficult to treat through re-irradiation with curative intent.

Toxicity

All the published series found toxicity to be low (Tables 1 and 2). The most relevant problem after SBRT of bone metastases is fracture - this being the cause underlying the only reported case of grade 3 toxicity[26]. Low-grade toxicity was generally limited to gastrointestinal effects such as nausea, and was consistently observed in < 20% of the treated patients. The largest published series on SBRT applied to non-spinal bone metastases documented a fracture rate of approximately 8.5%, and concluded that SBRT is safe, since the risk of pathological fracture after cEBRT was estimated to be approximately 4%-5%[42].

The Spinal Instability Neoplastic Score (SINS)[43] predicts fracture risk and should be assessed prior to vertebral SBRT in all cases. The criteria for assessing SINS include the level of the metastasis targeted for irradiation, the type of pain, spinal malalignment, the presence of baseline vertebral compression fractures, the type of lesion, and whether the tumor involves the posterior wall. The SINS classifies patients as stable (SINS 0-6), potentially unstable (SINS 7-12), or unstable (SINS 13-18). In the case of SINS ≥ 7, the risk of fracture is increased and vertebroplasty or surgical stabilization prior to SBRT is recommended[44].

ADT-FS

Five studies in oligorecurrent patients[34,45-48] analyzed ADT-FS as primary endpoint - this parameter being defined as the time interval between the first day of SBRT and the start of ADT. The reported range in median ADT-FS was 15.6-39.7 mo. The studies included second and subsequent cycles of SBRT, delaying palliative treatment with ADT and its side effects[34,45]. After a median follow-up of three years, the STOMP study[20], as the first prospective, randomized trial of MDT and delayed ADT in oligometastatic PCa versus observation, found the median ADT-FS to be 13 mo for the observation group and 21 mo for the MDT group. In the POPSTART study[26] the ADT-FS rate at two years was 48%.

PFS

The PFS rates at 1-2 years are shown in Table 1, and range from 40%-72% at one year

to 35%-45% at two years. The median PFS values range from 7.3-31.6 mo. The use of hormone treatment is also highly variable. In contrast to cEBRT, the contribution of ADT used in combination with SBRT is not known, though it may improve tumor control by exerting a synergistic effect.

The largest reported series[29], a multi-institutional study pool, used PFS (defined as the absence of new metastatic lesions) as the primary endpoint, with rates of 31% and 15% at 3 and 5 years, respectively, and with a median PFS of 21 mo.

Oligoprogressive patients: Special mention must be made of the assessment of SBRT in oligoprogressive patients. Five series[30,47,49,50] include oligorecurrent and oligoprogressive, castration-resistant patients. Stereotactic body radiation therapy appears to be useful also in this group of patients with a poorer prognosis. In the POPSTAR trial[26] the PFS rate at one and two years was 58% and 39%, respectively. In the prospective study by Ahmed *et al*[49], 6 of the 11 castration-resistant patients achieved undetectable or decreasing PSA levels with a median follow-up of 4.8 mo.

The third study is a multicenter trial[47] describing 41 oligoprogressive patients (70 lesions) - this being the largest number of patients reported to date. With a median follow-up of 23.4 mo, the PFS rate at two years was 22% in this subgroup versus 43% in oligorecurrent patients of the same series.

In the Spanish phase II of the GICOR group[50], all patients had at least two years of ADT prior to SBRT, and 12 cases of oligoprogression were included, of which 66% with a median follow-up of 9.8 mo remained progression-free without the need for a new line of systemic treatment (hormonal or chemotherapy).

ONGOING STUDIES

Different ongoing studies assess the benefit of treatment of the primary tumor in the setting of oligometastatic disease, associated to SBRT of all the metastatic sites. However, we here focus on ongoing trials in oligorecurrent (hormone-sensitive) and oligoprogressive patients (castration-resistant). A summary of these trials is provided in Table 3. All of them are phase II trials, including mostly 1-5 bone and/or lymph node lesions, and their primary endpoints are fundamentally time to disease progression.

Among these studies, mention should be made of the different randomized trials. The ORIOLE study (NCT02680587)[51] is the first randomized study to evaluate the efficacy of SBRT as measured by the quantification of circulating tumor cells in hormone-sensitive oligometastatic PCa. Its preliminary findings have been presented at the ESTRO 2018 Congress[52]. The ongoing CORE study compares the best available best SOC with or without SBRT (NCT02759783)[53], although it also includes patients with breast cancer and non-small cell lung cancer. The PEACE V study (STORM, NCT03569241)[54] randomizes patients to MDT (lymphadenectomy or SBRT) versus MDT plus pelvic radiotherapy (45 Gy in 25 fractions). It will attempt to establish the standard treatment in lymph node oligorecurrent PCa. Lastly, the PCS IX (NCT02685397)[55] will analyze the role of enzalutamide associated to SBRT.

CONCLUSION

SBRT is safe and effective. It has been able to offer excellent LC rates, with minimal toxicity. It has also been shown to slow disease progression and therefore to delay the introduction of ADT and its associated side effects. The impact of these results upon OS in oligometastatic patients is not known. It is obvious that we need phase III trials to answer these questions, though on the basis of the ongoing trials such answers are not to be expected for several years.

However, due to the LC and symptoms control achieved, the convenience of administration, the delaying of side effects of ADT or the delaying of second systemic therapy lines, SBRT has become increasingly widely used in radiation oncology units and should be offered to well-informed patients who request such treatment. Knowing this situation, the European Organisation for the Research and Treatment of Cancer and the European Society for Radiotherapy and Oncology have launched the OligoCare Project, a broad registry of standard practice that will provide information on the contribution of SBRT to oligorecurrence and oligoprogression in PCa, among other tumor sites. In the absence of strong evidence, treatment should be personalized, established by agreement with well-informed patients, and the patient circumstances and preferences should be taken into account.

Table 3 Summary of clinical trials investigating treatment with stereotactic body radiation therapy in oligometastatic prostate cancer

Study	Study type	Type of patient	No. of metastases	Site of metastases	Intervention	Primary endpoint
NCT02680587 Sidney, Kimmel Comprehensive Cancer Center (ORIOLE)[51]	Phase II	HS	≤ 3	Bone or soft tissue	Observation *vs* SBRT	Time to progression (Time Frame: 6 mo)
NCT02759783 Royal Marsden Hospital (CORE)[53]	Phase II/III	HS/CR	≤ 3	Extracranial	Standard of Care *vs* SBRT	Progression Free Survival (Time Frame: 60 mo post treatment)
NCT03569241 PEACE V (STORM) Ghent[54]	Phase II	HS	≤ 3	Pelvic LN	MDT (salvage lymph node dissection or SBRT) *vs* MDT + WPRT. ADT (6 mo in the two arms)	Metastases-free survival (Time Frame: 2 yr)
NCT02685397 PCS IX[55]	Phase II/III	CR	≤ 4	Any location excluding brain and liver metastasis	LHRH agonist + Enzalutamide *vs* LHRH agonist + Enzalutamide + SBRT	Radiographic Progression-free Survival (Time Frame: 5 yr)
NCT03361735 City of Hope Medical Center[63]	Phase II	HS	≤ 4	Bone. One lung lesion < 2 cm allowed	ADT + SBRT + Radium Ra223 dichloride	Time to treatment failure (Time Frame: Assessed up to 5 yr)
NCT01818986 Southwestern Medical Center Texas[64]	Phase II	CR	Any number of metastatic site are allowed. However, only up to six sites will be selected for SBRT	Any location except brain metastasis	Sipuleucel-T and SBRT	Time to progression (Time Frame: 4 yr)
NCT02816983 Mayo Clinic Rochester[65]	Phase II	CR	≤ 3	Any location	SBRT	PSA-progression free survival (Time Frame: 1 yr) Overall Survival (Time Frame: 2 yr)
NCT02192788 GICOR Castellon[66]	Phase II	HS/CR	≤ 4	Bone or LN	SBRT	No. of patients without disease progression (Time Frame: 5 yr)

ADT: Androgen deprivation therapy; CR: Castration resistant; HS: Hormone-sensitive; LHRH: Luteinizing hormone-releasing hormone; LN: Lymph node; MDT: Metastasis-directed therapy; PSA: Prostate-specific antigen; SBRT: Stereotactic body radiation therapy; WPRT: Whole pelvic radiotherapy.

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MINIREVIEWS

Existing anti-angiogenic therapeutic strategies for patients with metastatic colorectal cancer progressing following first-line bevacizumab-based therapy

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Abstract

Continuous inhibition of angiogenesis beyond progression is an emerging treatment concept in the management of metastatic colorectal cancer patients with prior bevacizumab exposure. Treatment options include the continuation or reintroduction of bevacizumab during the second-line chemotherapy or switching to a different antiangiogenic monoclonal antibody such as aflibercept or ramucirumab. In the selection of treatment, patient-based factors such as performance status, age, tumor burden, and tolerance and sensitivity to the first-line bevacizumab-based therapy, as well as treatment-related factors such as toxicity, efficacy, and cost, should be taken into consideration.

Key words: Angiogenesis inhibition; Second-line chemotherapy; Colorectal cancer; Bevacizumab; Aflibercept; Ramucirumab

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Core tip: Anti-angiogenic treatment is an essential part of the current armamentarium against metastatic colorectal cancer (mCRC). For now, bevacizumab is the only drug licensed for the treatment of chemotherapy-naïve patients with mCRC. However, patients undergoing first-line bevacizumab-based therapy eventually develop disease progression and become candidates for second-line chemotherapy. In this manuscript, we discuss the available anti-angiogenic therapeutic strategies that have been proven to be useful in the treatment of patients with mCRC in whom first-line bevacizumab-based therapy was ineffective.

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INTRODUCTION

The medical treatment of metastatic colorectal cancer (mCRC) has become more diversified over the past few decades owing to the successful integration of targeted therapy agents, which block either epidermal growth factor signaling pathway or angiogenesis, into cytotoxic drug combinations[1]. Concordantly, a dramatic improvement in survival has been achieved among patients suffering from mCRC. Moreover, extensive preclinical efforts were able to identify additional targetable molecular alterations in these patients such as *BRAF* mutation, human epidermal growth factor receptor 2 amplification, and microsatellite instability[2-4]. The clinical application of compounds that can inhibit signaling pathways in cancer cells activated by these genetic events seems to provide additional survival gains in selected patients with mCRC.

Among the molecular targets mentioned above, tumor-driven angiogenesis is still an attractive target in mCRC[5-7]. The United States Food and Drug Administration has approved a total of four drugs that block angiogenesis (bevacizumab, aflibercept, ramucirumab, and regorafenib) in the treatment of mCRC (Table 1). Of these, bevacizumab is the only drug licensed for the treatment of chemotherapy-naïve patients with mCRC.

Bevacizumab is a murine-derived monoclonal antibody (muMAb A4.6.1) that inhibits angiogenesis by targeting the vascular endothelial growth factor (VEGF)-A. Belonging to the VEGF family, (VEGF)-A is a crucial angiogenic cytokine (Figure 1) that is produced by cancer and benign stromal cells, particularly in a hypoxia-inducible factor-1-dependent manner. It triggers angiogenic signals via interaction with endothelial cell-surface tyrosine kinase receptors [VEGF receptor-1 (VEGFR-1) and -2 (VEGFR-2)]. The binding of VEGF-A to the extracellular domain of these receptors induces their dimerization and autophosphorylation and the subsequent activation of intracellular pathways that contribute to cell proliferation (*e.g.*, phospholipase-C-gamma and extracellular signal-regulated kinases 1/2 pathway), migration (*e.g.*, focal adhesion kinase and p38 pathway), and survival (*e.g.*, phosphatidylinositol 3-kinase/Akt pathway)[8-11]. Other members of the VEGF family, such as VEGF-B, -C, and -D, and placental growth factor (PIGF) play supporting roles in the process of angiogenesis[10,12].

Bevacizumab is conventionally administered in combination with oxaliplatin- or irinotecan-based doublet [*i.e.*, FOLFOX (5-FU, leucovorin, and oxaliplatin) and FOLFIRI (5-FU, leucovorin, and irinotecan)] or triplet [*i.e.*, FOLFOXIRI (5-FU, leucovorin, oxaliplatin, and irinotecan)] chemotherapy regimens. A recent meta-analysis of the first-line chemotherapy for mCRC confirmed that the addition of bevacizumab results in a significant improvement in progression-free survival [PFS; hazard ratio (HR) 0.66, $P < 0.0001$] and overall survival (OS; HR 0.84, $P = 0.0001$), compared with chemotherapy alone[13]. In addition, the clinical activity of bevacizumab is not influenced by currently validated predictors of treatment response and/or survival outcomes in mCRC, such as the mutational status (*KRAS* and *BRAF* genes) and anatomic location (left *vs* right side of the colon) of the primary tumor.

On the other hand, patients undergoing first-line bevacizumab-based therapy eventually develop disease progression (usually within 9 mo) and become candidates for second-line chemotherapy[13]. Available data strongly favor the continuous inhibition of angiogenesis (using maintenance bevacizumab therapy or switching to another antiangiogenic monoclonal antibody) during second-line chemotherapy to achieve a satisfactory clinical outcome[14,15]. In this article, we discuss therapeutic strategies that have been proven to be useful in the treatment of patients with mCRC in whom first-line bevacizumab-based therapy was ineffective.

CONTINUATION OF BEVACIZUMAB BEYOND DISEASE PROGRESSION

Several United States-based non-randomized observational studies, such as the

Table 1 Food and Drug Administration-approved antiangiogenic drugs for the treatment of metastatic colorectal cancer

Agent	Class	Target	Indication	Approved for	Recommended dose
Bevacizumab	Humanized Moab	VEGF-A	First- and second-line	Use in combination with oxaliplatin and irinotecan-based chemotherapy	5 mg/kg or 10 mg/kg *i.v.* every 2 wk
Aflibercept	Fully human Moab	VEGF-A, -B, and PIGF	Second-line	Use in combination with FOLFIRI	4 mg/kg *i.v.* every 2 wk
Ramucirumab	Fully human Moab	The extracellular domain of VEGFR-2	Second-line	Use in combination with FOLFIRI	8 mg/kg *i.v.* every 2 wk
Regorafenib	Oral multikinase inhibitor	VEGFR-1, -2, and -3 (in addition to RET, KIT, PDGFR, and FGFR	Beyond second-line	Single-use	160 mg once daily, days 1-21 of 28-d cycle

Moab: Monoclonal antibody; VEGF: Vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; PIFG: Placental growth factor; PDGF: Platelet derived growth factor; FGFR: Fibroblast growth factor; FOLFIRI: 5-fluorouracil, leucovorin, irinotecan.

Bevacizumab Regimens: Investigation of Treatment Effects and Safety and the Avastin Registry: Investigation of Effectiveness and Safety, initially reported that the continuation of bevacizumab during second-line chemotherapy had a beneficial impact on the survival of patients with mCRC in whom first-line bevacizumab-based therapy was ineffective[16-18]. Further evidence in support of this treatment strategy was provided by the phase III ML18147 trial (Table 2)[19].

The ML18147 trial was designed by German and Austrian investigators to evaluate the effectiveness of continuing with bevacizumab-based therapy following disease progression in patients with mCRC who had previously received irinotecan- and oxaliplatin-based chemotherapy regimens in combination with bevacizumab[19]. However, the study excluded patients who exhibited progression within the first 3 mo of first-line therapy (rapid progressors), those who showed progression 3 mo after the last bevacizumab administration, and those who received bevacizumab for < 3 consecutive months of first-line therapy. Overall, 820 patients were randomized to receive a novel chemotherapy regimen (fluoropyrimidine plus oxaliplatin or irinotecan) plus bevacizumab (equivalent of 2.5 mg/kg *i.v.* per week) or chemotherapy alone. Therapy was continued until the development of disease progression or intolerable toxicity. Patient stratification was conducted based on the first-line chemotherapy regimen, first-line PFS (≤ 9 mo *vs* > 9 mo), time from last bevacizumab administration (≤ 42 d *vs* > 42 d), and performance status (ECOG 0-1 *vs* 2).

In comparison with patients receiving chemotherapy alone, those receiving chemotherapy plus bevacizumab had a significantly longer median PFS (5.7 mo *vs* 4.0 mo; HR 0.63; $P < 0.0001$) and median OS [11.2 mo *vs* 9.8 mo; HR 0.81; 95% confidence interval (CI): 0.69-0.94; $P = 0.0062$]. Bevacizumab was consistently beneficial across all subgroups, although the response rates were relatively low in both groups (5% *vs* 4%). However, the disease control rate was significantly higher in the chemotherapy plus bevacizumab group (68% *vs* 54%, $P < 0.0001$). In addition, the chemotherapy plus bevacizumab group was not associated with increased toxicity, with the exception of specific bevacizumab-related (grade 3-5) side effects including bleeding/hemorrhage (2% *vs* < 1%), gastrointestinal perforation (2% *vs* < 1%), and venous thromboembolism (5% *vs* 3%). There were four treatment-related deaths in the chemotherapy plus bevacizumab group and three in the chemotherapy alone group.

The Bevacizumab Beyond Progression (BEBYP) phase III trial was designed by Italian researchers to investigate the clinical effectiveness of continuing bevacizumab or reintroducing it (after a bevacizumab-free interval of > 3 mo) in combination with second-line chemotherapy in patients with mCRC who developed disease progression following first-line bevacizumab-based therapy[20]. However, following the presentation of data from the ML18147 trial, the study was prematurely discontinued after inclusion of only 185 patients. These patients were randomized to receive second-line chemotherapy alone or in combination with bevacizumab and stratified into subgroups according to their performance status, (ECOG 0 *vs* 1-2), chemotherapy-free interval (> 3 mo *vs* < 3 mo), bevacizumab-free interval (> 3 mo *vs* < 3 mo), and the second-line chemotherapy regimen administered (FOLFIRI *vs* FOLFOX). The bevacizumab-free interval was longer than 3 mo in 50% of the patients in the chemotherapy plus bevacizumab group. After a median follow-up of 45.3 mo, when compared with chemotherapy alone, the continuation or reintroduction of bevacizumab with second-line chemotherapy was associated with a significantly

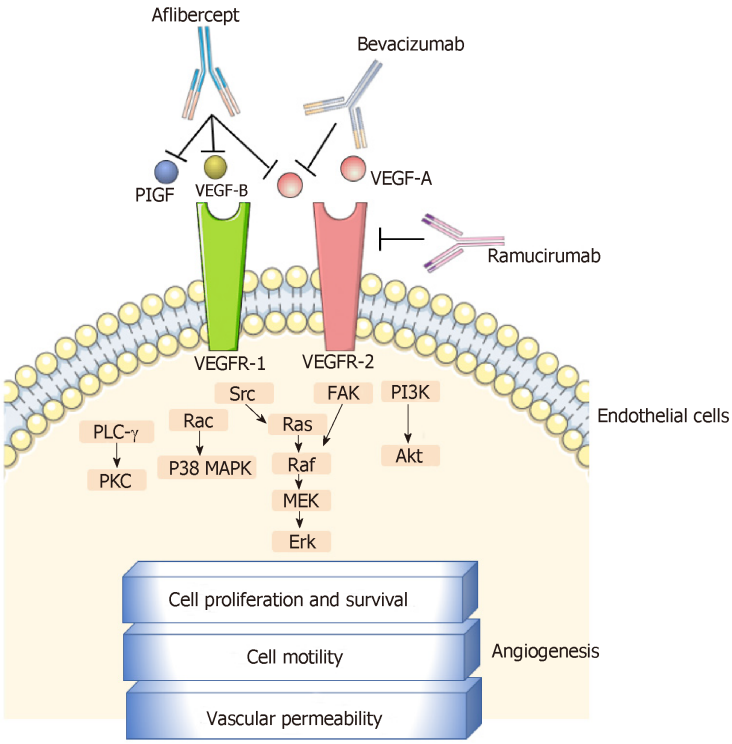

Figure 1 Approved anti-vascular endothelial growth factor monoclonal antibodies in the treatment of metastatic colorectal cancer and their mechanisms of action. VEGF: Vascular endothelial growth factor; PIGF: Placental growth factor; FAK: Focal adhesion kinase; PI3K: Phosphoinositide 3-kinase; PLC-γ: Phospholipase C gamma; PKC: Protein kinase C; MAPK: Mitogen-activated protein kinases; Erk: Extracellular signal-regulated kinase.

higher median PFS (6.8 mo *vs* 5.0 mo; adjusted HR 0.70; 95%CI: 0.52–0.95; stratified log-rank P = 0.010) and median OS (15.5 mo *vs* 14.1 mo; adjusted HR 0.77; 95%CI: 0.56–1.06; stratified log-rank P = 0.043); this benefit was consistently observed across all patient subgroups. The response rates observed between the groups were not significantly different (17% *vs* 21%; P = 0.573). Subgroup analyses revealed an equivalent survival benefit regardless of whether bevacizumab was continued or reintroduced. The safety profile and frequency of adverse events were also similar in the treatment groups.

SWITCHING TO A DIFFERENT ANTI-VEGF MONOCLONAL ANTIBODY

Aflibercept

Aflibercept is a recombinant protein that is constructed from the second extracellular ligand-binding domain of VEGFR-1 and the third extracellular ligand-binding domain of VEGFR-2, fused to the constant region of a human immunoglobulin G1 molecule[21-25]. In contrast to bevacizumab that only inhibits VEGF-A, aflibercept can bind to other angiogenic cytokines (*e.g.*, VEGF-B and PIGF) that are thought to play a role in resistance to bevacizumab[21-25]. This biological advantage of aflibercept may explain its superior antitumor activity when compared with bevacizumab in patient-derived xenograft models of CRC[21]. In addition, studies in tumor xenografts have demonstrated that switching to aflibercept during disease progression following bevacizumab therapy resulted in a higher tumor response than the cases receiving continued bevacizumab-based therapy[26].

The phase III VELOUR trial was designed to evaluate the effectiveness of aflibercept in combination with FOLFIRI regimen during the second-line chemotherapy of patients with mCRC who had developed disease progression either during or after completion of oxaliplatin-based chemotherapy without a biologic agent[27]. Moreover, patients who relapsed within 6 mo of the completion of adjuvant oxaliplatin-based chemotherapy were also included in this study. Patients with prior exposure to irinotecan were not eligible, although those previously treated with bevacizumab were included. Patients were randomized to receive either FOLFIRI plus

Table 2 Randomized clinical studies comparing the efficacy of second-line chemotherapy plus antiangiogenic agent with chemotherapy alone (or plus placebo) in metastatic colorectal cancer

Study	Type of study	The proportion of patients who received prior BEV	Treatment arms (No. of patients)	ORR (%)	mPFS (mo)	HR	mOS (mo)	HR
BRiTE[16]	Observational cohort	100%	CT + BEV (642)	NA	19.2	0.49	31.8	0.48
			CT alone (531)	NA	9.5		19.9	
			No treatment (253)	NA	3.6	2.05	12.6	
ARIES[17]	Observational cohort	100%	CT + BEV (438)	NA	14.4	0.84	NA	
			CT alone (667)	NA	10.6		NA	
Cartwright *et al*[18]	Observational cohort	100%	CT+ BEV (267)	NA	14.6	0.74	27.9	0.76
			CT alone (306)	NA	10.1		21.4	
ML18147[19]	Phase 3	100%	FOLFOX/FOLFIRI + BEV (409)	5	5.7	0.68	11.2	0.81
			FOLFOX/FOLFIRI + placebo (411)	4	4.1		9.8	
BEBYP[20]	Phase 3	100%	FOLFOX/FOLFIRI + BEV (92)	21	6.8	0.70	15.5	0.77
			FOLFOX/FOLFIRI + placebo (92)	17	5.0		14.4	
VELOUR[27]	Phase 3	30%	FOLFIRI + Aflibercept (612)	19.8	6.9	0.76	13.5	0.82
			FOLFIRI + placebo (614)	11.1	4.7		12.0	
RAISE[37]	Phase 3	100%	FOLFIRI + Ramucirumab (536)	13.4	5.7	0.79	13.3	0.84
			FOLFIRI + placebo (536)	12.5	4.5		11.7	

BEV: Bevacizumab; mPFS: Median progression-free survival; mOS: Median overall-survival; HR: Hazard ratio; CT: Chemotherapy; NA: Not available; FOLFOX: 5-FU, leucovorin, oxaliplatin; FOLFIRI: 5-FU, leucovorin, irinotecan.

aflibercept (4 mg/kg *i.v*. every 2 wk) (n = 612) or FOLFIRI plus placebo (n = 614), and stratified according to ECOG performance status (0 *vs* 1 *vs* 2), prior bevacizumab exposure (approximately 30.5% of patients in both treatment arms had received first-line bevacizumab-based therapy), age, sex, anatomic location of primary tumor, number of involved organs, hepatic metastasis, prior hypertension, and geographical region. Treatment was continued until the development of disease progression or intolerable toxicity. The primary endpoint was OS.

After a median follow-up of 22.3 mo, patients receiving FOLFIRI plus aflibercept demonstrated a significantly longer PFS (median, 6.90 mo *vs* 4.67 mo; HR 0.758; 95%CI: 0.661-0.869; P < 0.0001) and OS (median, 13.5 mo *vs* 12 mo; HR 0.817; 95.34%CI: 0.713-0.937; P = 0.0032) than those receiving placebo plus FOLFIRI. The aflibercept group had a higher ORR than the placebo group (28% *vs* 18.7%)[28,29]. Subsequent subgroup analyses revealed that patients previously exposed to bevacizumab also benefited from a longer OS (albeit less pronounced) through the application of aflibercept; the median OS values were 12.5 and 11.7 mo with the aflibercept and placebo groups, respectively (HR 0.862). However, the most significant benefit from aflibercept treatment was observed among patients with liver-only metastases and among those with no previous exposure to bevacizumab[30,31].

Compared with the placebo group, the aflibercept group were found to experience more grade ≥ 3 anti-VEGF class-specific side effects, which included hypertension (19.5% *vs* 1.5%), hemorrhage (2.9% *vs* 1.7%), arterial thromboembolic events (1.8% *vs* 0.5%), and venous thromboembolic events (7.9% *vs* 6.3%). In addition, aflibercept administration led to an increase in the incidence of chemotherapy-related toxicities such as neutropenia, diarrhea, asthenia, stomatitis, infections, and palmar-plantar

erythrodysesthesia. Patients aged ≥ 65 years appeared to be particularly vulnerable to these adverse events[32,33].

Ramucirumab

Ramucirumab is another inhibitor of the VEGF/VEGFR axis. It selectively targets VEGFR-2 and induces conformational changes in the extracellular domain of the receptor, which prevents the binding of all VEGF ligands and receptor activation[34]. Several preclinical studies suggest that the inhibition of VEGFR-2 using monoclonal antibodies, such as DC101, inhibits the growth of CRC cells that are resistant to other angiogenesis inhibitors[35,36]. Therefore, the use of potent and selective VEGFR-2 inhibitors, such as ramucirumab, provides a rational therapeutic option for patients with mCRC who developed disease progression despite receiving first-line bevacizumab-based therapy.

The multicenter, randomized, double-blind, phase III RAISE trial compared the effectiveness of ramucirumab versus placebo, both in combination with second-line FOLFIRI regimen[37]. The study included patients with mCRC who developed disease progression within 6 mo after the final dose of first-line oxaliplatin-based chemotherapy plus bevacizumab. Patients who had received bevacizumab (within 28 d) or chemotherapy (within 21 d) before randomization were excluded. Overall, 1072 patients were randomized to receive ramucirumab (8 mg/kg every 2 wk) plus FOLFIRI or placebo plus FOLFIRI (n = 536 in each group). Stratification variables included the geographical location (North America *vs* Europe *vs* all other regions), KRAS exon 2 status (mutant *vs* wild-type), and time to disease progression after first-line therapy (< 6 mo *vs* ≥ 6 mo). Of the patients, 83% had received at least 3 mo of first-line bevacizumab-based therapy. Treatment continued until the development of disease progression or intolerable toxicity. The primary endpoint of the study was OS.

After a median follow-up of 21.7 mo, OS was significantly longer in the ramucirumab group than the placebo group (13.3 mo *vs* 11.7 mo; HR 0.844; 95%CI: 0.730–0.976; P = 0.0219). An improved PFS also was detected in patients receiving ramucirumab (5.7 mo *vs* 4.5 mo; HR 0.793; 95%CI: 0.697-0.903; P = 0.0005). The survival benefit was consistent across all patient subgroups that received ramucirumab plus FOLFIRI. However, the response rates in the ramucirumab and placebo groups were comparable (ORR 13.4% *vs* 12.5%; P = 0.63).

The addition of ramucirumab to chemotherapy was associated with higher rates of neutropenia, hypertension, diarrhea, and fatigue. Despite the transient deterioration in the quality of life of these patients, the adverse events were manageable.

In a prospective biomarker analysis of the RAISE trial, the efficacy of ramucirumab was compared with pretreatment plasma levels of several angiogenic cytokines[38]. In particular, ramucirumab plus FOLFIRI therapy was found to be more beneficial in patients with elevated plasma VEGF-D levels, with an improvement of 2.4 mo in OS (13.9 mo *vs* 11.5 mo). However, this therapy was associated with reduced OS in patients with low VEGF-D levels, compared with the placebo group (12.6 mo *vs* 13.1 mo).

Comments and conclusions

The data presented above shows that the maintenance of angiogenesis inhibition using bevacizumab, aflibercept, or ramucirumab beyond the initial development of disease progression is an effective and tolerable strategy with a consistent and significant improvement in OS (approximately 1.4 mo) observed in patients with mCRC. In fact, no notable differences between these three drugs were found in terms of their contribution to survival and safety profile. The estimated HR for OS values were similar in the ML18147 (0.81), BEBYP (0.77), VELOUR (0.82), and RAISE (0.84) studies. Accordingly, the most recent version of the European Society of Medical Oncology consensus guidelines for the management of mCRC recommended either the continuation of bevacizumab or switching to aflibercept or ramucirumab (only in combination with FOLFIRI and in irinotecan-naïve patients) for the second-line chemotherapy of patients in whom first-line bevacizumab-based therapy was ineffective (category 1A)[39].

At present, a head-to-head randomized clinical study comparing the efficacy of these three angiogenesis inhibitors in this setting has not been undertaken. Moreover, useful biomarkers that could be integrated into an ideal treatment protocol are not available. Although the measurement of pretreatment plasma levels of angiogenic cytokines (particularly VEGF-D) is a promising approach in this setting, the process is inconvenient for routine clinical use.

The clinical course of patients during first-line therapy may assist clinicians in their decision-making. In this context, patients who exhibit rapid progression (*i.e.*, within 3 mo) following the initiation of first-line bevacizumab-based therapy are usually good candidates for treatment with aflibercept or ramucirumab. It should be noted that

such patients were not included in the ML18147 study, and it is possible that they have an intrinsic resistance to bevacizumab.

Cost-effectiveness is also a factor that influences the clinician's decision. Goldstein and El-Rayes calculated the costs of these agents for the treatment of mCRC based on average US prices[40]. They estimated that ramucirumab leads to a more than two-fold increase in the cost of treatment compared with bevacizumab and aflibercept. Morlock *et al*[41] indirectly compared the total cost and clinical outcomes of using bevacizumab plus chemotherapy and aflibercept plus chemotherapy as second-line chemotherapeutic strategies for mCRC using Butcher's method. Bevacizumab plus chemotherapy was found to be more cost-effective than aflibercept plus chemotherapy ($39104 less per treated patient), with similar effectiveness (OS 13.3 mo *vs* 12.5 mo; HR 0.94). Therefore, the use of bevacizumab beyond disease progression appears to be the most reasonable therapeutic approach in selected patients.

For patients with RAS wild-type mCRC in whom the first-line bevacizumab-based treatment was ineffective, the optimal second-line chemotherapy remains controversial. The data from two small phase II studies, the SPIRITT and PRODIGE 18, suggests that switching from bevacizumab to an epidermal growth factor inhibitor (panitumumab or cetuximab) in the second-line chemotherapy of patients with KRAS wild-type mCRC does not provide a survival benefit that is superior to the continuation of bevacizumab[42,43]. However, the SPIRITT study demonstrated that a switch from bevacizumab to panitumumab might be associated with increased tumor response (19% *vs* 32%)[42]. Therefore, when a rapid response is desired, the continuation of treatment with an EGFR inhibitor may be more appropriate.

In conclusion, based on current evidence, we propose a simple algorithm for the management of patients with mCRC who developed disease progression following first-line bevacizumab-based therapy (Figure 2). The identification of clinically useful predictive markers reflecting tumor sensitivity to a specific antiangiogenic agent would improve the effectiveness of treatment and reduce costs.

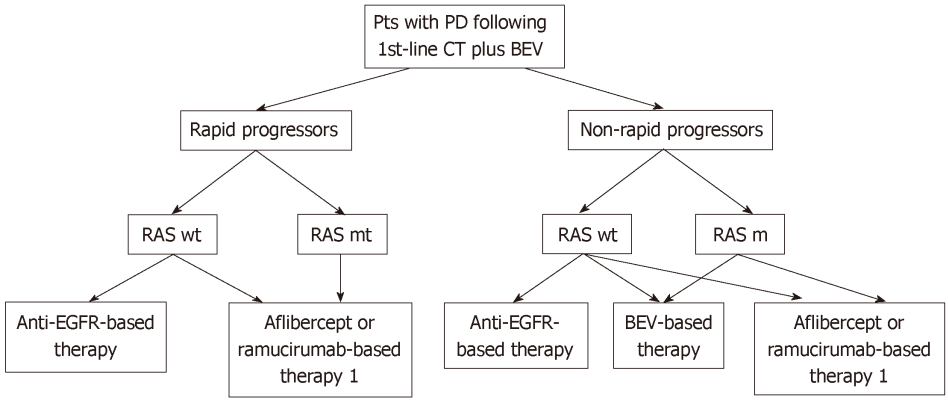

Figure 2 A proposed algorithm for the management of patients with metastatic colorectal cancer after disease progression following bevacizumab-based first-line therapy. Rapid progressors: Patients progressing within 3 mo after starting first-line chemotherapy. [1]In patients who did not receive irinotecan-based first-line chemotherapy and only in combination with FOLFIRI. Pts: Patients; PD: Progressive disease; CT: Chemotherapy; BEV: Bevacizumab; wt: Wild-type; mt: Mutant; EGFR: Epidermal growth factor receptor.

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MINIREVIEWS

Rational-emotive behavioral intervention helped patients with cancer and their caregivers to manage psychological distress and anxiety symptoms

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Abstract

There is a dearth of evidence-based data on how psychological distress and death anxiety symptoms experienced by cancer patients and caregivers are treated in developing regions. This article sheds light on the report of the findings from a 2016 study that revealed a rational-emotive behavioral intervention helped a select group of cancer patients and their family caregivers to manage problematic assumptions, psychological distress, and death anxiety symptoms in Nigeria. Based on my experience as a co-investigator and corresponding author of this previous study, I addressed the challenges of conducting such a study and the implications for future research in this article. This article encourages future researchers to replicate the study and endeavor to overcome the limitations of the previous study. Funders were also encouraged to ensure increased access to funds for conducting similar studies with cancer patients and their family caregivers in developing countries and other parts of the world.

Key words: Cancer patients; Caregivers; Death anxiety; Psychological distress; Psychological intervention; Rational-emotive behavioral intervention; Rational-emotive hospice care therapy

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Core tip: Emerging evidence seems to be boosting our understanding of how psychological interventions can be adapted to help improve the lives of cancer patients and their caregivers. This article reveals the importance of utilizing rational-emotive behavioral intervention to alleviate psychological distress and death anxiety symptoms experienced by cancer patients and their caregivers based on the outcomes from a 2016 study. The practical implications and future directions for clinicians who might want to use rational-emotive behavioral therapy intervention to improve the psychological health of cancer patients and caregivers were highlighted. Funders were also encouraged to

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ensure increased access to funds to enable researchers to conduct similar studies.

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INTRODUCTION

Published research on how psychological distress and death anxiety symptoms experienced by cancer patients and caregivers are treated in developing regions is lacking. Available data indicate that deaths due to cancer in developing nations are expected to increase from 6.7 million in 2015 to 8.9 million in 2030[1]. On the other hand, cancer deaths in developed nations are expected to remain quite stable over the next 20 years[1]. About 70% of patients with cancer in developing nations are detected at a very late stage of the illness when treatment is ineffective[2]. In such situations, the only feasible intervention is palliative care. However, palliative care intervention often fails to reach more than five million terminally ill patients with cancer as well as their caregivers each year[3].

Emerging evidence appears to boost our understanding of how psychological interventions can be adapted to palliative/hospice care settings to help improve the lives of patients with cancer as well as that of their caregivers in the developing regions. For instance, a new study on this subject by researchers at the University of Nigeria Nsukka found that rational-emotive behavioral therapy (REBT) adapted for use in a palliative/hospice care intervention was effective in helping to decrease the problematic assumptions, psychological distress, and death anxiety symptoms of patients with cancer and their caregivers[4]. The findings from the study suggest that this type of psychological intervention can be employed by clinicians in different regions to assist cancer patients and caregivers in managing cancer-related distress and death anxiety. It is important to note that the psychological treatment of patients with tumor using REBT cannot be overstated. A 2012 randomized controlled trial by Mahigir *et al*[5] found that REBT was effective in decreasing pain intensity scores of patients with cancer in two countries – India and Iran. It is against this backdrop that this article sheds light on the findings of the study by the researchers at University of Nigeria Nsukka.

RATIONAL-EMOTIVE BEHAVIORAL INTERVENTION

In the Onyechi *et al*[4] study, the REBT model of psychotherapy developed by Dr Albert Ellis was adapted to help cancer patients and their caregivers in Nigerian outpatient settings. According to practitioners of the REBT theory, irrational beliefs such as awfulizing, catastrophizing, demandingness, low frustration tolerance, and self/others/life-downing beliefs are the root cause of emotional disturbance in healthy and sick people[6-8]. Thus, Onuigbo *et al*[8] observed that changing self-limiting beliefs, expectations, and attitudes are essential to a successful REBT intervention. Onyechi *et al*[4] innovatively adapted the REBT theory and called the intervention "rational-emotive hospice care therapy (REHCT)." As a randomized controlled trial, the study participants were assigned to one of two groups: intervention group (patients, n = 16; caregivers, n = 26) and usual care control groups (patients, n = 16; caregivers, n = 26). The intervention was manualized and delivered via group format. All participants were assessed for the presence of problematic assumptions, psychological distress, and death anxiety symptoms at pre-treatment, post-treatment, and follow-up periods using validated outcome measures. There was no report of adverse effects of the intervention. Also, completion rate of the intervention by the study participants was 100%. The study revealed that the beneficiaries of the REHCT showed significant improvements on problematic assumptions, psychological distress, and death anxiety symptoms reduction in contrast to participants in the usual care control group. It is worthy to note that the study by Onyechi *et al*[4] provided evidence-based preliminary data and treatment modality for use by clinicians and researchers who work with cancer patients at advanced stage of the

illness and their family caregivers and ushered in a novel direction in end-of-life care, cancer patient education, and oncology counseling practice in the Nigerian context.

IMPLICATIONS AND FUTURE DIRECTIONS

The Onyechi *et al*[4] article has attracted a number of citations from peer reviewed journal articles focusing on the REBT theory[8,9] as well as those investigating death anxiety[10,11] and other mental health issues in cancer patients[12]. The implication of this article is that it encourages further studies on this research area and sheds light on the fact that the objective of end-of-life interventions for cancer patients that in part aims at alleviating psychological symptoms and promoting mental health of patients can be achieved through the use of psychological interventions such as the REHCT. Thus, further clinical trials are required to substantiate the efficacy of this psychological intervention by Onyechi *et al*[4] in various oncology counseling contexts and other countries. Psychological interventions whose objective is to improve and maintain mental health and psychological wellbeing of patients with advanced cancer at the end-of-life and their family caregivers might benefit from implementing the REHCT. Investigators who would like to anchor their interventions on the REBT framework should note that cognitive, emotive, and behavioral factors are key mechanisms of change in an REBT intervention[13]. In other words, an REBT intervention often focus on patients' thought processes, belief systems, feelings, and attitudes as the mechanisms of change in that they play vital roles in how REBT intervention demonstrates its clinical impacts[14]. Studies have shown that through a variety of techniques, REBT intervention can help individuals in group therapy to manage anxiety disorders and alter their illogical beliefs[15].

As a co-investigator and corresponding author of the Onyechi *et al*[4] study, I was very pleased to receive this invitation from the *World Journal of Clinical Oncology* to contribute an article that falls under the scope of the journal. This invitation provided the opportunity for me to shed light on this research with cancer patients and their family caregivers in Nigeria. The study opened up new avenues for adaptation of psychological interventions for cancer patients and their family caregivers in this region. But the challenges of supporting and providing this intervention type to this category of patients and their family caregivers cannot be overemphasized. Funds were not secured from any organization or agency and as such all costs were undertaken by the investigators. I would like to use this opportunity to encourage funding organizations and agencies to expand access to their funds to cover this type of study targeting cancer patients and their family caregivers for researchers in developing regions such as Nigeria. This is important because it might help advance the course of action towards achieving the sustainable development goal number three of the United Nations which aims at ensuring good health and wellbeing for every individual at all ages[16]. As a sub-goal, the sustainable development goal number three aims at a one third reduction in premature death due to non-communicable diseases via prevention and treatment as well as promotion of mental health and well-being by the year 2030[16]. Strengthening researchers' access to funds for implementation of psychological interventions such as the REHCT might be one of the various ways to assist them in contributing to the attainment of this goal of sustainable development in developing countries.

In view of health economy, it is important to clarify the basis for allocating research funds to REBT more than other health programs related to this area. Gilbert *et al*[17] showed that an REBT program that integrated both individual and group therapy sessions with primary care and specialist mental health services provided an alternative to expensive in-patient admissions. The authors reported that the REBT program was cost-effective by minimizing the request for acute hospital beds, satisfactory to the patients, and yielded considerable improvements in patients' symptoms, subjective wellbeing, and functioning[17]. Also, in a randomized clinical trial of 170 Romanian patients that examined the cost-effectiveness of treatment interventions, which yielded significant positive changes in depression, depression-free days, and quality-adjusted life years scores of patients, the authors demonstrated that REBT intervention attracted lower cost compared to other health programs like pharmacotherapy with similar therapeutic effects[18]. Therefore, it might be reasonable to allocate more research funds to treatment interventions with similar clinical effects on patients' symptom management like other health programs but would require a lower cost to execute. These previous research reports suggest that, in view of health economy, an REBT program might require more support with research funding than other health programs related to this area because it appears to be less expensive and can have better cost-utility. The implication is that more patients can be treated

through an REBT program and funders would be able to disburse funds to more REBT researchers than they would to other researchers whose interventions might cost more to execute especially when a large number of patients are to be treated.

Despite the promising evidence of psychological interventions such as REBT, I would like to agree with Syrjala *et al*[19] that multidisciplinary teams are important in oncology settings for the integration of care and expertise in the delivery of psycho-behavioral treatments in standard care for cancer patients' symptom management. Because intense cancer pain is associated with increased levels of anxiety and depression[20] and increased levels of psychological distress and catastrophizing[21], one important task that multidisciplinary teams have to carry out is to examine the efficacy of REBT in the reduction of cancer pain and related psychological concerns. Given that changes in pain-related psychological variables such as catastrophizing and other pain-related beliefs have also been found to be significantly linked to changes in pain intensity, pain interference, and psychological functioning[22], the use of REBT to improve pain management in cancer patients is suggested for future researchers and healthcare teams who aim to reduce the perception of pain among such patients. In fact, studies are advancing support for further recognition of the relevance of psychological interventions in cancer pain management[23]. Future investigators focusing on this subject and would like to replicate the Onyechi *et al*[4] study should endeavor to use alternative research designs such as mixed methods design, employ robust statistical analysis tools, carryout a responder analysis, measure therapeutic adherence, and document the details of their intervention in clinical trial registries as this would help to further promote transparency in and public access to such a study.

CONCLUSION

This article focused on the findings of a 2016 study in which the author was a co-investigator and corresponding author. The previous study demonstrated that a rational-emotive behavioral intervention helped a select group of cancer patients and their family caregivers to manage problematic assumptions, psychological distress, and death anxiety symptoms in Nigeria. Thus, this article encourages future researchers to replicate the study and endeavor to overcome the limitations of the previous study. Funders were also encouraged to ensure increased access to funds to enable researchers to conduct similar studies with cancer patients and their family caregivers in developing countries, and other parts of the world.

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MINIREVIEWS

Pancreatic cancer screening in patients with presumed branch-duct intraductal papillary mucinous neoplasms

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Abstract

Because delayed diagnosis is one of the causes of poor prognosis in pancreatic ductal adenocarcinoma (PDAC), early detection is a key for overall improvement of prognosis. Towards this end, periodic screening is recommended for individuals considered high-risk for PDAC. Advances in diagnostic imaging modalities have increased the frequency of incidental findings of pancreatic cysts, including the intraductal papillary mucinous neoplasm (IPMN) - a major risk factor of PDAC, having 1% annual prevalence of concomitance with IPMN. Proper retainment of patients with IPMN and regular follow-up by routine imaging examination will likely improve early detection and better prognosis of PDAC. Unfortunately, current guidelines only address management of PDAC derived from IPMN and overlook PDAC concomitant with IPMN. Screening of patients with IPMN, by endoscopic ultrasonography (currently the most reliable modality for detecting small PDAC), may facilitate early detection of both IPMN-derived and -concomitant PDAC. Prospective studies to evaluate the usefulness of endoscopic ultrasonography in screening of IPMN-concomitant PDAC will also help in determining the optimal surveillance strategy for more widespread applications.

Key words: Intraductal papillary mucinous neoplasm; Pancreatic ductal adenocarcinoma; Endoscopic ultrasonography; Screening; Early diagnosis

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Core tip: Advances in diagnostic imaging modalities have increased the frequency of incidental findings of pancreatic cysts, including of the intraductal papillary mucinous neoplasm (IPMN) - a major risk factor of pancreatic ductal adenocarcinoma (PDAC). Proper retainment of patients with IPMN and regular follow-up by routine imaging examination will likely improve early detection and better prognosis of PDAC.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) persists worldwide as a remarkably lethal malignancy with extremely poor prognosis. The National Cancer Center Japan estimated that 39800 Japanese individuals developed PDAC in 2017, with 34100 among them having died; likewise, the 5-year survival rate for Japanese PDAC patients was only 7.8%. One of major causes of poor prognosis for PDAC is the generally delayed diagnosis, which results in over 90% of diagnoses being made at stages III or IV[1]. Egawa *et al*[2] reported the 5-year survival rates of PDAC according to the UICC International Union Against Cancer stages (6th edition) as 68.7% for stage IA, 59.7% for IB, 30.2% for IIA, 13.3% for IIB, 4.7% for III, and 2.7% for IV. This pattern of steady decline in survival suggests that even if patients with PDAC were to be diagnosed in the earliest stage (I), the prognostic outcomes would still be remarkably poor.

On the contrary, it was reported that the 5-year survival rate for early PDAC of size 10 mm or less was relatively good, at 80.4%; although the detection of such a small size PDAC could be made in up to only 0.8% of the total patient population. The range of challenges to small PDAC detection encompass patient-related features (*e.g.*, asymptomatic presentation) and clinic-related limitations (*e.g.*, lack of established screening guidelines and the limits of visualization in ultrasonography (US), commonly used to observe the whole pancreas in screening). Therefore, periodic screening is recommended for patients with PDAC, especially those identified as high-risk - such as patients with PDAC family history, diabetes mellitus, or chronic pancreatitis[3-6].

Pancreatic cysts, including the intraductal papillary mucinous neoplasms (IPMNs), are another risk factor for PDAC[7-9]. Hence, proper identification of affected patients and steady follow-up with routine imaging examinations will likely improve early detection rates and, consequently, prognosis of PDAC. Unfortunately, there remains a lack of coalesced knowledge on IPMN case management for PDAC. This review aimed to provide an informational foundation for a proper screening strategy for follow-up of IPMN cases, for IPMN-concomitant PDAC.

PREVALENCE OF PANCREATIC CYSTS

With the recent advancements in diagnostic imaging technologies involving magnetic resonance imaging (MRI), the frequency of incidental detection of pancreatic cystic lesions has increased[10]. Moreover, the minimum size for detection of a pancreatic cyst has decreased, with solitary cysts of only a few millimeters in size being identifiable[10].

The previous studies on the prevalence of incidental pancreatic cyst are summarized in Table 1. Pancreatic cysts belong to a heterogeneous group of tumors, ranging from benign to malignant[11]. The latter includes the precursor lesions of PDAC, such as the IPMNs and mucinous cystic neoplasms[12]. The IPMNs are further subdivided according to location in the ducts. The 2017 revised international guidelines[13] distinguished IPMNs in the main duct from those in the branch ducts. Specifically, the branch-duct (BD)-IPMN was defined as located in the branch duct with dilation, having > 5 mm cyst size, and interacting with the main pancreatic duct.

An investigation by Kimura *et al*[14] of the epithelial growth of small cystic lesions in 300 consecutive autopsy cases found cystic lesions in 24.3% (n = 73). Histological analysis identified 47.5% as normal epithelium, 32.8% as papillary hyperplasia

Table 1 Previous studies on prevalence of incidental pancreatic cysts

Article	Country	Design	Method of detection	Population	Prevalence, %
Kimura *et al*[14], 1995	Japan	Retrospective	Autopsy	300 consecutive autopsies in an elderly population	24.3
Zhang *et al*[20], 2002	United States	Retrospective	1.5 T MRI	1444 patients who underwent a MRI, including 323 patients performed for pancreatic or biliary indication	19.6
Laffan *et al*[17], 2008	United States	Retrospective	16-MDCT	2832 16-MDCT performed for nonpancreatic indication	2.6
Lee *et al*[21], 2010	United States	Retrospective	1.5 T MRI	616 MRI performed for nonpancreatic indication	13.5
Girometti *et al*[16], 2011	Italy	Retrospective	1.5 T MRI	152 MRI performed for nonpancreatic indication	44.7
Ip *et al*[18], 2011	United States	Retrospective	CT or MRI*	17443 patients who underwent a CT and 2700 patients who underwent a MRI	CT 2.2, MRI 15.9
Matsubara *et al*[22], 2012	Japan	Retrospective	1.5 T MRI	1226 MRI performed for nonpancreatic indication	10
Sey *et al*[23], 2015	United States	Prospective	EUS	341 EUS performed for nonpancreatic indication	9.4
Soroida *et al*[19], 2016	Japan	Retrospective	US	5198 US performed as part of a general health examination	3.5
Moris *et al*[10], 2016	United States	Retrospective	1.5 T or 3 T MRI	500 MRI performed for nonpancreatic indication	41.6
Martínez *et al*[24], 2018	Spain	Prospective	EUS	298 EUS performed for nonpancreatic indication	21.5

*There is no description of the MRI instrument model. CT: Computed tomography; EUS: Endoscopic ultrasonography; MRI: Magnetic resonance imaging; PDAC: Pancreatic ductal adenocarcinoma; US: Ultrasonography.

without atypia, 16.4% as atypical hyperplasia, and 3.4% as carcinoma *in situ*. Apparently, the cystic lesions without normal epithelium were equivalent to IPMN. In addition, Fernández-del Castillo *et al*[15] reported that most pancreatic cysts are mucinous cystic tumors (including IPMNs), and Girometti *et al*[16] found that 70.6% of the detected pancreatic cysts presented IPMN-like patterns (*i.e.*, polycystic, main pancreatic duct interaction, and > 5 mm) or an indeterminate pattern. Considering these collective data, it seems that the majority of pancreatic cysts are actually representatives of IPMNs.

The reported prevalence rates for pancreatic cysts have varied depending on the imaging method used for detection. Namely, the reported detection rates have been for 2.2%-2.6%[17,18] for computed tomography (CT), 3.5%[19] for US, 10%-44.7%[10,16,18,20-22] for MRI, and 9.4%-21.5%[23,24] for endoscopic ultrasonography (EUS). A similar amount of reports[10,14,16,17,19-21,23,24] have demonstrated aging as a significant risk factor for pancreatic cysts; in general, the frequency of pancreatic cysts among the elderly is over 20%.

PDAC CONCOMITANT WITH IPMN

Definitions of PDAC concomitant with IPMN and PDAC derived from IPMN

Unlike the PDAC derived from IPMN, PDAC occurring concomitantly with IPMN features PDAC and IPMN that developed from different parts of the pancreatic

parenchyma. It has been suggested that these two forms of PDAC - that derived from IPMN and that concomitant with IPMN - should be considered as different diseases[25]. However, in the case of PDAC having developed from tissue adjacent to the IPMN, the distinction between PDAC derived from IPMN and PDAC concomitant with IPMN will be difficult. Molecular biomarkers, including the expression profile of MUC and the mutational status of GNAS and KRAS, may help to distinguish these two types of PDAC more clearly[26,27].

Assessment of concomitant PDAC in surgically resected IPMN

There have been several studies for PDAC concomitant with IPMN since the first report in 2002 by Yamaguchi *et al*[28]. The reported incidence rates of PDAC concomitant with IPMN are 9%[28] and 4%[29], determined in two studies of surgically resected IPMN case series. Ingkakul *et al*[30] found that 9.3% (n = 22) of patients with IPMN (n = 236) had concomitant PDAC, either synchronously or metachronously. In addition, Yamaguchi *et al*[25] found 31 cases of PDAC concomitant with IPMN among 765 IPMN resections. However, it seems that these results might represent underestimations of the actual number of cases of PDAC concomitant with IPMN because of the study design used (*i.e.*, retrospective evaluation of surgically resected specimens).

Conversely, Matsubara *et al*[22] reported that, among a total of 116 PDAC patients, 65 (56%) presented with both PDAC and pancreatic cysts. Moreover, 5 presented with cystic lesions (identified at least 2 year before the PDAC diagnosis) located upstream of the PDAC and 28 with lesions downstream of the PDAC. These 33 cases with pancreatic cystic lesions were classified as "preexisting" PDAC, and accounted for 28% of the total 116 patients evaluated. Accordingly, the actual frequency of PDAC concomitant with IPMN might be higher than the rates reported to date.

Frequency of PDAC concomitant with IPMN among patients with BD-IPMNs

The previous studies that have examined the duration of concomitant PDAC development during the follow-up period for IPMNs are summarized in Table 2[7-9,31-37]. Interestingly, the incidence of PDAC concomitant with IPMN tends to be higher in Japan (about 1% per year[7,8]), as compared to the reports from the United States and Italy. One of the Japanese studies, by Tanno *et al*[8], investigated 89 BD-IPMN patients without any mural nodule and followed each up for at least 2 year (median: 64 mo; range: 25-158 mo), and identified 4 cases of PDACs located distant from the BD-IPMN in 552 patient-years of follow-up (7.2 per 1000 patient-years).

Another Japanese study, by Maguchi *et al*[9], analyzed 349 follow-up BD-IPMN patients who had no mural nodules on EUS exam at initial diagnosis, and identified 7(2.0%) concomitant PDAC cases within the follow-up period (median: 3.7 year; range: 1-16.3 year). Likewise, Kamata *et al*[36] showed a 6.9% incidence of concomitant PDAC development in 102 BD-IPMN patients without mural nodule during the follow-up period (median: 42 mo). Finally, Uehara *et al*[7] found a 1.1% per year incidence of PDAC among patients with BD-IPMN, whereas the expected incidence of PDAC in the age- and gender-matched control group was calculated to be 0.045% per year.

Taken together, the frequency of concomitant PDAC in Japanese patients with BD-IPMNs is not low, suggesting that these patients should be considered for a screening strategy, particularly examining the whole pancreas.

Characteristics of PDAC concomitant with IPMN

As described above, screenings for patients with IPMN should be conducted not only to monitor the primary IPMN lesions but also to track the possible development of concomitant PDAC. However, due to the large number of IPMN patients, it will be important to limit the surveillance target population and to decide on the appropriate screening interval for the imaging examinations. Understanding the distinctive characteristics of PDAC concomitant with IPMN may be helpful for determining the optimal detection parameters of PDAC.

Tanno *et al*[8] reported that the incidence of PDACs located distant from the BD-IPMNs was significantly higher for older patients (> 70 year) and for women. Ideno *et al*[26,28] showed that distinct PDACs frequently develop in the pancreas presenting benign gastric-type IPMN without GNAS mutations. In addition, it had been reported that IPMN patients with a family history of PDAC are at higher risk of developing PDAC concomitant with IPMN. A study by Nehra *et al*[39] of 324 patients with resected IPMNs revealed that patients with a family history of PDAC developed concomitant PDAC more frequently than did those without (11.1% *vs* 2.9%, P = 0.002). Likewise, a study of 300 patients with IPMN by Mandai *et al*[40] revealed that concomitant PDAC occurred more frequently in patients with affected first-degree relatives than in those without (17.6% *vs* 2.1%, P = 0.01). Thus, individuals with the above characteristics

Table 2 Frequency of concomitant pancreatic ductal adenocarcinoma in patients with branch-duct - intraductal papillary mucinous neoplasm during follow-up

Article	Country	Design	*n*	Diameter of IPMN in mm*	Follow-up inmo*	Surveillancei nterval	Imaging(optio nal imaging)	Incidence of concomitant PDAC,*n* (%)
Kobayashi *et al*[31], 2005	Japan	Retrospective	47	28.2	41.0	No description	EUS	3 (6.4)
Tada *et al*[32], 2006	Japan	Prospective	80	22.0	48.0	q6 mo	US, CT, MRI, EUS	2 (2.5)
Uehara *et al*[7], 2008	Japan	Retrospective	60	No description	87.0	q3-6 mo	US (CT, MRI, EUS)	5 (8.3)
Sawai *et al*[33], 2010	Japan	Retrospective	103	18.0	59.0	At least yearly	EUS	2 (1.9)
Tanno *et al*[8], 2010	Japan	Prospective	89	20.0	64.0	q6-12 mo	CT, MRI, EUS	4 (4.5)
Maguchi *et al*[9], 2011	Japan	Retrospective	349	19.0	44.0	No description	US, CT, MRI, EUS, ERCP	7 (2.0)
Ohno *et al*[34], 2012	Japan	Retrospective	142	22.3	42.5	q6 mo	CE-EUS, CT	5 (3.5)
Sahora *et al*[35], 2013	United States	Retrospective	411	16.0	60.0	q3-24 mo	CT, MRI	3 (0.7)
Kamata *et al*[36], 2014	Japan	Retrospective	102	No description	42.0	q3 mo	US, CT, MRI, EUS	7 (6.9)
Malleo *et al*[37], 2015	Italy	Prospective	569	18.0	56.0	At least yearly	MRI (EUS)	3 (0.5)

*Mean, or, if not available, median or midpoint of range. CT: Computed tomography; EUS: Endoscopic ultrasonography; MRI: Magnetic resonance imaging; PDAC: Pancreatic ductal adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasm; US: Ultrasonography.

have a higher risk of PDAC and should be checked more attentively for early detection of concomitant PDAC.

Collective studies have shown that malignancy of primary IPMNs does not correlate with incidence of concomitant PDAC. Tada *et al*[32] reported that IPMNs with concomitant PDAC found in cases with small cyst diameter are probably indicative of benign IPMNs. Also, Ingkakul *et al*[30] reported that, in their study population, all of the detected concomitant PDAC cases involved patients with BD-IPMN or BD-IPM adenoma. The current IPMN guidelines[13,41] describe surveillance strategies for PDAC derived from IPMN and state that the smaller the size of the IPMN, the longer the interval between screening examinations. In addition, the American Gastroenterological Association guidelines[41] recommend canceling the follow-up if there are no changes within 5 year; although, Mandai *et al*[40] reported that 6 of 9 concomitant PDAC cases were detected at 6 year or later after the detection of IPMN. Thus, a more cautious screening strategy may be essential for early detection of concomitant PDAC in the patients with BD-IPMN.

Imaging modalities for early detection of PDAC concomitant with BD-IPMN

In recent years, several imaging modalities have been applied in surveillance of BD-IPMN; these include US, CT, MRI and EUS. However, it is still unclear which of these imaging modalities should be selected for screening and what the optimal length of interval is for each in follow-up, to best achieve early detection of both IPMN-derived and -concomitant PDAC. As described above, while current guidelines[13,41] mention surveillance strategies for PDAC derived from IPMN, these remarks are, unfortunately, irrelevant for the early detection of IPMN-concomitant PDAC.

Kanno *et al*[42] retrospectively analyzed 200 PDAC cases of stage 0 and stage I, and identified the dilated main pancreatic duct as an indirect imaging feature of early PDAC - detectable to a similar degree in all imaging modalities: 74.8% in US, 79.6% in CT, 82.7% in MRI, and 88.4% in EUS. In contrast, direct imaging features of early PDAC could be seen most clearly in EUS (76.3%) compared with the others (52.6% in US, 51.5% in CT, and 45.1% in MRI). Kamata *et al*[36] reported that among the 102 BD-IPMN patients without mural nodule, who were followed-up with image diagnosis every 3 mo (by EUS semiannually and by US/CT and MRI annually, performed respectively between the two EUS examinations), 7(6.9%) developed concomitant PDAC, with an average diameter of 16 mm (range: 7-30 mm) during the follow-up period (median: 42 mo; range, 12-74 mo). The study also determined that EUS was the

only imaging modality capable of detecting concomitant PDAC at a curable stage; the detection rates of PDAC concomitant with IPMN during the follow-up period were 100% by EUS, 0% by US, 43% by CT and 43% by MRI.

Although EUS was demonstrated to be superior in detecting PDAC concomitant with IPMN, another previous study demonstrated that EUS does not have marginal use in surveillance of BD-IPMNs[43]. In particular, the statistical associations of EUS with different rates of morphologic progression, surgery, malignancy and death all fell below the threshold of significance. However, the meta-analysis had some limitations in the study design that may have impacted the results - namely, that most included articles reported on retrospective studies and that several of the studies included data from patients who were followed up with EUS at long intervals.

Hopefully, future prospective studies will be conducted to confirm the usefulness of EUS in surveillance of patients with IPMNs for potential development of concomitant PDAC. Furthermore, these studies are necessary to determine the optimal surveillance strategy (intervals and imaging modalities) for BD-IPMN patients in particular. As this is an ongoing unresolved health issue, impacting populations across the globe, there is urgency to performing such studies.

CONCLUSION

Appropriate retainment of patients with IPMNs, especially those with BD-IPMNs, for periodic screening with routine imaging examinations, particularly EUS, will help to promote early detection and better prognosis of both IPMN-derived and -concomitant PDAC. To this end, further evaluations are needed to confirm the most efficient surveillance strategies for presumed BD-IPMN.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective evaluation of FOLFIRI3 alone or in combination with bevacizumab or aflibercept in metastatic colorectal cancer

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Institutional review board statement: The database was declared to the National French Commission for bioinformatics data and patient liberty (CNIL). The study was performed in accordance with French regulations with approval from the local institutional review boards.

Informed consent statement: A general informed consent was signed by all cancer patients at the time of their first hospitalization in the cancer centre. This consent allows the use of their clinical and biological data in the cohort study.

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

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Abstract

BACKGROUND

The treatment of metastatic colorectal cancer (mCRC) relies of chemotherapy. The efficacy of the standard FOLFIRI-therapy could be improved by a modification of the regimen by splitting the dose of irinotecan on day 1 and day 3 in the FOLFIRI3 regimen.

AIM

To determine safety and efficacy of FOLFIRI3 regimen.

METHODS

This is a monocentric retrospective study evaluating the efficacy and safety of the FOLFIRI3 regimen given alone or in combination with bevacizumab or aflibercept in patients with previously treated mCRC.

RESULTS

One hundred and fifty-three consecutive patients were included (18 treated with FOLFIRI3, 99 with FOLFIRI3 plus bevacizumab and 36 with FOLFIRI3 plus aflibercept). The overall response rate (ORR) and disease control rate were 51% and 62%, respectively. Similar ORRs were observed in all 3 cohorts. Median progression-free survival (PFS) and overall survival (OS) were 3.9 mo (95%CI: 3.2-4.9) and 9.4 mo (95%CI: 6.6-12), respectively. Median PFS and OS values were improved in the FOLFIRI3 plus aflibercept group. The most common grade 3-4 adverse events were diarrhoea (21.6%) and neutropenia (11.8%), and these toxicities were more frequent in the FOLFIRI3 plus aflibercept group. According to the multivariate Cox proportional model, previous surgery of metastasis and

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aflibercept were associated with outcomes.

CONCLUSION
The modification of the FOLFIRI regimen impacted treatment response of mCRC patients. The addition of an antiangiogenic agent, in particular aflibercept, enhanced the clinical benefit and improved survival.

Key words: Colorectal cancer; Chemotherapy; Irinotecan; Second-line; Aflibercept

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Core tip: This retrospective study suggests that modified FOLFIRI with injection of irinotecan at day 1 and 3 is interesting for patients with previously treated metastatic colorectal cancer. Surprisingly the efficacy of the FOLFIRI3-aflibercept seems superior the FOLFIRI3 alone or in combination with bevacizumab. Prospective randomized trial comparing FOLFIRI-aflibercept to FOLFIRI3-aflibercept in second line are warranted.

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INTRODUCTION

Metastatic colorectal cancer (mCRC) is a common disease in western countries[1]. In the absence of resection of all metastatic and primary tumours, the treatment of mCRC remains palliative. The standard of care involves chemotherapeutic protocols that include fluoropyrimidine in combination with oxaliplatin or irinotecan. Anti EGFR mAb and antiangiogenic drugs such as bevacizumab and aflibercept can be used in combination with chemotherapy to improve response rate, progression free survival and overall survival (OS)[2]. Recently, regorafenib and TAS-102 were developed as new therapeutic options upon failure of classical chemotherapeutic regimens[3,4]. In most mCRC patients, doublet chemotherapy using fluoropyrimidine-based chemotherapy with either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) in combination with anti EGFR or an antiangiogenic agent is considered the standard first-line of treatment. Second-line drug selection mainly depends on the regimen used in the first-line chemotherapy. Chemotherapy is frequently used in combination with antiangiogenic agents (bevacizumab, aflibercept, ramucirumab) or anti-EGFR agents when the *RAS* mutation is present[5-10].

Previous reports proposed that the standard FOLFIRI regimen could be optimized by splitting the dose of irinotecan into two days. Half of the total dose is administered on day 1 prior to 5-FU dosing and the other half of the dose is administered on day 3 after 5-FU dosing. This protocol was named FOLFIRI3 regimen[11]. Despite their similarities, the FOLFIRI3 regimen benefits from an increased response rate compared to the classical FOLFIRI regimen[11,12]. A previous report suggests that FOLFIRI3 plus bevacizumab could also be used to improve the response rate and overcome resistance to previous treatment with FOLFIRI[13].

Recently, aflibercept was approved as a second-line chemotherapy in combination with FOLFIRI for mCRC patients whose cancer progressed after oxaliplatin based chemotherapy. This treatment is a new second-line chemotherapeutical option in addition to the previously established[8], but association with of aflibercept with FOLFIRI3 was not reported and compared with FOLFIRI3 or FOLFIRI3 plus bevacizumab.

In this retrospective study, we report a large cohort of patients treated with the FOLFIRI3 regimen and compare the safety and efficacy of FOLFIRI3 alone and in combination with bevacizumab or aflibercept.

MATERIALS AND METHODS

Study design
This study was a retrospective, monocentric study performed at Centre Georges François Leclerc, Dijon France.

Participant
Study includes all consecutive patients treated with the FOLFIRI3 regimen for mCRC in our centre. From January, 2008 to December, 2017, patients were identified through the chemotherapy prescription computer software programme used at the cancer centre (CHIMIO®, Computer Engineering). The database was declared to the National French Commission for bioinformatics data and patient liberty (CNIL). The study was performed in agreement with French regulations with approval from the local institutional review boards. A general informed consent was signed by all cancer patients at the time of their first hospitalization in the cancer centre, enabling patient clinical and biological data analysis in this cohort study. Demographics, cancer history, toxicity according to the Common Toxicity Criteria [Common Toxicity Criteria (CTC) v2.0 (http://cancer.gov/)], and treatment outcomes, as well as pathological, clinical, biological, and radiological data [tumour response according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria], were retrospectively collected from medical records. To be evaluable, all patients must have received at least four cycles of chemotherapy. Patients were classified as follows: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). For statistical analysis, the best tumour response was selected. Patients with either CR, PR, or SD were classified as responders and patients with PD as non-responders.

Settings
Patients were treated with bevacizumab at a dose of 5 mg/kg on day 1 every two weeks. The FOLFIRI3 regimen was given every 14 d as follows: on day 1, irinotecan 100 mg/m^2 as a 1-h infusion, running concurrently with leucovorin 200 mg/m^2 as a 2-h infusion via a Y-connector, followed by 5-FU 2000 mg/m^2 as a 46-h infusion using an electric pump. On day 3, irinotecan 100 mg/m^2 as a 1-h infusion was repeated, at the end of the 5-FU infusion. Bevacizumab was given as a 30 min infusion every 2 wk at 5mg/kg. Aflibercept was given as a 1-h infusion every 2 wk at 4 mg/kg.

Statistical analysis
All patients were followed until death, loss to follow-up, or termination of the study (or whichever occurred first). The objective response rate (ORR) was defined as the proportion of patients having either a CR or PR according to RECIST version 1.1. The disease control rate (DCR) was defined as the percentage of patients who achieved CR, PR or SD. Progression-free survival (PFS) was defined as the time between the treatment start date and the date of disease progression or death from any cause. Patients who were alive without PD at the time of the final analysis were censored. OS was defined as the time between the date and the date of patient death from any cause or to the last date the patient was known to be alive. Patients still alive at the time of the analysis were excluded. Disease characteristics were examined using the χ^2 test or Fisher's exact test for qualitative variables and the Kruskal-Wallis rank sum test for continuous variables, as appropriate. Univariate and multivariate survival analyses were performed using the Cox regression model. Survival probabilities were estimated using the Kaplan-Meier method. OS and PFS medians were calculated with the reverse Kaplan-Meier method and survival curves were compared using the log-rank test. Patients were categorized into one of two cohorts according to their irinotecan status (irinotecan-naïve and those who were previously treated with irinotecan). Patients were also categorized into one of three cohorts according to the treatment regimen they received: FOLFIRI3 alone, FOLFIRI3 plus bevacizumab and FOLFIRI3 plus aflibercept. Data analysis was performed using the statistical software R (http://www.R-project.org/) and representations were made with Prism 7 (GraphPad, San Diego, CA, United States). All tests were two-sided, and *P*-values < 0.05 were considered statistically significant.

Availability of data and materials
The clinical datasets collected and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Patient characteristics

Between January 2008 and December 2017, a total of 153 patients received at least one injection of the FOLFIRI3 regimen at the Department of Medical Oncology, Georges-Francois Leclerc Cancer Centre, Dijon, France. Eighteen received the FOLFIRI3 regimen, 99 received bevacizumab plus the FOLFIRI3 regimen and 36 received aflibercept plus FOLFIRI3. The main clinical characteristics of patients included in this retrospective study are shown in Table 1. The study included 84 males and 69 females and median age was 64 years (range 33-86). The performance status of this population was good with only 14% of patients having an ECOG performance status of 2. Only 29% of the patients had a right-side tumour. RAS and/or BRAF mutations were observed in 53% of the assessable samples. All patients had previously received at least one line of systemic chemotherapy. Only 28 (18%) of the patients were irinotecan-naïve. 28% of the patients previously received bevacizumab, and 30% were previously treated with an EGFR therapy. Patients receiving either FOLFIRI3, bevacizumab plus FOLFIRI3 or aflibercept plus FOLFIRI3 did not differ in their clinical characteristics (Table 1).

Toxicity and feasibility

A total of 1517 cycles of chemotherapy were administered (median 7; range 1–42). One toxic death was reported due to primary tumour perforation followed by haemorrhagic syndrome and septic shock. Bleeding syndrome (digestive or epistaxis) was observed in 12 patients, all treated with antiangiogenic therapies. The most frequent toxicity was a digestive toxicity, grade 3-4 diarrhoea, which occurred in 33 patients (21.6%). Haematological toxicities mainly involved neutropenia. The main toxic events are listed in Table 2. Aflibercept plus the FOLFIRI3 regimen appeared to have increased toxicity compared to the other chemotherapy regimens with both diarrhoea and neutropenia showing increased incidence.

Objective tumour responses and survival

At the time of analysis, 142 patients (93%) had died with a median follow-up of 9.3 mo (range 0.2–40.7 mo).

Considering all patients included in the study, the ORR and DCR were 51% and 62%, respectively. In the irinotecan-experienced group, the ORR and DCR were 46% (13/28) and 64% (18/28), respectively. We then analysed the data according to the treatment regimen in the FOLFIRI3 alone group, we observed an ORR and DCR of 61% and 66%, respectively. In the bevacizumab plus FOLFIRI3 group, we observed an ORR and DCR of 51.5% and 60.5%, respectively. Finally, in the aflibercept plus FOLFIRI3 group, we observed an ORR and DCR of 45% and 64%, respectively. For the entire study population, median PFS and OS were 3.9 mo (95%CI: 3.2-4.9) and 9.4 mo (95%CI: 6.6-12), respectively. Irinotecan-naïve patients did not show significantly improved PFS or OS with median PFS of 5.2 mo *vs* 3.7 mo (log-rank test $P = 0.15$) and median OS of 12 mo *vs* 9.3 mo (log-rank test $P = 0.38$). Median PFS and OS were 3.0 mo (95%CI: 0.8-6.9) and 5.6 mo (95%CI: 4.0-20.2), 3.7 mo (95%CI: 3.0-5.3) and 8.5 mo (95%CI: 6.4-10.7), and 4.7 mo (95%CI: 3.3-12.8) and 13.7 mo (95%CI: 7.9-18.7) for FOLFIRI3, FOLFIRI3 plus bevacizumab and FOLFIRI3 plus aflibercept, respectively. Kaplan-Meier curves illustrating PFS and OS in the whole cohort are shown in Figures 1A and B while Figures 1C and D illustrate PFS and OS for the patient subgroups treated with FOLFIRI3, FOLFIRI3 plus bevacizumab and FOLFIRI3 plus aflibercept. The log-rank test shows significantly improved PFS and OS in the FOLFIRI3 plus aflibercept group. Using the Cox univariate model, good performance status, previous surgery of metastases, first through third line therapy and aflibercept usage were associated with better prognosis in terms of PFS. Good performance status and aflibercept usage were also associated with better prognosis in terms of OS (Table 3). Using the Cox multivariate model, only previous surgery of metastasis and aflibercept usage were associated with better prognosis in terms of PFS while good performance status and aflibercept usage were associated with better prognosis in terms of OS (Table 4).

DISCUSSION

This retrospective study is the largest to date reporting FOLFIRI3 regimen efficacy in mCRC. It is also the first study comparing efficacy and safety of the FOLFIRI3 regimen alone or in combination with bevacizumab or aflibercept. This study demonstrates the safety of these three regimens in heavily pre-treated patients with good performance status. The combination of FOLFIRI3 plus aflibercept gives a higher rate of toxic events as a significant number of the patients in this cohort (33%) presented severe diarrhoea in comparison to 11% and 19% in the FOLFIRI3 or FOLFIRI3 plus bevacizumab cohorts. The frequency of severe diarrhoea was also

Table 1 Patients characteristics *n* (%)

Characteristic	Folfiri 3 (*n* = 18)	Bevacizumab folfiri 3 (*n* = 99)	Aflibercept folfiri 3 (*n* = 36)	All (*n* = 153)	Comparison betweentreatments test *P*-value
Median age, yr (range)	62.5 (44-83)	64 (38-86)	66 (33-83)	64 (33-86)	0.33
Gender					
Male	14 (67)	50 (51)	22 (61)	84 (55)	0.31
Female	6 (33)	49 (49)	14 (39)	69 (45)	
Who performance status					
0	2 (11)	12 (12)	6 (17)	20 (13)	0.47
1	11 (61)	75 (76)	25 (69)	111 (73)	
2	5 (28)	12 (12)	5 (14)	22 (14)	
Primary location					
Right colon	3 (17)	33 (33)	8 (22)	44 (29)	0.51
Left colon	9 (50)	38 (39)	15 (42)	62 (41)	
Rectum	6 (33)	28 (28)	13 (36)	47 (30)	
Initial cancer status					
Synchronous	14 (88)	26 (26)	20 (56)	46 (30)	0.09
Metachronous	4 (22)	73 (74)	16 (44)	107 (70)	
Number of metastases					
0 and 1	6 (33)	29 (29)	9 (25)	44 (29)	0.40
2	8 (40)	45 (46)	12 (33)	65 (42)	
3 and more	4 (22)	25 (25)	15 (42)	44 (29)	
Surgery of primary					
No	7 (39)	38 (38)	14 (39)	59 (39)	1.00
Yes	11 (61)	61 (62)	22 (61)	94 (61)	
Surgery of metastases					
No	14 (78)	78 (79)	28 (88)	120 (81)	0.53
Yes	4 (22)	21 (21)	4 (12)	29 (19)	
Unknown	-	-	4	4	
Line of therapy					
Second	5 (28)	17 (17)	4 (12)	26 (17)	0.52
Third	3 (17)	22 (22)	11 (31)	36 (24)	
More	10 (55)	60 (61)	21 (57)	91 (59)	
Irinotecan chemotherapy-naive					
No	13 (72)	81 (82)	31 (86)	125 (82)	0.46
Yes	5 (28)	18 (18)	5 (14)	28 (18)	
RAS/BRAF mutation status					
Not mutated	11 (69)	36 (44)	16 (44)	63 (47)	0.18
At least one mutated	5 (31)	46 (56)	20 (56)	71 (53)	
Unknown	2	17	-	19	
Best overall response					
PD	3 (17)	8 (8)	0 (0)	11 (7)	0.20
SD	1 (5)	9 (9)	7 (19)	17 (11)	
PR	11 (61)	48 (48.5)	15 (42)	74 (48)	
CR	0 (0)	3 (3)	1 (3)	4 (3)	
NE	3 (17)	31 (31.5)	13 (36)	47 (31)	
Median PFS, mo (95%CI)	3.0 (0.8-6.9)	3.7 (3.0-5.3)	4.7 (3.3-12.8)	3.9 (3.2-4.9)	-
Median OS, mo (95%CI)	5.6 (4.0-20.2)	8.5 (6.4-10.7)	13.7 (7.9-18.7)	9.4 (6.6-12.0)	-

PD: Progression disease; SD: Stable disease; PR: Partial response; CR: Complete response; NE: None evaluable; PFS: Progression free survival; OS: Overall survival.

Table 2 Summary of chemotherapy toxicity *n* (%)

Characteristic	Folfiri 3 (*n* = 18)	Bevacizumab folfiri 3 (*n* = 99)	Aflibercept folfiri 3 (*n* = 36)	All (*n* = 153)
Anemia				
No	14	79	29	122
Grade 1	2	10	5	17
Grade 2	0	8	0	8
Grade 3	2	1	2	5
Grade 4	0	1	0	1
Thrombopenia				
No	17	91	31	139
Grade 1	0	5	3	8
Grade 2	0	2	0	2
Grade 3	1	0	0	1
Grade 4	0	1	2	3
Neutropenia				
No	13	87	26	126
Grade 1	1	0	1	2
Grade 2	2	1	4	7
Grade 3	1	9	4	14
Grade 4	1	2	1	4
Diarrheoa				
No	9	48	11	68
Grade 1	2	18	8	28
Grade 2	5	14	5	24
Grade 3	2	14	11	27
Grade 4	0	5	1	6
Stomitis				
No	13	83	27	123
Grade 1	2	5	5	12
Grade 2	2	8	4	14
Grade 3	0	1	0	1
Grade 4	1	2	0	3
Nausea				
No	17	81	28	126
Grade 1	1	8	5	14
Grade 2	0	10	3	13
Vomiting				
No	17	90	31	138
Grade 1	0	3	4	7
Grade 2	0	3	1	4
Grade 3	1	3	0	4
Hyperblood pressure				
No	18	98	36	152
Yes	0	1	0	1
Bleeding				
No	17	95	30	142
Yes	1	4	6	11
Venous thrombosis				
No	18	97	36	151
Yes	0	2	0	2
Digestive perforation				
No	18	98	36	152
Yes	0	1	0	1

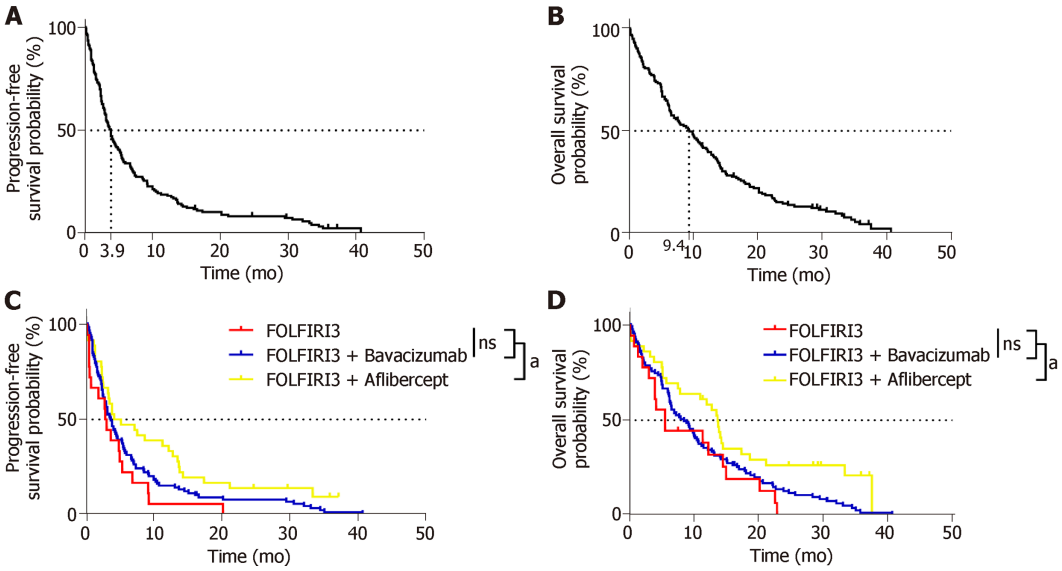

Figure 1 Survival curves for progression free survival and overall survival. A, B: Kaplan-Meier estimates for progression-free survival (A) and overall survival (B); C, D: Kaplan-Meier estimates for progression-free survival (C) and overall survival (D); patients were stratified according to their treatment: FOLFIRI3 (in red), FOLFIRI3 plus bevacizumab (in blue) or FOLFIRI3 plus aflibercept (in yellow). [a]*P*-value < 0.05.

more prevalent than what has been previously reported in the VELOUR study, where only 19% of patients had grade 3 or higher diarrhoea[8]. A similar level of diarrhoea was observed in the recent retrospective study of Carola, in which 38% of patients experienced severe diarrhoea events[14]. Our group previously reported the association between severe diarrhoea induced by aflibercept and microscopic colitis[15,16]. Aflibercept inhibits placental growth factor (PIGF), which prevents colonic ischaemia and, consequently, induces colitis. In preclinical models, the absence of PIGF promotes dextran sodium sulphate-induced colonic mucosal angiogenesis and increases mucosal hypoxia[17]. Other toxicities such as neutropenia and stomatitis occurred at similar rates across all three chemotherapy regimens[8,18,19]. Few cases of febrile neutropenia were observed probably because 65% of the patients received prophylactic G-CSF treatment. In addition, only 18% of the patients were irinotecan-naïve. Such data may result from selection bias, since only patients who had few prior toxic events while being treated with irinotecan were included and further treated with the FOLFIRI3 regimen.

Irinotecan hinders DNA replication by inhibiting type I topoisomerase. Inhibition of type I topoisomerase induce single strand DNA breaks. After this initial DNA damage, failure to repair the DNA breaks results in increased apoptosis. Preclinical studies show that the anti-proliferative activity of 5-FU in combination with irinotecan is schedule dependent[20-22]. For example, several studies showed that delayed administration of irinotecan increases FOLFIRI cytotoxicity. Likewise, the FOLFIRI2 regimen (irinotecan delivery post 5-FU injection) induced promising objective responses but suffered from major haematological toxicity[23]. In contrast, FOLFIRI3 has an improved toxicity profile and previous studies showed that this regimen is active in mCRC resistant to FOLFIRI. Furthermore, in the absence of a targeted agent, response rates range from 17 to 23%, with median PFS of 4-7 mo and median OS of 9-12 mo[11,12,24].

In a similar setting, our group previously reported that FOLFIRI3 plus bevacizumab resulted in a 53% response rate and median PFS and OS of 7 and 13 mo, respectively. Importantly, these results did not differ from the FOLFIRI3 results without a targeted therapy[13]. A recent retrospective report on the usage of FOLFIRI3 in combination with aflibercept demonstrated a response rate of 35%[14]. Results were improved in irinotecan-naïve patients in comparison to the irinotecan-experienced cohort with median PFS and OS of 11.3 mo and 17.0 mo, respectively, for the irinotecan-naïve group and 5.7 mo and 14.3 mo for the irinotecan-experienced group. Our study mainly involved patients that were previously treated with irinotecan and, in the FOLFIRI3 plus aflibercept cohort, only 5 of the 36 patients were irinotecan-naïve. In this cohort, median PFS and OS were 4.7 mo and 13.7 mo, respectively. This study supports the hypothesis that aflibercept increases the efficacy of the FOLFIRI3 regimen. The main limitation of this study is the retrospective design with a relatively low number of patients per cohort.

Table 3 Results of Cox univariate analyses

Characteristic	Progression-free survival			Overall survival		
	Hazard ratio	95%CI	*P*-value	Hazard ratio	95%CI	*P*-value
Age, yr						
Continuous	0.999	0.984; 1.016	0.98	1.002	0.986; 1.018	0.81
Gender						
Female	1			1		
Male	0.827	0.597; 1.145	0.25	0.898	0.645; 1.251	0.53
Who performance status						
0	1			1		
1	1.569	0.926; 2.660	0.09	2.039	0.143; 3.639	0.02
2	2.827	0.473; 5.428	0.002	5.335	2.647; 10.75	< 0.01
Primary location						
Right colon	1			1		
Left colon	0.979	0.660; 1.454	0.92	0.945	0.634; 1.410	0.78
Rectum	1.018	0.671; 1.545	0.93	1.029	0.673; 1.572	0.90
Initial cancer status						
Synchronous	1			1		
Metachronous	0.815	0.572; 1.162	0.26	0.839	0.583; 1.208	0.34
No. of metastastatic sites						
1	1			1		
2	1.225	0.823; 1.823	0.32	1.241	0.824; 1.870	0.30
≥ 3	1.361	0.883; 2.098	0.16	1.490	0.954; 2.326	0.08
Surgery of primary						
No	1			1		
Yes	0.789	0.564; 1.104	0.17	0.799	0.568; 1.124	0.20
Surgery of metastases						
No	1			1		
Yes	0.592	0.388; 0.903	0.01	0.725	0.475; 1.107	0.13
Line of therapy						
Second	1			1		
Third	1.055	0.615; 1.812	0.85	1.126	0.646; 1.962	0.68
More	1.728	1.060; 2.816	0.03	1.531	0.931; 2.517	0.09
Treatment						
FOLFIRI	1			1		
FOLFIRI3 + Bevacizumab	1.055	0.615; 1.812	0.85	0.791	0.471; 1.329	0.38
FOLFIRI3 + Aflibercept	1.728	1.060; 2.816	0.03	0.470	0.255; 0.866	0.02
Irinotecan chemotherapy-naive						
	1			1		
No *vs* yes	0.731	0.474; 1.127	0.15	0.838	0.539; 1.303	0.43
RAS/BRAF mutation status						
Not mutated	1			1		
Mutated	0.910	0.641; 1.293	0.60	0.986	0.690; 1.408	0.94

The FOLFIRI3 regimen demonstrates efficacy and safety in patients previously treated with irinotecan and is an alternative strategy for multi-treated patients. The combination of aflibercept and FOLFIRI3 appears more efficacious than FOLFIRI3 alone or in combination with bevacizumab. A randomized trial comparing FOLFIRI3 plus bevacizumab *vs* FOLFIRI3 plus aflibercept should be conducted to validate this hypothesis.

Table 4 Results of Cox univariate analyses

Characteristic	Progression-free survival			Overall survival		
	Hazard ratio	95%CI	*P*-value	Hazard ratio	95%CI	*P*-value
Age, yr						
Continuous	0.990	0.968; 1.012	0.36	0.988	0.968; 1.007	0.22
Gender						
Female	1			1		
Male	1.003	0.673; 1.497	0.99	0.992	0.655; 1.502	0.97
Who performance status						
0	1			1		
1	1.588	0.832; 3.034	0.16	2.157	1.086; 4.284	0.03
2	2.165	0.925; 5.068	0.08	4.865	2.061; 11.49	< 0.001
Primary location						
Right colon	1			1		
Left colon	0.953	0.589; 1.541	0.84	0.919	0.556; 1.520	0.74
Rectum	1.054	0.634; 1.752	0.84	0.879	0.525; 1.470	0.62
Initial cancer status						
Synchronous	1			1		
Metachronous	0.862	0.554; 1.340	0.51	0.887	0.562; 1.398	0.60
Number of metastastatic sites						
1	1			1		
2	1.040	0.640; 1.692	0.87	1.085	0.654; 1.798	0.75
≥ 3	1.347	0.796; 2.279	0.27	1.449	0.847; 2.476	0.18
Surgery of primary						
No	1			1		
Yes	0.947	0.622; 1.442	0.80	0.893	0.575; 1.387	0.61
Surgery of metastases						
No	1			1		
Yes	0.562	0.342; 0.924	0.02	0.754	0.458; 1.241	0.27
Line of therapy						
Second	1			1		
Third	0.878	0.421; 1.832	0.73	0.944	0.441; 2.020	0.88
More	1.340	0.655; 2.740	0.42	1.155	0.548; 2.432	0.71
Treatment						
FOLFIRI3	1			1		
FOLFIRI3 + Bevacizumab	0.547	0.304; 0.983	0.04	0.647	0.354; 1.180	0.16
FOLFIRI3 + Aflibercept	0.354	0.181; 0.694	0.002	0.367	0.184; 0.729	0.004
Irinotecan chemotherapy-naive						
No	1			1		
Yes	0.979	0.548; 1.748	0.94	1.114	0.609; 2.038	0.73
RAS/BRAF mutation status						
Not mutated	1			1		
Mutated	1.045	0.679; 1.611	0.84	1.232	0.784; 1.935	0.37

ARTICLE HIGHLIGHTS

Research background

FOLFIRI3 is a modification of the classical FOLFIRI regimen with injection of irinotecan at day 1 and 3. This treatment is used as second or further line in many French Centre's based of previous retrospective data. This chemotherapeutic regimen could be used alone or in combination with antiangiogenic agent but comparison of efficacy of FOLFIRI3, FOLFIRI3 bevacizumab and FOLFIRI3 aflibercept has never been performed.

Research motivation

Our objective was to compared efficacy and toxicity of FOLFIRI3, FOLFIRI3 bevacizumab and

FOLFIRI3 aflibercept regimen.

Research objectives
The main objective of the study is to evaluate the safety and efficacy of the FOLFIRI3-used alone or in combination with bevaicuzmab or aflibercept.

Research methods
This is a monocentric retrospective study evaluating the efficacy and safety of the FOLFIRI3 regimen given alone or in combination with bevacizumab or aflibercept in patients with previously treated metastatic colorectal cancer (mCRC).

Research results
One hundred and fifty-three consecutive patients were included (18 treated with FOLFIRI3, 99 with FOLFIRI3 plus bevacizumab and 36 with FOLFIRI3 plus aflibercept). Median progression-free survival (PFS) and overall survival (OS) were 3.9 mo (95%CI: 3.2-4.9) and 9.4 mo (95%CI: 6.6-12), respectively. Median PFS and OS values were improved in the FOLFIRI3 plus aflibercept group. Grade 3-4 adverse events (diarrhoea and neutropenia) were more frequent in the FOLFIRI3 plus aflibercept group.

Research conclusions
The modification of FOLFIRI regimen had an impacton mCRC patients' treatment response. The addition of an antiangiogenic agent, in particular aflibercept, enhanced the clinical benefit and improved survival.

Research perspectives
Prospective randomized trial comparing FOLFIRI-aflibercept to FOLFIRI3-aflibercept are warranted.

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ORIGINAL ARTICLE

Retrospective Study

Impact of conditioning regimen on peripheral blood hematopoietic cell transplant

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Abstract

AIM

To investigate infused hematopoietic cell doses and their interaction with conditioning regimen intensity +/- total body irradiation (TBI) on outcomes after peripheral blood hematopoietic cell transplant (PBHCT).

METHODS

Our retrospective cohort included 247 patients receiving a first, T-replete, human leukocyte antigen-matched allogeneic PBHCT and treated between 2001 and 2012. Correlations were calculated using the Pearson product-moment correlation coefficient. Overall survival and progression free survival curves were generated using the Kaplan-Meier method and compared using the log-rank test.

RESULTS

Neutrophil engraftment was significantly faster after reduced intensity TBI based conditioning [reduced intensity conditioning (RIC) + TBI] and > 4 × 10^6 CD34+ cells/kg infused. A higher total nucleated cell dose led to a higher incidence of grade II-IV acute graft-versus-host disease in the myeloablative + TBI regimen group (P = 0.03), but no significant difference in grade III-IV graft-versus-host disease. A higher total nucleated cell dose was also associated with increased incidence of moderate/severe chronic graft-versus-host disease, regardless of

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conditioning regimen. Overall and progression-free survival were significantly better in patients with a RIC + TBI regimen and total nucleated cell dose > 8 × 10^8/kg (3 years, overall survival: 70% *vs* 38%, $P = 0.02$, 3 years, progression free survival: 64% *vs* 38%, $P = 0.02$).

CONCLUSION
TBI and conditioning intensity may alter the relationship between infused cell doses and outcomes after PBHCT. Immune cell subsets may predict improved survival after unmanipulated PBHCT.

Key words: Total body radiation; Peripheral blood hematopoietic cell transplant; Total nucleated dose; Neutrophil engraftment; Graft-versus-host-disease

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Core tip: This study investigated infused hematopoietic cell doses and their interaction with conditioning regimen intensity on outcomes after peripheral blood hematopoietic cell transplant. Our retrospective cohort included 247 patients receiving a first, T-replete, human leukocyte antigen-matched allogeneic peripheral blood hematopoietic cell transplant. Neutrophil engraftment was significantly faster after reduced intensity total body irradiation and > 4 × 10^6 CD34+ cells/kg infused. Overall and progression-free survival was significantly better in patients with a reduced intensity conditioning and total body irradiation regimen and total nucleated cell dose > 8 × 10^8/kg.

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INTRODUCTION

Peripheral blood hematopoietic cell transplant (PBHCT) is the most commonly used allogeneic hematopoietic cell source due to its faster rate of neutrophil engraftment[1-4]. The optimal CD34+ cell dose range to minimize time to neutrophil and platelet recovery without increasing risk of acute graft-versus-host disease (GvHD) is 4-10 × 10^6/kg[5-11]. Some studies have reported a higher CD34+ cell dose yields improved overall survival (OS)[9,12-14], while others have found no significant association[7,10,15-18].

A higher total nucleated cell (TNC) dose has been reported to improve survival after PBHCT[14,16], but analyses of specific T-cell subsets (CD4+, CD8+, natural killer cells) have been inconsistent[17-19]. Factors such as T-cell depletion, conditioning regimen intensity, use of total body irradiation (TBI), and donor age may be interacting with graft cell doses to generate different effects on PBHCT outcomes. In addition, flow cytometric enumeration of cell doses are not standardized (except for CD34+ cell dose) and may also lead to differences in results between studies.

In our retrospective study, we explored whether the collected and infused CD34+, CD3+, CD4+, CD8+, or TNC dose influenced engraftment, OS, progression free survival (PFS), and incidence of acute and chronic GvHD, and whether the results were affected by conditioning regimen intensity or use of TBI.

MATERIALS AND METHODS

Study design

This retrospective cohort study included 247 consecutive adult (≥ 18 years old) patients receiving their first allogeneic PBHCT between January 2001 and September 2012. Patients receiving syngeneic, human leukocyte antigen (HLA)-mismatched, T-cell depleted, or bone marrow transplants were excluded from this analysis. This study was reviewed and approved by the Institutional Review Board of Roswell Park

Cancer Institute.

Conditioning regimens

Four conditioning regimen groups were defined a priori as (1) myeloablative (MA) without TBI (MA-noTBI), (2) myeloablative with TBI (MA + TBI), (3) reduced intensity conditioning (RIC) without TBI (RIC-noTBI) and (4) RIC with TBI (RIC + TBI). These are described in Table 1. Conditioning regimens were assigned based on institutional standards including: (1) patients aged ≥ 60 years: received RIC regimens, (2) patients aged 41-59 years: a RIC regimen was preferred for patients with any of the following criteria: HLA mismatch, Karnofsky Performance Score (KPS) < 70, extensive co-morbidities, recent smoking history, (3) patients aged 19-40 years: a myeloablative regimen was preferred unless the patient had an HLA mismatched donor, KPS < 70, severe co-morbidity, and (4) patients aged ≤ 40 years with acute lymphoid leukemia: TBI regimen.

PBHC mobilization and collection

Donor marrow was stimulated with 10 mg/kg of granulocyte-colony stimulating factor for a minimum of 2 d and continued until white blood cell count was > 8000 × 10^9/L; the attending bone marrow transplant physician provided a target CD34+ cell dose to be collected and, for related donors, approved the final dose collected and the end of apheresis. Most donors underwent apheresis for 1 d.

Cell dose definitions

Apheresis product cell doses were determined using multi-parameter flow cytometry. CD34+ cell counts were obtained using the ISHAGE protocol[20], substituting 7-aminoactinomycin D with TO-PRO. CD3+, CD4+, and CD8+ cell counts used standard methodology[21]. TNC doses were determined by multiplying the white blood cell count (× 10^8/mL) on the day of apheresis by the volume of the product. Each cell count in the final infused product was divided by the actual recipient weight in kilograms measured within 2 d of the start of conditioning regimen to calculate the cell dose infused.

CD34+ cell dose was analyzed using previously published categories of < 4, 4-8, > 8 × 10^6/kg. CD3+, CD4+, and CD8+ cell doses were analyzed above and below the respective median cell doses in the study population. TNC dose was analyzed as above and below the median cell doses and also with various doses ranging from 7-10 × 10^8 cells/kg to determine an optimal TNC dose threshold.

Post-transplant outcome definitions

Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count > 0.5 × 10^9/L. Platelet engraftment was defined as the first date with a platelet count > 20 × 10^9/L after 7 consecutive days with no platelet transfusions. PFS was calculated as the time from PBHC infusion to date of first disease progression post-PBHCT or date of death from any cause; survivors without disease progression were censored at date of last follow-up. OS was calculated as the time from PBHC infusion to date of death from any cause with survivors censored at date of last follow-up. Acute and chronic GvHD were graded using standard definitions[22-23].

Statistical analysis

The statistical methods of this study were reviewed by Yali Zhang from Roswell Park Comprehensive Cancer Center. Correlations between TNC dose and CD3+ dose, CD4+ dose, CD8+ dose, and CD34+ dose were calculated using the Pearson product-moment correlation coefficient. The cumulative incidence of acute and chronic GvHD was analyzed adjusting for the competing risk of disease relapse. Univariable analysis of OS and PFS were analyzed as time-to-event; survival curves were generated using the Kaplan-Meier method and were compared using the log-rank test. Multivariable analyses tested each cell dose while adjusting for significant factors in the univariate analysis, first in all patients and then stratified by the four conditioning regimen groups. Variables included in the multivariable analyses were age (≥/< 40 years), KPS (≥/< 80) at time of transplant, and BMI (≥/< 35 kg/m^2). All analyses were performed using SAS version 9.4.

RESULTS

The cohort consisted of 135 sibling and 112 unrelated donor transplant recipients. Sibling donors were 6/6 HLA-matched at HLA-A, -B, and -DRB1. Unrelated donors were 10/10 HLA-matched at HLA-A, -B, -C, -DRB1, and DQB1 (3 patients were 8/8

Table 1 Conditioning regimen descriptions

Conditioning regimen	Number of patients	Protocol
Myeloablative without TBI (MA-noTBI)	38	Bu 12.8 mg/kg intravenous total dose and Cy 120 mg/kg total dose
Myeloablative with TBI (MA + TBI)	51	Cy 120 mg/kg total dose and TBI 1000-1350 cGy
Reduced intensity conditioning without TBI (RIC-noTBI)	118	Flu 125 mg/m^2 total dose and Mel 140 mg/m^2 total dose
Reduced intensity conditioning with TBI (RIC + TBI)	40	Flu 160 mg/m^2 total dose, Mel 50-75 mg/m^2 total dose, and TBI 400 cGy

Bu: Busulfan; Cy: Cyclophosphamide; Flu: Fludarabine; MA: Myeloablative; Mel: Melphalan; TBI: Total body irradiation.

HLA-matched at HLA-A, -B, -C, -DRB1). Patients who received a MA regimen were significantly younger, had a higher KPS, more commonly had a sibling donor, tacrolimus/methotrexate GvHD prophylaxis regimen, and were treated for different diseases than patients who received a RIC regimen (Table 2).

Peripheral blood apheresis cell doses

Median (range) cell doses for the whole cohort were 264.3 (10.4-1137.5) × 10^6/kg for CD3+, 166.2 (8.3-590.9) × 10^6/kg for CD4+, 103.7 (2.2-590.9) × 10^6/kg for CD8+, 6.5 (0.9-27.6) × 10^6/kg for CD34+, and 8.3 (1.4-21.4) × 10^8/kg for TNC. Graft composition for conditioning subgroups are detailed in Supplementary Table 1.

Neutrophil engraftment

The cumulative incidence of neutrophil engraftment was 99% at day 28 post-PBHCT. Six patients died on days 3, 5, 12, 20, 26, and 36 before neutrophil engraftment. Overall, patients who received a CD34+ cell dose > 4 × 10^6/kg experienced faster neutrophil engraftment (median 13 d *vs* 15 d, $P = 0.05$) as compared to patients who received a CD34+ cell dose < 4 × 10^6/kg. Analysis by conditioning regimen demonstrated significantly faster neutrophil engraftment for an infused CD34+ cell dose > 4 × 10^6/kg in the RIC + TBI group (median 15 d *vs* 18 d, $P = 0.01$) and no statistically significant differences by CD34+ cell dose for the other three conditioning regimen groups (Table 3). There were no significant differences in time to neutrophil engraftment by CD3+, CD4+, CD8+, and TNC dose either overall or in any conditioning subgroup (Supplementary Table 2).

Platelet engraftment

Five patients did not nadir their platelet count below 20000/mm^3 post-PBHCT and were excluded from the analysis of platelet engraftment. The cumulative incidence of platelet engraftment was 89% at day 40 post-PBHCT. One patient failed to engraft platelets and had a second transplant on day 44. Ten patients died before day 40, three patients died between days 41 to 100, and one patient died 6 mo post-PBHCT without platelet engraftment. Overall, patients who received a CD34+ cell dose > 4 × 10^6/kg experienced significantly faster platelet engraftment (median 16 d *vs* 20 d, $P = 0.001$) as compared to patients with a CD34+ cell dose < 4 × 10^6/kg. Analysis by conditioning regimen demonstrated significantly faster platelet engraftment in patients with a CD34+ cell dose > 4 × 10^6/kg for the MA + TBI group (median 20 d *vs* 34 d, $P = 0.001$), and the RIC-noTBI group (median 17 d *vs* 22 d, $P = 0.01$), but no statistically significant differences in time to platelet engraftment by CD34+ cell dose for the other two conditioning regimen groups (Table 3). Platelet engraftment was significantly faster in patients who received a higher CD3+ or CD8+ cell dose in the RIC-noTBI group, but not in any of the other conditioning regimen groups. CD4+ and TNC cell doses were not significant (Supplementary Table 2).

Graft-versus-host disease

In the MA + TBI conditioning regimen group, there was a higher incidence of grade II-IV acute GvHD in patients who received a TNC dose > 8 × 10^8/kg, however there was no difference in grade III-IV acute GvHD (Figure 1A and 1B). Conversely, there was a higher incidence of grade III-IV acute GvHD in patients who received a lower CD34+ cell dose (≤ 8 × 10^6/kg), however there was no difference in grade II-IV acute GvHD by CD34+ cell dose (Figure 1C and 1D). These effects with TNC and CD34+ dose in MA + TBI were not seen in any of the other conditioning regimen groups. There were no statistically significant associations of CD3+, CD4+, or CD8+ dose with acute GvHD overall or in any conditioning regimen subgroup.

There was no significant association of chronic GvHD incidence with a TNC dose of > 8 × 10^8/kg either overall or by conditioning regimen. There was a significantly

Table 2 Patient characteristics for each of four conditioning regimen groups, *n* (%)

	MA-noTBI (*n* = 38)	MA+TBI (*n* = 51)	RIC-noTBI (*n* = 118)	RIC+TBI (*n* = 40)	*P*
Age at BMT					< 0.0001
Median-years (range)	47 (26-58)	36 (19-51)	54 (23-73)	61 (23-71)	
< 40	6 (16)	29 (57)	22 (19)	3 (8)	
≥ 40	32 (84)	22 (43)	96 (81)	37 (93)	
Gender					NS
Female	21 (55)	19 (37)	45 (38)	22 (55)	
Male	17 (45)	32 (63)	73 (62)	18 (45)	
Diagnosis					< 0.0001
ALL	0	20 (39)	7 (6)	6 (15)	
AML	11 (29)	28 (55)	58 (49)	14 (35)	
CML	7 (18)	1 (2)	3 (3)	1 (3)	
MDS/MPD	11 (29)	1 (2)	23 (19)	10 (25)	
NHL/CLL/PLL	8 (21)	1 (2)	25 (21)	8 (20)	
Other	1 (3)	0	2 (2)	1 (3)	
Karnofsky Performance Status					0.03
≤ 70	8 (21)	8 (16)	35 (30)	13 (33)	
80	13 (34)	15 (29)	51 (43)	14 (35)	
≥ 90	17 (45)	28 (55)	32 (27)	13 (33)	
BMT Regimen					< 0.0001
BuCy	36 (95)	0	0	0	
CyTBI	0	47 (92)	0	0	
FluCy	0	0	12 (10)	0	
FluMel	0	0	102 (86)	0	
FluMelTBI	0	0	0	40 (100)	
Other	2 (5)	4 (8)	4 (3)	0	
Sex Match					NS
Matched	24 (63)	30 (59)	70 (59)	27 (68)	
Mismatched	14 (37)	21 (41)	48 (41)	13 (33)	
Donor					< 0.0001
HLA Matched Related	33 (87)	31 (61)	54 (46)	17 (43)	
HLA Matched Unrelated	5 (13)	20 (39)	64 (54)	23 (58)	
GvHD Prophylaxis					< 0.0001
TacMtx	18 (47)	35 (69)	33 (28)	0	
TacMMF	4 (11)	2 (4)	18 (15)	0	
TacmMtxMMF	15 (39)	7 (14)	64 (54)	40 (100)	
Single Agent	1 (3)	7 (14)	3 (3)	0	
CMV Status					NS
R+D+	6 (16)	8 (16)	28 (24)	9 (23)	
R+D-	14 (37)	12 (24)	35 (30)	12 (30)	
R-D+	0	8 (16)	18 (15)	4 (10)	
R-D-	18 (47)	23 (45)	37 (31)	15 (38)	
BMI kg/m^2					NS
Normal (< 30)	15 (39)	25 (49)	34 (29)	13 (33)	
Overweight (25-< 30)	12 (32)	14 (27)	40 (34)	15 (38)	
Obese (≥ 30-< 35)	7 (18)	7 (14)	28 (24)	7 (18)	
Morbid (≥ 35)	4 (11)	5 (10)	16 (14)	5 (13)	

MA: Myeloablative; TBI: Total body irradiation; RIC: Reduced intensity conditioning; ALL: Acute lymphoid leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; MDS: Myelodysplastic syndrome; MPD: Myeloproliferative disorder; NHL: Non-Hodgkin lymphoma; CLL: Chronic lymphocytic leukemia; PLL: Prolymphocytic leukemia; Bu: Busulfan; Cy: Cyclophosphamide; Flu: Fludarabine; Mel: Melphalan; Tac: Tacrolimus; Mtx: Methotrexate; mMt: Micro dose methotrexate; MMF: Mycophenylate mofetil ; R: Recipient; D: Donor; BMI: Body mass index; NS: Not significant ($P > 0.05$).

higher incidence of moderate to severe chronic GvHD in all patients who received a

Table 3 Time to neutrophil and platelet engraftment by CD34+ dose for each conditioning regimen group

	Conditioning group			
	MA-noTBI (*n* = 38)	MA + TBI (*n* = 51)	RIC-noTBI (*n* = 118)	RIC + TBI (*n* = 40)
	Median days to engraftment (range)			
Absolute neutrophil count > 500/mm^3				
CD34+ dose > 4 × 10^6/kg	14 (10-22)	14 (9-28)	14 (3-36)	15 (10-22)
CD34+ dose < 4 × 10^6/kg	14.5 (12-19)	19 (13-28)	15 (10-21)	18 (16-24)
P	NS	NS	NS	0.01
Platelet count > 20000/mm^3				
CD34+ dose > 4 × 10^6/kg	17 (3-171)	20 (13-81)	17 (3-1515)	17 (10-866)
CD34+ dose < 4 × 10^6/kg	19.5 (15-32)	34 (20-228)	22 (14-275)	18 (11-20)
P	NS	0.001	0.01	NS

MA: Myeloablative; TBI: Total body irradiation; RIC: Reduced intensity conditioning; NS: Not significant ($P > 0.05$).

TNC dose > 9 × 10^8/kg ($P = 0.004$) but was not statistically significant in any conditioning regimen subgroup. There was no association of CD34+, CD3+, CD4+, or CD8+ cell dose with chronic GvHD either overall or in any conditioning regimen group.

Overall and progression-free survival

Median follow-up in all patients was 4.8 years (range 1.6-12 years). CD34+, CD3+, CD4+, and CD8+ cell doses were not associated with either OS or PFS in all patients or stratified by conditioning regimen. TNC dose showed no significant difference in OS or PFS when analyzed in all patients (Figure 2A). However, a significant improvement in OS was seen in patients with TBI-based conditioning regimens who received higher (> 8 × 10^8/kg) TNC doses (Figure 2B). Further analysis showed this effect was restricted to the RIC + TBI (Figure 2D) group with no significant difference in the MA + TBI group (Figure 2C). Similar results were found with PFS: a higher (> 8 × 10^8/kg) TNC dose was associated with improved PFS in patients who received TBI-based conditioning regimens, which was driven by the RIC + TBI subgroup.

Multivariate analysis

Based on the univariate analysis, age, KPS, and BMI were included as covariates in the multivariable analysis of each cell dose with OS, and KPS and BMI were included as covariates in the multivariable analysis of each cell dose with PFS (Table 4). Similar to the univariate analysis, TNC dose > 8 × 10^8 cells/kg was associated with improved OS and PFS in patients who received TBI-based conditioning regimens. However, upon further stratification, this finding was statistically significant only in the RIC + TBI conditioning group.

Correlations between cell populations

To investigate potential correlations between cell types, Table 5 summarizes the matrix of Pearson correlations between cell doses. While most cell doses are significantly and positively correlated with the others ($P < 0.001$), most correlation coefficients were low. Pearson $r^2 < 0.5$ means < 50% of the difference between cell doses can be explained by the linear relationship between the two. CD3+ cell dose is correlated with CD4+, CD8+, and TNC cell doses (r^2: 0.5-0.83, Table 4), however CD34+ cell dose is not correlated with any of the other cell types ($r^2 < 0.05$) and is thus an independent cell type.

DISCUSSION

The effect of infused cell dose on post-transplant outcomes is complex. Our single center study is the first to analyze the relationship of conditioning regimen intensity and use of TBI with infused cell doses. A recent study demonstrated that in reduced intensity transplant without TBI, TNC dose was associated with improved PFS and OS similar to our results in reduced intensity conditioning with or without TBI[24]. Martin *et al*[24] reported that higher TNC dose was also associated with decreased relapse and increased incidence of chronic GvHD.

Our results indicate that overall CD34+ cell dose is not associated with OS or PFS in

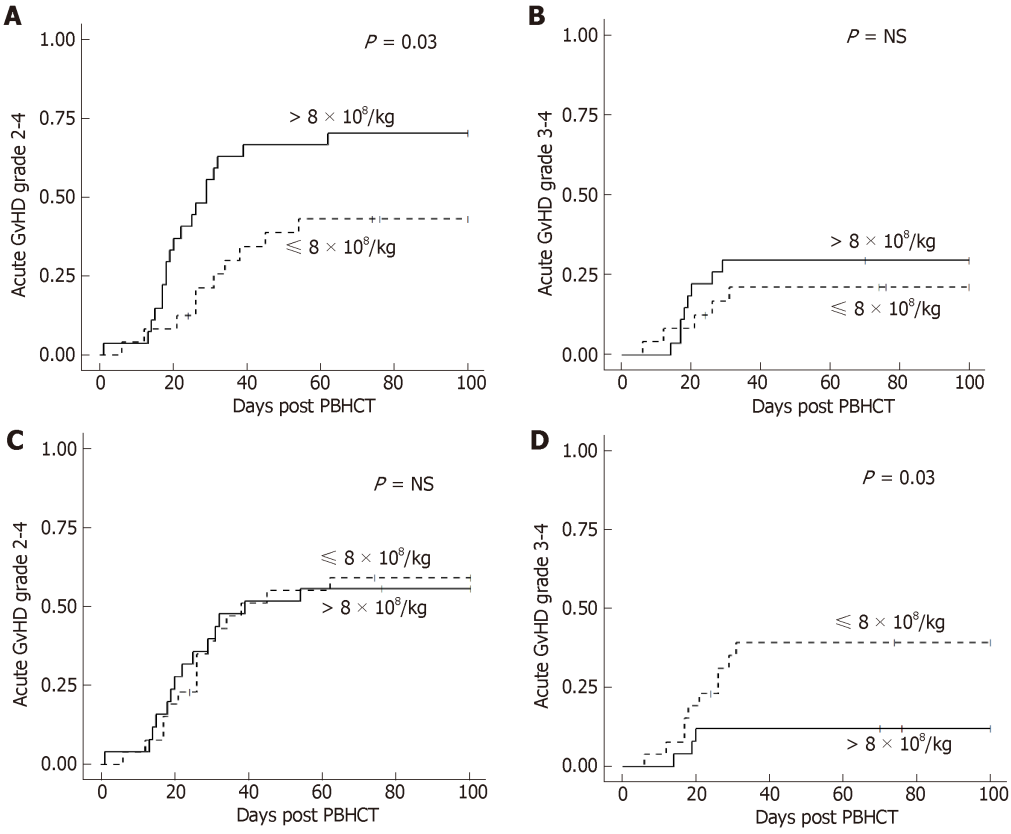

Figure 1 Cumulative incidence of acute GvHD by total nucleated cell dose in myeloablative + total body irradiation conditioning. A: Higher total nucleated cell dose had a higher incidence of acute GvHD grade II-IV; B: Total nucleated cell dose is not associated with acute GvHD grade III-IV; C: CD34+ cell dose is not associated with acute GvHD grade II-IV; D: Lower CD34+ cell dose has a higher incidence of acute GvHD grade III-IV. GvHD: Graft-versus-host disease.

our patient population as observed in other studies[9,11-13,24]. This differs from a study in T-cell depleted transplants after myeloablative TBI conditioning, which reported CD34+ doses between 4-8 × 10^6/kg were optimal for OS, and anything above or below this range resulted in increased mortality[25]. Gorin *et al*[16] demonstrated RIC + TBI patients receiving a TNC dose > 9.1 × 10^8/kg had improved PFS, which was similar to our results.

There was no association in patients with higher CD3+, CD4+, CD8+, or CD34+ doses and OS or GvHD, however recent studies indicated that an optimal CD34+ cell dose can lead to improved survival, less GvHD, and improved engraftment[5-11]. Our results demonstrated an association with TNC dose, which could indicate there is another graft cell subset that may better predict these outcomes. One candidate is the natural killer (NK) cell. A low donor NK cell dose was associated with significantly longer time to engraftment and worse OS[16]. NK cells have also been implicated as an important modulator of GvHD and the graft *vs* leukemia effect[26]. It is possible that increasing the donor NK cell dose could allow for a more robust graft *vs* leukemia effect without increasing risk of GvHD[27]. Focusing on the recipient, previous work demonstrated that host NK cells are relatively radiation-resistant and may decrease the incidence and severity of GvHD[28-30]. Thus, in the setting of low dose TBI, host NK cells could be preserved and mediate a decrease in GvHD while allowing for an improved graft *vs* leukemia effect, translating into an improved PFS/OS.

Further confirmation of our results in a larger, multi-center registry study could be performed. In addition, analysis of other cell populations (*i.e.*, NK cell dose) could explain our findings. Further understanding of the impact of graft composition on post-transplant outcomes, and their potential interactions with conditioning regimens could allow physicians to better target certain cell doses in order to improve post-transplant survival outcomes.

Table 4 Multivariable analysis shows no association of cell doses with overall survival or progression free survival, except for total nucleated cell dose in the reduced intensity conditioning + total body irradiation group

Variable	Overall survival[1]					Progression free survival[2]				
	All patients (*n* = 247)	MA-noTBI (*n* = 38)	MA + TBI (*n* = 51)	RIC-noTBI (*n* = 118)	RIC + TBI (*n* = 40)	All patients (*n* = 247)	MA-noTBI (*n* = 38)	MA + TBI (*n* = 51)	RIC-noTBI (*n* = 118)	RIC + TBI (*n* = 40)
CD3+ cell dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	1.1	1.0	0.5	1.3	0.8	1.0	1.1	0.4	1.4	0.6
95%CI	0.8-1.5	0.4-2.6	0.2-1.1	0.8-2.1	0.3-2.2	0.7-1.4	0.4-2.6	0.2-1.0	0.8-2.2	0.2-1.7
P	NS	NS	NS	NS	NS	NS	NS	0.05	NS	NS
CD4+ cell dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	1.2	1.1	0.6	1.2	2.0	1.1	1.1	0.5	0.3	1.5
95%CI	0.8-1.7	0.4-2.6	0.2-1.3	0.8-1.0	0.7-6.0	0.8-1.6	0.5-2.6	0.2-1.2	0.8-2.1	0.5-4.3
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CD8+ cell dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	1.2	1.5	1.0	1.3	0.5	1.1	1.1	0.9	1.2	0.7
95%CI	0.8-1.6	0.5-4.2	0.4-2.3	0.8-2.1	0.2-1.8	0.8-1.5	0.5-2.8	0.4-2.0	0.8-2.0	0.2-2.0
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
TNC dose										
< Median HR	1	1	1	1	1	1	1	1	1	1
> Median HR	0.8	1.0	0.7	0.9	0.2	0.8	1.1	0.7	1.1	0.2
95%CI	0.6-1.2	0.4-2.4	0.3-1.9	0.5-1.5	0.1-0.8	0.6-1.2	0.4-2.5	0.3-1.6	0.6-1.8	0.1-0.8
P	NS	NS	NS	NS	0.02	NS	NS	NS	NS	0.02
CD34+ cell dose										
< 4 × 10^6/kg HR	1	1	1	1	1	1	1	1	1	1
4-8 × 10^6/kg HR	1.0	0.5	1.3	1.1	0.6	0.8	0.7	1.2	1.0	0.6
95%CI	0.6-1.5	0.2-1.4	0.4-4.4	0.6-1.9	0.1-2.3	0.6-1.4	0.2-2.1	0.4-4.0	0.6-1.8	0.2-2.6
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
> 8 × 10^6/kg HR	1.0	1.3	0.7	1.1	0.5	0.9	1.5	0.6	1.1	0.5
95%CI	0.6-1.5	0.4-4.0	0.2-2.3	0.5-2.0	0.1-2.4	0.6-1.4	0.5-4.6	0.2-2.0	0.6-2.0	0.1-2.6
P	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

[1]Adjusted for age, KPS and BMI;
[2]Adjusted for KPS and BMI. KPS: Karnofsky performance score; BMI: Body mass index; HR: Hazard ratio; 95%CI: 95% confidence interval; MA: Myeloablative; TBI: Total body irradiation; RIC: Reduced intensity conditioning; NS: Not significant ($P > 0.05$).

Table 5 Summary of correlations between cell doses demonstrating low correlation between total nucleated cell dose and CD8+ and CD34+ cell doses and moderate correlation with CD3+ and CD4+ cell doses

	CD3+ dose	CD4+ dose	CD8+ dose	CD34+ dose
CD4+ dose				
R	0.91			
R2	0.83			
P	< 0.0001			
CD8+ dose				
R	0.81	0.55		
R2	0.66	0.30		
P	< 0.0001	< 0.0001		
CD34+ dose				
R	0.20	0.21	0.11	
R2	0.04	0.04	0.01	
P	0.0012	0.0009	NS	
Total nucleated cell dose				
R	0.71	0.64	0.56	0.38
R2	0.50	0.41	0.31	0.14
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001

R: Pearson product moment correlation coefficient, $R > 0.8$ indicates highly correlated cell doses, $R < 0.4$ indicates low correlation between cell doses, R^2: The square of the Pearson correlation, R^2: 0.83 indicates 83% of the variance in one cell dose (*e.g.*, CD3+) is determined by the other (*e.g.*, CD4+); NS: Not significant ($P > 0.05$).

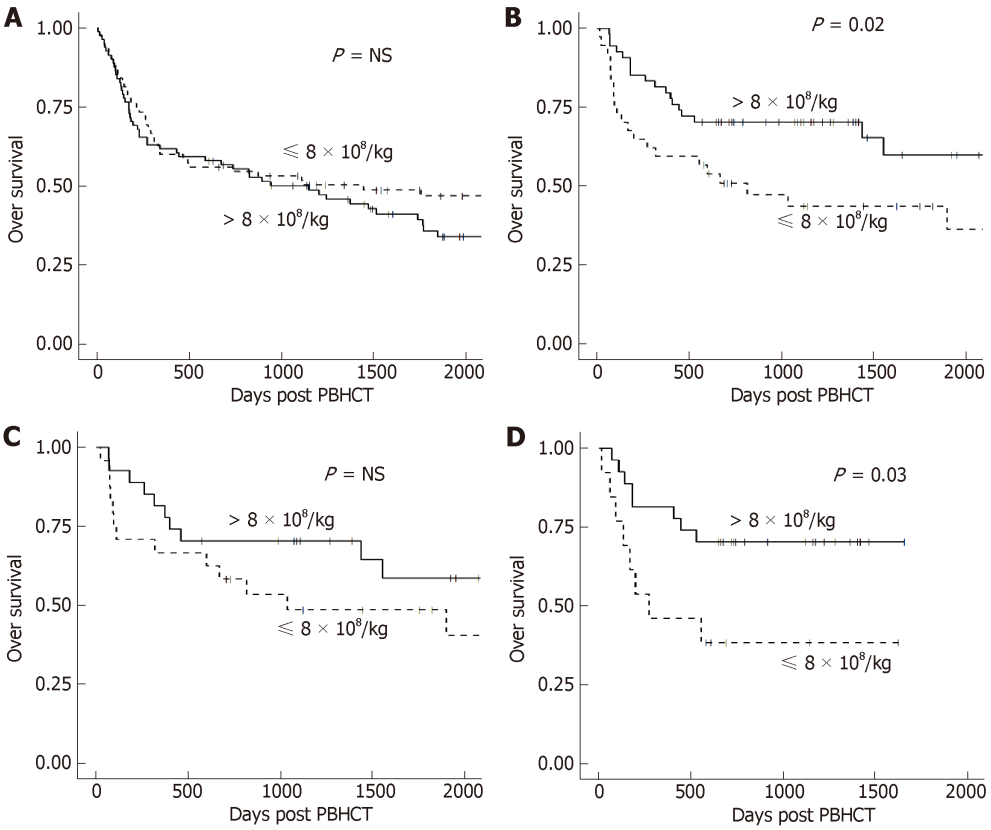

Figure 2 OS by total nucleated cell dose. A: OS was not significantly different in patients conditioned without TBI; B: OS was significantly better with a higher total nucleated cell dose in patients conditioned with TBI; C: OS was not significantly different in patients conditioned with myeloablative TBI; D: OS was significantly better with a higher total nucleated cell dose in patients conditioned with reduced intensity TBI. OS: Overall survival; TBI: Total body irradiation.

ARTICLE HIGHLIGHTS

Research background

Peripheral blood hematopoietic cell transplant (PBHCT) is the most commonly used allogeneic hematopoietic cell source due to its quick rate of neutrophil engraftment. A higher total nucleated cell (TNC) dose has been reported to improve survival after PBHCT, but analyses of specific T-cell subsets have been inconsistent. Factors such as T-cell depletion, conditioning regimen intensity, use of total body irradiation (TBI), and donor age may be interacting with graft cell doses to generate different effects on PBHCT outcomes. In addition, flow cytometric enumeration of cell doses are not standardized and may also lead to differences in results between studies.

Research motivation

While the optimal CD34+ cell dose range to minimize time to neutrophil and platelet recovery without increasing risk of acute graft-versus-host disease has been found to be 4-10 × 10^6/kg, some studies have reported a higher CD34+ cell dose yields improved overall survival while others have found no significant association. Further understanding of the impact of graft composition on post-transplant outcomes, and their potential interactions with conditioning regimens, could allow physicians to better target certain cell doses in order to improve post-transplant survival outcomes.

Research objectives

The objectives of this study were to examine whether the collected and infused CD34+, CD3+, CD4+, CD8+ or TNC dose influenced engraftment, overall survival, progression free survival, and incidence of acute and chronic GvHD, and whether the results were affected by conditioning regimen intensity or use of TBI.

Research methods

Four conditioning regimen groups were defined a priori as (1) myeloablative (MA) without TBI (MA-noTBI), (2) myeloablative with TBI (MA + TBI), (3) Reduced intensity conditioning (RIC) without TBI (RIC-noTBI) and (4) RIC with TBI (RIC + TBI). Correlations between TNC dose and CD3+ dose, CD4+ dose, CD8+ dose, CD34 dose were calculated using the Pearson product-moment correlation coefficient. The cumulative incidence of acute and chronic GvHD was analyzed adjusting for the competing risk of disease relapse. Univariable analysis of OS and progression free survival (PFS) were analyzed as time-to-event; survival curves were generated using the Kaplan-Meier method and were compared using the log-rank test. Multivariable analyses tested each cell dose while adjusting for significant factors in the univariate analysis, first in all patients and then stratified by the four conditioning regimen groups. These analyses allowed us to explore the interaction of conditioning regimen and allogeneic donor apheresis product composition in relation to outcomes after unmanipulated peripheral blood hematopoietic cell transplantation.

Research results

The cohort consisted of 135 sibling and 112 unrelated donor transplant recipients. Overall, patients who received a CD34+ cell dose > 4 × 10^6/kg experienced faster neutrophil engraftment and platelet engraftment as compared to patients who received a CD34+ cell dose < 4 × 10^6/kg. Analysis by conditioning regimen demonstrated significantly faster neutrophil engraftment for an infused CD34+ cell dose > 4 × 10^6/kg in the RIC + TBI group. Overall and progression-free survival was significantly better in patients with a RIC + TBI regimen and TNC dose > 8 × 10^8/kg. Our results indicated that overall CD34+ cell dose is not associated with OS or PFS in our patient population, similar to other studies. We did find an overall and progression-free survival benefit in patients with a RIC + TBI regimen and TNC dose > 8 × 10^8/kg, which could indicate there is another graft cell subset that may better predict these outcomes.

Research conclusions

Our single center study is the first to analyze the relationship of conditioning regimen intensity and use of TBI with infused cell doses. Neutrophil engraftment was significantly faster after reduced intensity TBI based conditioning and > 4 × 10^6 CD34+ cells/kg infused. In addition, overall and progression-free survival were significantly better in patients with a RIC + TBI regimen and TNC dose > 8 × 10^8/kg. Our study suggested that TBI and conditioning intensity may alter the relationship between infused cell doses and outcomes after PBHCT. Our results demonstrated that immune cell subsets may predict improved survival after unmanipulated PBHCT.

Research perspectives

This study suggests that TBI and conditioning intensity may alter the relationship between infused cell doses and outcomes after PBHCT. Further confirmation of our results in a larger, multi-center registry study could be performed. In addition, analysis of other cell populations, such as NK cell dose, could explain our findings. Further understanding of the impact of graft composition on post-transplant outcomes, and their potential interactions with conditioning regimens could allow physicians to better target certain cell doses in order to improve post-transplant survival outcomes.

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ORIGINAL ARTICLE

Observational Study

Hong Kong female's breast cancer awareness measure: Cross-sectional survey

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Abstract

BACKGROUND

In women worldwide, breast cancer is the most common cancer. Breast cancer accounted for 26.6% of all new cancers in females diagnosed in 2015 in Hong Kong.

AIM

To examine women's awareness, perception, knowledge, and screening practice of breast cancer in Hong Kong.

METHODS

We carried out a population-based survey using random telephone interviews to women aged 18 or above using the United Kingdom Cancer Research Breast Cancer Awareness Measure (United Kingdom CAM). The data was analysed using proportions, chi-square test (χ^2-test) and adjusted odds ratios (ORs).

RESULTS

A total of 1000 participants completed the CAM questionnaire from 1,731 responses (response rate = 57.8%) from September to October 2017. One in five and one in four respondents recalled ≥ 3 early warning signs and ≥ 2 risk factors of breast cancer respectively. The majority (62.6%) reported they were not confident that they would notice a change in their breasts. Among the respondents, 16.8% would have regular mammography at least every two years.

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In general, 4 in 10 women had tried practices on preventing breast cancer. Respondents with better result in recalling breast cancer signs and symptoms were more likely to seek immediate medical help when noticed a change in their breasts (χ^2-test $P = 0.038$), and more likely had tried prevention practice (χ^2-test $P < 0.001$). Respondents received higher education (secondary school or above) had higher breast cancer awareness (OR = 2.83, CI: 1.61-4.97), more frequent screening (OR = 2.64, CI: 1.63-4.26) and more had tried prevention practices (OR = 2.80, CI: 1.96-4.02) when compared to those with lower education. Those in age groups 31-45 and 46-60 had higher percentages in performing breast self-exam and mammography when compared to the 18-30 and 61 or above age groups.

CONCLUSION
Population-wide public health initiatives should emphasize on prevention and early detection of breast cancer in women, with targeted strategy for those with low education level and advance in age.

Key words: Breast cancer; Cancer Awareness Measure; Awareness; Screening practice; Behaviour; Attitude

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Core tip: Breast cancer is the top cancer in women worldwide. In this study, we used the United Kingdom Cancer Research Breast Cancer Awareness Measure to assess the awareness, perception, knowledge, and screening practice of this cancer among the female population in Hong Kong, China. In general, women with higher education and in age groups 31-45 and 46-60 had better breast cancer awareness and more frequent screening tests. Respondents recalled more breast cancer signs and symptoms were more likely to seek immediate medical help when noticed a change in their breasts, and more likely had tried prevention practice.

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INTRODUCTION

Breast cancer is the most common cancer in women worldwide[1]. In Hong Kong, breast cancer accounted for 26.6% of all new cancers in females diagnosed in 2016[2]. In the same year, 4,108 new cases of female breast cancer were diagnosed and the crude incidence rate was 103.7 per 100000 in the female population. The age-standardised incidence rate of female breast cancer had an upward trend between 1983 and 2016. In adults aged 20 to 74 years, the most common cancer was breast cancer for females, with a lifetime risk of 1:15[2].

Epidemiological studies reveal that lifestyle factors such as increased body mass index and weight gain in postmenopausal women and drinking play an important role in the development of breast cancer[3]. Therefore, lifestyle modification and early detection through screening is considerably important to reduce mortality and morbidity. Several local surveys had been conducted in the past two decades exploring the knowledge, perception and behaviours related to breast cancer and screening practices[4-8]. These surveys used self-constructed or modified questionnaires.

The emphasis of previous research conducted in Hong Kong focused a lot on knowledge, perception and behavior on screening tests, rather than disease awareness. It was found that 29%-58% of women respondents never heard of mammography (MMG)[4,6]. The percentage of women with regular Breast Self-examination (BSE), Clinical Breast Examination (CBE) and MMG were 29%-33.3%, 37.8%-44.0% and 18.0%-32.7% respectively[4,8].

In addition to screening practices, this survey aims to examine women's awareness about breast cancer. Breast cancer awareness would include awareness of breast

cancer being the most frequent cancer in women, knowledge on signs and symptoms of breast cancer, knowledge on risk factors of breast cancer and primary prevention practices, and knowledge on early detection method which MMG is considered the most effective in shifting of earlier staging and mortality reduction.

There is no territory-wide breast cancer screening in Hong Kong. The Cancer Expert Working Group on Cancer Prevention and Screening formulates local recommendations for breast cancer prevention and screening. The Cancer Expert Working Group recommended women classified with high and moderate risk of breast cancer to have a MMG screening every year and every 2-3 years respectively[9]. It did not recommend breast screening for general female population at average risk[9].

Online search of validated questionnaires on awareness of breast cancer yielded three validated tools: The Cancer Awareness Measure (CAM) of the Cancer Research United Kingdom[10], The Chinese Breast Cancer Screening Beliefs Questionnaire developed (CBCSB) by the University of Sydney in Australia[11], and the Breast Cancer Awareness Scale tool Thai Women (B-CAS) developed by Khon Kaen University in Thailand[12]. The United Kingdom CAM has been validated to Indonesian version[13], and translated to be used in China[14], Egypt[15], Indonesia[16], Oman[17] and United Arab Emirates[18].

Studies have demonstrated that beliefs about causation of breast cancer is associated with age, socioeconomic status, and education level[19,20]. For women who are more knowledgeable about breast cancer risk factors and screening recommendations, they may be more likely to be screened[21]. Early cancer detection and diagnosis saves lives, because treatments are most likely to be effective in people who are diagnosed at an earlier stage. It is of interest to know how women of different age vary in awareness of the risks of breast cancer, so that public health promotion intervention would be customized to distinct subpopulations.

The aim of this study is to examine Hong Kong women's awareness, perception, knowledge, and screening practice of breast cancer.

MATERIALS AND METHODS

Ethical considerations

This research had been approved by the Survey and Behavioural Research Ethics Committee of the Chinese University of Hong Kong. Before each interview, the interviewer would inform the respondent about the nature and purpose of the study and invited her voluntary participation. Interviewee was asked to respond only after informed consent was obtained. No incentive was given.

Survey tool

The United Kingdom Breast-Cancer Awareness Measure (Breast-CAM) Toolkit (version 2) (referred as United Kingdom CAM below)[10] was selected as the survey instrument because it is relatively comprehensive for assessing awareness, knowledge and breast checking behaviour, when compared with other validated questionnaires. It was developed by Cancer Research United Kingdom, King's College London and University College London in 2009. The original United Kingdom CAM collects data in seven domains, which are listed as 1 to 6 in Table 1. Domains 7 and 8 were additional domains not in the original United Kingdom CAM. There were a total of 11 questions and 10 follow-up questions.

Modification of survey tool

The original questions in the United Kingdom CAM asked about the National Health Service (NHS)'s breast cancer screening programme, questions in this domain were modified according to the local context as there is no national breast cancer screening in Hong Kong. The demographic questions were also modified. Items on gender, language spoken at home, marital status, living arrangement, how many years living in United Kingdom, and family or close friends who had cancer were not included. We replaced items "postcode" by "residential district", and "car or van ownership" by "household income". We invited females who speak Chinese as participants so questions on gender and language spoken at home were unnecessary.

Sampling method

The target population was Chinese women in Hong Kong, aged 18 years or above, who were able to speak Chinese. This sampling method constituted a randomly sampled telephone survey of the general population in Hong Kong.

Interviews were carried out by experienced interviewers, between 10:00 and 22:00 on weekdays and other periods, including weekends and public holidays. Upon successful contact with a target household, one qualified member of the household

Table 1 Domains of the survey compared to United Kingdom breast-CAM

	This survey	United Kingdom CAM
Awareness of signs and symptoms of cancer	Q9+Q10	Q1+Q2
Awareness of age-related risk	Q3	Q5
Awareness of risk factors for cancer	Q6+Q7	Q7+Q8
Confidence and behaviour in detecting a breast change	Q1	Q3
Perception and Practice of examination and screening	Q4, Q5	Q6*
Delay in seeking medical help	Q2	Q4
Prevention practices on breast cancer[1]	Q8	NA
Access to information on breast cancer[1]	Q11	NA

[1]Questions that are not in the United Kingdom CAM questionnaire. CAM: Cancer Awareness Measure.

was selected among those family members using the last-birthday random selection method.

Sample size

We calculated the sample size using an online calculator (http://www.raosoft.com-/samplesize.html) with a confidence interval of 99%, margin of error 5% and response distribution of 50% for the population of 3438200 adult females. An additional 40% sample was added as non-response rate and the final sample size of 930 respondents was calculated.

Pilot

A pilot with 20 successfully interviewed respondents was performed from 1 to 6 September 2017. The response rate for pilot was 58%. After the pilot, there was a discussion on the questionnaire design and logistics arrangements. The sequence of the survey questions were rearranged. There was also fine adjustments to the Chinese translation of the questions.

Statistics analysis

Categorical demographic data and variables were compared using the "N-1" chi-square test (χ^2-test) for categorical variable as recommended by Campbell[22] and Richardson[23]. Multiple logistic regression analysis was performed, and demographic data on age, education level, employment status and family income were adjusted. The regression model is a built-in formula in the SPSS software. The participants were divided into groups aged 18 to 30, 31 to 45, 46 to 60 and 61 or above. These age groups were compared by percentages and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The Bonferroni correction was applied to counteract the problem of multiple comparisons. There were 11 questions in the questionnaire and assuming $\alpha = 0.05/11$, then each corrected hypothesis was $\alpha = 0.0045$. All statistical tests were two-tailed and variables were considered significant at a significance level of $P \leq 0.0045$.

RESULTS

The interview was carried out from 8 September to 13 October 2017. The response rate was 57.8%. A total of 1731 numbers were sampled and among these 1000 subjects were successfully interviewed. The interview time ranged from 10 to 12 min.

Demography

The age distribution and socioeconomic indicators of the 1,000 respondents are shown in Table 2. The vast majority of respondents (99.4%) stated that they were ethnically Chinese, 0.1% were from other ethnics and 0.5% refused to answer. Except for 12 respondents, the majority had no previous history of breast cancer.

The groups aged 18 to 30, 31 to 45, 46 to 60, and 61 or above were distinct groups which differed in education level, occupation and monthly household income. In general the younger the age group, the larger the proportion with higher education of secondary school or above ($\chi^2 = 386$, $P < 0.001$) and being employed ($\chi^2 = 492$, $P < 0.001$). The age group 31 to 45 was the highest proportion with monthly income higher than HKD$30,000 (USD$3822).

Respondents aged above 60 constituted nearly half (47.9%) of the total and 70

Table 2 Demographic data of all participants

	Total(*n* = 1000)	Percentage (%)
Age (median age group)	56-60	-
18 - 30	67	6.7
31-45	179	17.9
46-60	272	27.2
61 or above	479	47.9
Education		
Primary school or below	379	37.9
Secondary school	472	47.2
Diploma or above	119	11.9
Occupation		
Housewife	354	35.4
Employed	241	24.1
Retired or unemployed	361	36.1
Monthly household income		
HKD$10000 or below	231	23.1
HKD$10001-20000	164	16.4
HKD$20001-30000	108	10.8
HKD$30001 or above	190	19.0
District		
Reside in 5 districts with lowest domestic household monthly income[1]	281	28.1

[1]Sham Shui Po, Kwun Tong, Kwai Tsing, North and Wong Tai Sin District.

constituted a quarter (25.8%). When comparing with the mid-2017 census female population by age group which was 23.5% in the population, there was double in proportion of female respondents > 60 or above in this survey[24]. Respondents below 35 year-old were half of the female population distribution, it was 10.5% compared to 21.0% in the population. The highest proportion (35.5%) of the respondents was retirees, which cohered with the age distribution that nearly half of them were aged 60 or above. Around one-third (35.4%) were full-time housewives.

More than one quarter (28.1%) of the respondents resided in five districts with the lowest domestic household monthly income among all 18 districts in Hong Kong. Half (50.3%) of all respondents had a monthly household income less than HKD$30000. The median monthly household income in Hong Kong was HK$24900 in 2016[25]. The low median domestic household income of the respondents could be explained by the high proportion of retirees (35.5%) and above age 60 (47.9%) among our respondents.

Awareness of signs and symptoms

A paired question on awareness of signs and symptoms of breast cancer was asked. The respondents was first asked an open question aiming to find out how many early warning signs the respondent could think of without specific prompting. Afterwards respondents were asked about 11 different symptoms. All may be early warning signs of breast cancer, although most may also indicate other less serious conditions (Table 3).

When asked openly, 80.5% of the respondents recalled at least one symptom and half (49.4%) listed two or more. The majority (75%) of respondents can tell "a lump or thickening in breast" could be a sign of breast cancer. Around one-fifth of respondents named "lump or thickening under armpit" (22.7%), "pain in one of breasts or armpit" (21.2%), or "discharge or bleeding from nipple" (20.5%) as other symptoms.

When asked about different symptoms, the majority of respondents chose "yes" (correct answer) when asked the above four signs and symptoms of breast cancer. This cohered with the results in the open question. Comparatively many respondents did not know "nipple rash" (48.4% answered correctly), "redness of breast skin" (41.2%), "change in the position of nipple" (35.6%), and "changes in the size of breast or nipple" (34.1%) were possible signs of breast cancer.

Those with higher education and in the 31 to 45 age group recalled most signs and symptoms of breast cancer without prompting when compared to those with lower

Table 3 Breast cancer awareness

	Awareness of signs and symptoms of breast cancer[1]		Awareness of age-related lifetime risk		Awareness of risk factor for breast cancer[2]	
	Yes %	OR_{adj} (95%CI)	Yes %	OR_{adj} (95%CI)	Yes %	OR_{adj} (95%CI)
Total (n = 1000)	20.3	--	26.5	--	25.7	--
Age						
18 - 30 (n = 67)	10.4	0.46 (0.19-1.11)	15.2	0.45 (0.21-0.98)	38.8	2.18 (1.15-4.14)
31 - 45 (n = 179)	40.8	2.83 (1.61-4.97)	19.8	0.66 (0.38-1.15)	41.3	2.38 (1.39-4.08)
46 - 60 (n = 272)	23.9	1.44 (0.85-2.41)	30.9	1.20 (0.77-1.89)	34.6	2.10 (1.30-3.37)
61 or above (n = 479)	11.9	1.00	28.1	1.00	25.8	1.00
Education						
Secondary school or above (n = 262)	27.9	2.80 (1.77-4.44)	24.8	0.91 (0.60-1.32)	34.5	1.76 (1.16-2.66)
Below secondary school (n = 641)	9.3	1.00	29.4	1.00	13.0	1.00

[1]Can recall three or more early warning signs of breast cancer;
[2]Can recall two or more risk factors for breast cancer.

education (OR = 2.80, 1.77-4.44) and other age groups (OR = 2.83, 1.61-4.97). Besides, these groups recognised more signs and symptoms when they were mentioned. There was no significant difference in odds ratio when comparing employment status, district one resided and family income.

Awareness of risk factors

Again, we asked risk factors for breast cancer in paired questions. First, an open question and afterwards about 10 different risk factors that were risk factors of breast cancer, in which all were the correct answers (Table 3).

When asked openly, 58.5% of the respondents could name at least one risk factor and 25.7% could list two. "Having a close relative with breast cancer" was the most commonly listed risk factor of breast cancer and 45.3% of respondents named this without prompting. The listing of other risk factors remained low, and 4.8% of respondents answered "smoking".

When prompt, the three answers with highest number of respondents who answered "strongly agree" were: "having a close relative with breast cancer" (48.1%); "a past history of breast cancer" (23.2%); and "feeling stressful (> 50% of time)" (18.7%). These three risk factors were "agreed" or "strongly agreed" by > 70% of the respondents as factors that increase the chance of breast cancer.

Those in the 31 to 45 and 46 to 60 age groups recalled most risk factors without prompting when compared to those in the 61 or above age groups (OR = 2.38, 1.39-4.08) and (OR = 2.10, 1.30-3.37). Those in the 18 to 30 age group and with higher education also performed better in recalling risk factors, but the result was not statistically significant using $P < 0.0045$. Again, there was no significant difference in odds ratio when comparing employment status, district one resided and family income.

Awareness of age-related risk

On women's awareness of how age relates to breast cancer, the majority (76.1%) got a wrong answer. The suggested correct answer to the question "In the next year, who is most likely to develop breast cancer?" is "a 70 year old woman". As the median age of breast cancer patients was 56 in Hong Kong, the answer "a 50 year old woman" was also considered correct. The majority of all respondents (56.4%) answered "A woman of any age". In fact, the risk of breast cancer usually increases with increasing age. Most women who get breast cancer are past their menopause (Table 3).

Perception and practice of regular breast examination and MMG screening

The original United Kingdom CAM in this section is about the NHS breast cancer screening programme. Therefore questions in this survey were modified to those related to breast examination and MMG screening. There was 78.8% of respondents opined that regular breast examination was required by those even without a family history. The highest percentage (22.6%) of respondents suggested that age group 30 to 34 would be a good age to start regular breast exams (Table 4).

A large proportion of female (42%) rarely or never perform BSE, 10% did it once every 6 months, 21% once every month, and 27% at least once a week. A total of 48%

Table 4 Breast cancer screening and perception

	Monthly or more frequent breast self-exam		Have mammography at least once every 2 yr		Agree that breast exam is needed for those without family history	
	Yes %	OR_{adj} (95%CI)	Yes %	OR_{adj} (95%CI)	Yes %	OR_{adj} (95%CI)
Total (n=1000)	48.0	--	16.8	--	78.5	--
Age						
18 - 30 (n = 67)	35.8	0.36 (0.20-0.67)	6.0	0.22 (0.07-0.65)	94.0	2.96 (1.00-8.82)
31 - 45 (n = 179)	58.7	0.86 (0.53-1.39)	23.5	1.02 (0.55-1.89)	93.9	2.20 (1.04-4.65)
46 – 60 (n = 272)	60.7	1.19 (0.80-1.79)	24.6	1.35 (0.79-2.31)	85.3	1.05 (0.63-1.73)
61 or above (n = 479)	38.6	1.00	11.3	1.00	67.2	1.00
Education						
Secondary school or above (n = 262)	58.2	2.38 (1.71-3.31)	22.5	2.64 (1.63-4.26)	88.5	2.17 (1.47-3.12)
Below secondary school (n = 641)	33.3	1.00	8.3	1.00	64.8	1.00

All three questions in this table are not in the United Kingdom CAM questionnaire. CAM: Cancer awareness measure.

of the respondents reported BSE at least once a month. There was no difference in BSE compared by age, district, employment status and family income, but those with higher education had more monthly or frequent BSE (OR = 2.39, 1.71-3.31) (Table 4).

MMG examination was known by 73.5% of the respondents, while 26.5% had never heard of it before. In all respondents, 16.8% would have regular MMG at least every two years, while 61.8% of respondents never had an MMG. There was a 2.7 times by proportion of those with higher education had 2-yearly or more frequent MMG than those with lower education (OR = 2.64, CI: 1.63-4.26).

There was no association of the frequency of BSE with the residing districts (χ^2-test $P < 0.686$). However, there was a statistical significant association of having a less frequent MMG with residing in low-income districts. The proportion of women having a two yearly or more frequent MMG living in lower-income districts was 4.7%, compared to 23.4% in higher-income districts (χ^2-test $P < 0.0001$).

We asked the 61.8% of the respondents who never had an MMG for their reasons. "I am healthy, do not see the need" (31.3%) and "Have not heard of MMG" (18.9%) were the most common reasons, constituting a half of this group of respondents. "Expensive", "do not have time", "doctor does not see the need" and "I am still young" were some of the other reasons. "To prevent getting breast cancer" (16.9%), "I am not young, see the need" (16.3%) and "It is included in my body checkup" (11.3%) were the top reasons for going for an MMG in this survey.

In all, 62.6% of respondents reported that they were "not at all confident" or "not very confident" that they would notice a change in their breasts, whereas only 37.4% expressed they were fairly or very confident.

Seeking medical help

There is no right or wrong answer to this question. The majority (78.4%) would go to consult a doctor immediately about a change they noticed in their breasts. However, the remaining (19.2%) expressed "do not know" if they would consult a doctor or not. Multiple choices were given to those who answered "do not know". Around half (49.5%) said they would visit a doctor within one week, while nearly half (46.7%) still expressed they were uncertain how soon they would visit a doctor.

Respondents with better result in recalling breast cancer signs and symptoms were more likely to seek immediate medical help when noticed a change in their breasts (χ^2-test $P = 0.038$).

Prevention practices

The survey asked an open question aiming to find out what the respondent did to prevent breast cancer without specific prompting. A lot of people (44.2%) did nothing to prevent breast cancer. Respondents with better result in recalling breast cancer signs and symptoms were more likely had tried prevention practice(s) (χ^2-test $P < 0.001$). Thirty-one percent (31.2%) stated they had a "regular breast exam" to prevent breast cancer. In fact, breast exam is secondary prevention for early detection of symptom, but in itself does not reduce the chance of having breast cancer. Those with higher education level were more proactive in prevention practices, and more had tried prevention practices (OR = 2.80, 1.96-4.02).

Access to information

The last 4 questions were related to access to information on breast cancer. These are additional questions which were not in the United Kingdom CAM. They were asked because we wanted to know what the preferred ways of receiving breast cancer information were.

Half of the respondents (49.2%) said there was sufficient information on breast cancer, but the other half answered "no" (28.0%) or "don't know" (22.8%). The younger age groups of 18 to 30 and 31 to 45 had a lower proportion opined that there was sufficient information on breast cancer, when compared to the 61 or above age group (OR 0.17, 0.09-0.32; OR 0.42, 0.26-0.69).

When asked about where the respondents obtained information related to breast health, cancer and problems, many of them said they got their information from media (71.3%), general practitioners (31.3%), internet (23.4%), friends (18.1%), gynaecologist (17.3%), and others. When asked about respondents' preferred way of receiving information on breast cancer related information, TV (79.9%) and internet (25.4%) were the chosen ways of receiving information by the majority.

Lastly we asked how the respondents would like to receive reminder messages for breast check-ups. Telephone or SMS (70.8%) were the most popular methods; followed by letter invitation (22.7%) and email with educational information (9.2%).

DISCUSSION

This survey is a territory-wide representative sample of 1000 Chinese women aged above 18 years. In reviewing the literature we found no other study using a validated measure to assess cancer awareness in a population based sample in Hong Kong.

Breast cancer awareness

The recall rates of breast cancer signs/symptoms and risk factors was unsatisfactory. The recall rate of cancer warning signs using an open question was < 25% for all signs and symptoms, except "lump or thickening in breast", which was mentioned by 75.0% of respondents. A 58.5% of the respondents could name at least one risk factor and 25.7% could list two. The recall of most other risk factors remained low, and each were recalled by < 7% of respondents. This would be contributed by a large number of respondents aged above 60 constituted nearly half (47.9%) of the total and 70 constituted a quarter (25.8%). In addition, one-third (37.9%) of the respondents had education level Primary school or below. The recognition scores were higher than the recall scores for both the cancer warning signs/symptoms and risk factors. It is difficult to determine which better captures the concept, but both are good indicators of cancer awareness. Those can recall three or more signs and symptoms were more likely to seek immediate medical help when noticed a change in their breasts (χ^2-test $P = 0.038$), and had tried prevention practice (χ^2-test $P < 0.001$). This suggest awareness of breast cancer may predict better behaviour in terms of disease prevention and early detection.

It was perceived by more than one-fifth of the respondents that a lot of women developed breast cancer in age around 50s. In fact, the older the age, the higher the risk in incidence and death from breast cancer. The pattern of age-specific incidence rate and the age-specific death rate due to female breast cancer increased with age. It is noteworthy that the incidence rate for age group 45 to 54 has a marked increasing trend from 1983 to 2000 from 77.5 to 123.9 per 100000[26]. In the Hong Kong Breast Cancer Registry, 66% of breast cancer patients were aged between 40 and 59[27]. The median age of breast cancer patients was 56 in Hong Kong, which is younger when compared with 62 in the US and 61 in Australia, but similar to 53 in Singapore[27-30].

It is recognised that the demography of the young and old respondents were different. The less than 61 year-old age groups had higher education level, more proportion being employed and with higher monthly household income than the 61 year-old or above age group. The odds ratios of the two groups in many variables were statistically significant even after adjustment of demography. These findings are coherent with previous evidence that women in higher socio-economic status and education were better knowledged on cancer risks and more likely to have breast screening[31]. In fact, these finding may also reflect memory loss or cognitive impairments in the older age group.

Perception and Practice of breast examination and screening

Evidence has showed that BSE screening has no clear benefit on mortality or detection of carcinoma in situ and may increase unnecessary surgical biopsies[32,33]. Breast cancers that are detected clinically or by BSE are typically of more advanced stage. A

Shanghai study on Chinese participants conducted earlier showed BSE has no benefit in mortality reduction after follow up of 5 years[34]. Therefore BSE is not recommended as an early detection tool.

However, BSE is part of breast cancer awareness and there are a lot of women detect breast cancer by BSE. As shown in the annual report of the Hong Kong Breast Cancer Foundation, the primary method of first breast cancer detection in the patient cohort was self-detection by chance (83.3%)[35]. The Department of Health in Hong Kong does not provide any firm recommendations on the frequency with which women should check their breasts[36]. The percentage of monthly or more frequent BSE among women in Hong Kong (48%) was higher when compared with ethnic groups South Asian (12.6%), Black (17.8%) and White (27.6%) in the 2010 United Kingdom Breast-CAM survey in London[37]. The reason why in United Kingdom women conducted less frequent BSE may because they have population-based screening. Women are invited and reminded to national screening by MMG.

The proportion of women having a two yearly or more frequent MMG living in high-income districts was 5 times higher when compared to low-income districts (χ^2-test $P < 0.0001$). Unlike United Kingdom, United States and Australia, Hong Kong has no population-based breast cancer MMG screening. This leads to a self-reliance on BSE to detect breast cancer early if finance is a barrier. Knowledge and screening practice is obviously skewed towards women from high-income districts. This echoes with a previous local study[38] that higher socioeconomic status and a higher educational level were associated with an earlier stage of the disease at the time of diagnosis, as MMG screening every 2 to 3 years were significantly associated with the earlier detection of breast cancer.

When compared to United Kingdom Breast-CAM done from 2009 to 2010[39], there were a much higher percentage of women recognised five or more non-lump symptoms of breast cancer in our surveyed population (79.1% *vs* 17.7%). Women in the United Kingdom survey were more confident to notice a change in breast (51.8% *vs* 37.4%) and fewer people reported breast checking at least once a month (22.6% *vs* 48%) when compared to this survey respondents.

Strengths and weaknesses of the study

We used a validated measure of cancer awareness, and adjusted our analyses for potential confounders with a reasonable large sample size. The response rate was 57.8%, which is acceptable. It is important to note that, while the sample was randomly sampled, there is an element of self-selection bias inherent in this voluntary survey. Besides, it can be assumed that the sample was biased towards those with interest in breast cancer. However, the sample size is sufficiently large to represent Hong Kong Chinese women who are interested in this topic. There were few missing data, and therefore responses are representative of the survey respondents.

There is a higher proportion of respondents at age > 60 or above and fewer in those age < 35 when compared to census population strata. As cancer is strongly related to increasing age, and many respondents were at relatively high risk due to their older age, the results would be applicable to the older and most at-risk group.

There are surveys using United Kingdom CAM reported socio-demographic differences in cancer symptom awareness and barriers to symptomatic presentation[31,39]. Further study can be performed to examine breast cancer awareness and disease risk perception in association with socioeconomic status. Besides, other studies to explore whether there are differences in cancer awareness in places with and without national screening programme would provide insights to the impact of territory-wide initiatives.

In conclusion, Women with higher education were better knowledged on breast cancer warning signs, more likely had breast screening and tried cancer prevention practices. The awareness of breast cancer was lower in age group 61 or above than the younger age groups. These results indicated a government-led public health initiatives should raise awareness on prevention and early detection of breast cancer in women, with targeted promotion strategy for those with low education level and advance in age.

ARTICLE HIGHLIGHTS

Research background

Breast cancer is the most common cancer in women worldwide. In Hong Kong, breast cancer accounted for 26.6% of all new cancers in females diagnosed in 2015. The median age of breast cancer patients was 51.0 in Hong Kong, which is younger, when compared with 62 in the United States and 61 in Australia.

Research motivation
The emphasis of previous research conducted in Hong Kong focused mainly on knowledge, perception and behavior on screening tests, rather than disease awareness. In reviewing the literature we found no other study using a validated measure to assess cancer awareness in a population based sample in Hong Kong. In addition to screening practices, this survey aims to examine women's awareness and knowledge about breast cancer. Online search of validated questionnaires on awareness of breast cancer yielded three validated tools. The Cancer Awareness Measure (CAM) of the Cancer Research United Kingdom was chosen.

Research objectives
The aim of this study is to examine Hong Kong women's awareness, perception, knowledge, and screening practice of breast cancer. Early cancer detection and diagnosis saves lives, because treatments are most likely to be effective in people who are diagnosed at an earlier stage. It is of interest to know how women of different age vary in awareness of the risks of breast cancer, so that public health promotion intervention would be customized to distinct subpopulations.

Research methods
We carried out a population-based cross-sectional survey using random telephone interviews to women aged 18 or above. The original United Kingdom CAM was modified according to the local context as there is no national breast cancer screening in Hong Kong. The data was analysed using proportions, chi-square test and adjusted odds ratios (ORs).

Research results
A total of 1000 participants completed the CAM questionnaire from 1731 responses (response rate = 57.8%) from September to October 2017. Respondents received higher education (secondary school or above) had better breast cancer awareness, more frequent screening and more had tried prevention practices when compared to those with lower education. Those in age groups 31-45 and 46-60 had higher percentages in performing breast self-exam and mammography when compared to the 18 - 30 and 61 or above age groups.

Research conclusions
The survey results indicated a government-led public health initiatives should raise awareness on prevention and early detection of breast cancer in women, with targeted promotion strategy for those with low education level and advance in age.

Research perspectives
Further study can be performed to examine breast cancer awareness and disease risk perception in association with socioeconomic status. Besides, other studies to explore whether there are differences in cancer awareness in places with and without national screening programme would provide insights to the impact of territory-wide initiatives.

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