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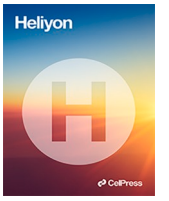

Review article

Advanced esophageal cancer with bone metastases: Prognostic biomarkers and palliative treatment

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ABSTRACT

Esophageal cancer (EC) is a common and devastating tumor of the upper digestive tract. Unfortunately, by the time any symptoms have manifested, the disease has often progressed to an advanced stage and is accompanied by macro- and micrometastases, including in the bones. The treatment of esophageal cancer with bone metastases remains clinically challenging, given the poor prognosis associated with this condition. Effective prognostic biomarkers can help medical staff choose the appropriate operation and treatment plan, that is for most beneficial for making patients. Current treatments for esophageal cancer with bone metastases include pain-relieving drugs, surgical therapy, radiotherapy (RT), chemotherapy (CT, including molecular-targeted drug therapy), endocrine therapy (ET), bisphosphonates (BPs) and interventional therapy. Of these robust measures, radiotherapy has emerged as a particularly promising therapy for bone metastases from esophageal cancer. Substantial progress has been made in radiation therapy techniques since the discovery of X-rays by Roentgen in 1895. In its palliative capacity, the key goals of radiotherapy are to relieve the patients' bone pain and debilitate effects, including relieving spinal cord compression, correcting the spinal deformity and restoring spinal stability. However, it is worth mentioning that RT for esophageal cancer has various side effects. Currently, the available studies focused exclusively on radiotherapy for ECBM are too small to draw any definitive conclusions, and each of these studies has significant limitations. In this review, in addition to the epidemiology described at the beginning, we will explore the current prognostic biomarkers and radiotherapy for esophageal cancer, with a particular focus on those with bone metastases.

1. Epidemiology of esophageal cancer with bone metastases

According to a recent analysis by Globocan 2020, esophageal cancer is an aggressive malignant tumor accounting for over 604,000 new cases and 544,000 deaths per year globally [1]. Histopathologically, esophageal cancer comprises two phenotypes: esophageal squamous cell cancer (ESCC), which accounts for >90 % of all cases, and esophageal adenocarcinoma (EAC) [2,3]. In terms of

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Table 1
Recent large-population-based studies from the SEER database.

Year of publication	Patient selection	The main research focus	Research outcomes	Risk factors	Poor prognostic factors	Limitations of research	Reference
2019	Patients with initial bone metastasis among EC patients (n = 2075/25,955) between 2010 and 2016	Risk and prognostic factors of ECBM	–	Age younger than 67 years, male sex, T4 stage grade III, N1-3, histological subtype of EAC or others, and metastasis to liver, lung, and brain	Unmarried	Unavailable information in the database including region, environment, genetic characteristics, a full description of cancer development, detail types of BM, detailed treatment and clinical course	[11]
2019	EC Patients with metastatic diseases between 2010 and 2014 (n = 5912)	The impact of RT on the OS of metastatic EC	RT could improve the survival of patients with metastatic EC	–	Metastatic disease to the brain, bone, lung and liver, age greater than 80 years, uninsured status, male sex, poor differentiation, and non-chemotherapy treatment	Unavailable information in the database including both primary and metastatic sites, dose of radiation therapy, comorbidities, performance status, the impact of chemotherapy regimens and the combination modalities of radiation and chemotherapy	[15]
2021	Metastatic MEC/FEC patients between 2010 and 2015 (n = 3454/615)	Differences in risk and prognostic factors between metastatic MEC and FEC patients	MEC patients with distant organ metastasis were more and less likely than their FEC counterparts to have bone metastasis only (14.0 % vs 10.9 %)	MEC patients with distant organ metastasis (vs FEC): Age younger than 60 years, white race, unmarried, primary lesion site in the lower 1/3 of the esophagus and overlapping esophagus segments, and non-chemotherapy treatment	Liver, lung, and bone metastases separately, and simultaneous liver and lung metastases	Unavailable information in the database including uncommon metastatic sites and asynchronous metastases, uncertain factors associated with the differences in metastatic patterns between men and women, and limited sample sources	[16]
2021	Elderly EAC patients with DM in stage IVB between 2010 and 2015 (n = 855)	DM patterns and prognosis of elderly EAC patients in stage IVB	The most common site of metastasis is liver, followed by lung, bone, and brain, and patients with bone-only metastasis have the worst OS and CSS among single-organ metastasis populations	–	No any treatment	Unavailable information in the database including many contributing factors and detailed clinical course, limited sample sources, small sample size of brain metastasis, no distinction between different patterns of multiple metastatic sites, uninvolved immunotherapy and targeted therapy	[17]
2021	Elderly ESCC patients with DM in stage IVB between 2010 and 2016 (n = 537)	DM patterns and prognosis of elderly ESCC patients in stage IVB	The most common site of metastasis is lung, followed by liver, bone and brain		No any treatment	Unavailable information in the database including detailed chemotherapy regimens, uncommon metastatic sites, limited sample sources, no distinction between different patterns of multiple	[18]

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Table 1 (*continued*)

Year of publication	Patient selection	The main research focus	Research outcomes	Risk factors	Poor prognostic factors	Limitations of research	Reference
						metastatic sites, uninvolved immunotherapy and targeted therapy	
2022	Patients with bone metastasis among EC patients (n = 462/8916) between 2010 and 2016	Risk and prognostic factors of ECBM	–	Age younger than 65 years, male sex, T1 stage, advanced N stage and non-bone organ metastases	ESCC, T1 and T4 stage, non-bone organ metastases, and no any treatment	Limited sample sources, underestimated true rate of ECBM, follow-up bias, and unavailable information about detailed clinical course	[19]

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; EC, esophageal cancer; ECBM, esophageal cancer with bone metastases; EAC, esophageal adenocarcinoma; BM, bone metastases; RT, radiotherapy; OS, overall survival; MEC, male esophageal cancer; FEC, female esophageal cancer; DM, distant metastasis; CSS, cancer-specific survival; ESCC, esophageal squamous cell carcinoma; CT, chemotherapy.

recurrence patterns, survival outcomes and prognostic factors, ESCC and EAC are significantly different [4]. The incidence and etiology of the two pathological types of esophageal cancer exhibit marked differences among WHO regions. In regions such as Asia and Sub-Saharan Africa, eating habits (e.g., nitrosamines, very hot food, betel, etc) are the major risk factors for ESCC [1, 5, 6]. Meanwhile, tobacco use and alcohol consumption are the most prevalent factors for esophageal cancer in well-developed Western countries; among these factors, EAC predominates [7]. Patients with EAC often suffer from obesity, gastroesophageal reflux disease, and Barrett's esophagus. In recent years, with improvements in living standards, food safety and living habits of human beings, the incidence rate of esophageal cancer has been decreasing. Of particular concern is a sex difference, which is another pronounced feature of esophageal cancer. There is a male predominance with a mean male-to-female ratio of 3:1 for esophageal squamous cell cancer and 6:1 for esophageal adenocarcinoma [8].

Esophageal cancer remains a highly lethal soft tumor that is highly metastatic [8,9]. Once any symptoms have manifested, the disease is often already at an advanced stage and accompanied by macro- and micrometastases [10]. Although the overall incidence of skeletal metastases from primary tumors of the gastrointestinal tract was not high, except for lung and liver, bone remains one of the most common sites of distant metastasis for EC [11, 12]. Metastatic bone tumors originating from ESCC are characterized by osteolytic

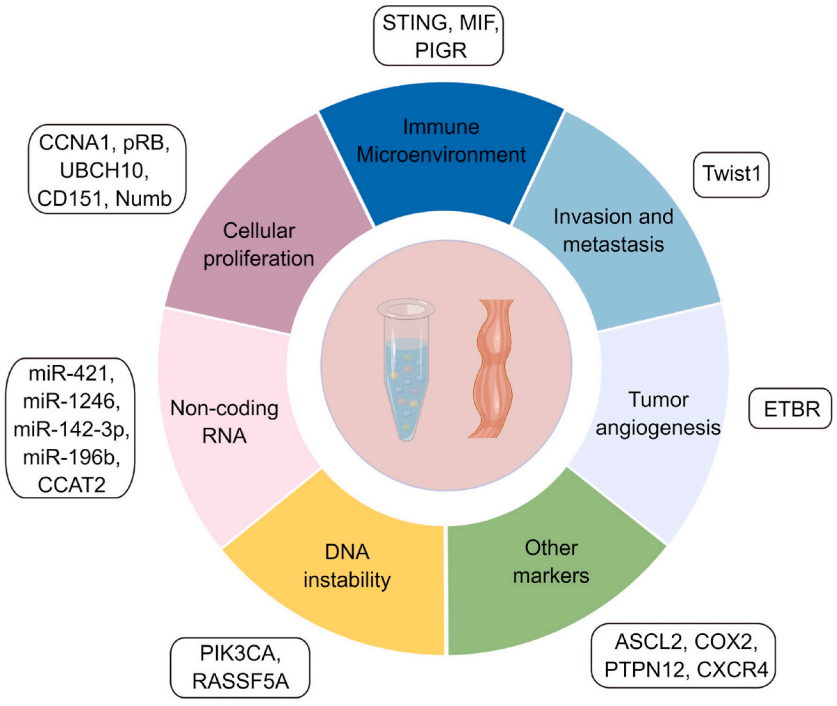

Fig. 1. Different types of prognostic molecular markers in esophageal cancer. As molecular biology research on esophageal cancer advances, more and more different biomarkers have been found and verified in the body fluid or body tissues.

Table 2
Characteristics of prognostic biomarkers for esophageal cancer.

Biomarker	Molecular mechanism	Tissue type	Previously received chemotherapy or radiotherapy	Measurement	Validation
CCNA1	Regulating the cell-cycle	ESCC	No	mRNA single-channel expression profile chip experiment, RT-qPCR, IHC	–
pRB	Regulating the cell-cycle	EAC, ESCC	No	LOH, IHC, PCR	–
UBCH10	Regulating the cell-cycle	ESCC	Yes	IHC	–
PIK3CA	Involving in the PI3K/Akt signal pathway	ESCC	No	IHC	–
CD151/ TSPAN24	Regulating cell adhesion, migration and invasion	EAC	Yes	IHC	Externally validated
Numb	Determining cell fate during cell division	ESCC	Yes	IHC, WB	Molecular Experimental Validation
Twist1	Involving in epithelial-mesenchymal transition	ESCC	Yes	IHC	Molecular Experimental Validation
ETBR	Promoting angiogenesis	ESCC	No	RT-qPCR, IHC	Molecular Experimental Validation
STING	Activating type I interferon in response to invading DNA viruses or bacteria	ESCC	No	IHC	–
MIF	Involving in tumorigenesis, tumor metastasis, tumor anginogenesis and tumor inflammatory	ESCC	No	IHC	–
PIGR	Embarking IgA onto mucosal surfaces	EC	Yes	IHC	–
ASCL2	Involving in the Wnt signal pathway	EAC	NO	IHC	Bioinformatic analysis
D-mannose	Involving in circulatory metabolism	EAC	Yes	Metabolite profiling	–
COX-2	Promoting angiogenesis	EAC	Yes	Automated immunostaining	–
PTPN12	Regulating the equilibrium of tyrosine phosphorylation	ESCC	NO	IHC, WB	–

Abbreviations: CCNA1, dysregulation of cyclin A1; RT-qPCR, reverse transcription quantitative polymerase chain reaction; IHC, immunohistochemistry; pRB, protein retinoblastoma; LOH, loss of heterozygosity; UBCH10, ubiquitin-conjugating enzyme H10; WB, western blots; ETBR, endothelin receptor type B; STING, stimulator of interferon genes; MIF, macrophage migration inhibitory factor; PIGR, polymeric immunoglobulin receptor; ASCL2, achaete scute-like 2; PTPN12, tyrosine-protein phosphatase nonreceptor type 12.

and osteoplastic bone metastases [13]. Typically, bone metastases from esophageal carcinoma are incurable and irreversible, accompanied by pathological fractures, severe pain, hypercalcemia, or medullar compression [14]. At the same time, compared to liver and lung metastases, BM had worse overall survival (OS) and typically indicated a poor prognosis in EC. There is very limited large cohort for esophageal cancer apart from SEER database (Table 1). A recent retrospective study analyzed 2075 EC patients with initial bone metastasis from 2010 to 2016 and found that common risk factors for BM are male sex, T4 stage, and brain and/or liver metastases [11]. Considering these factors can help to guide individualized diagnosis and treatment for esophageal cancer patients with bone metastases.

Moreover, early molecular screening with biomarkers is crucial to improve the survival rates of patients with ECBM because prognosis depends on the stage at which it is detected. Only rare patients with single bone metastasis can be cured; for a significant majority, all treatments are applied in the palliative setting mainly for alleviating pain, restoring function, and improving quality of life. Limited surgical resection is inadequate; therefore, effective multidisciplinary treatment modalities are needed [20]. Currently, pain-relieving drugs, surgical therapy, radiotherapy (RT), chemotherapy (CT, including molecular-targeted drug therapy), endocrine therapy (ET), bisphosphonates (BPs) and interventional therapy are the most commonly used therapies to treat bone metastases from esophageal carcinoma [20–24]. Among all therapeutic methods, radiation therapy remains the most common and effective treatment for ECBM patients [25,26]. This article will provide a basic summary of early molecular biomarkers and radiotherapy-assisted treatment and summarize the future prospects of noninvasive biomarkers for early detection and radiotherapy in ECBM.

2. Prognostic biomarkers

Advanced esophageal cancer presenting with distant bone metastases usually has a poor prognosis. We highlight biochemical factors derived from patients' fluid and tissues for determining the effect of the tumor on the patient and for predicting effects of the treatment. As molecular biology research on esophageal cancer advances, an increasing number of biomarkers have been found and verified (Fig. 1). Most are still in the research stage, and more large-scale clinical trials need to be carried out to accumulate enough data (Table 2). In the future, goals include not only predicting patients' prognoses with the help of biomarkers but also developing drugs that target markers and their downstream pathways specifically.

2.1. Cellular proliferation biomarkers

Abnormal cell cycle regulation is a key event in the malignant transformation of several solid tumor types. Cyclin A1 (CCNA1) serves as an important cell-cycle regulator, and research has revealed that CCNA1 has an oncogenic function associated with its effect on cellular proliferation [27]. In a study of 78 primary tumors of ESCC, CCNA1 mRNA and protein expression levels were found to be significantly elevated compared with those in adjacent noncancer tissues [28]. Moreover, survival analysis has indicated that overexpression of CCNA1 is associated with poorer outcomes. Therefore, CCNA1 is a novel and promising prognostic biomarker in ESCC. Protein retinoblastoma (pRB) plays a critical role in regulating the cell cycle, thus affecting tumor progression. Moreover, inactive pRB in ESCC is associated with T3/T4 tumors, N1 stage, and poor prognosis [29]. Ubiquitin-conjugating enzyme H10 (UBCH10), a ubiquitin-conjugating enzyme, is also essential in regulating cell cycle progression from metaphase to anaphase. Overexpression of UBCH10 might accelerate migration via the lymphatic stream and thus indicate a poor prognosis [30]. The PI3K/Akt signaling pathway is well known to be involved in the regulation of many biological processes, including cell proliferation, differentiation, apoptosis and glucose transport [31]. PIK3CA mutation could overactivate the PI3K/Akt signaling cascade, thereby encouraging tumor growth and metastasis. The current study indicated that PIK3CA overexpression is significantly associated with local recurrence in ESCC and is an independent risk factor for a poor prognosis only in female patients with ESCC [32]. In contrast, PIK3CA mutation indicated a poor prognosis only in PD-L1-negative ESCC patients [33]. The tetraspanin protein CD151/Tspan24 has complex and wide-ranging mechanisms of action in a variety of tumors. In untreated EAC patients specifically, CD151 overexpression is associated with better survival and prognosis, and measurements of tumor CD151 expression levels prior to treatment could inform effective and individualized treatments [34]. The above research conclusion has been externally validated. Although Numb has been recognized to be a tumor suppressor in breast and non-small cell lung cancers (NSCLC), Numb overexpression was detected in human ESCC tissues and cell lines. Furthermore, Numb overexpression predicts a poor prognosis in ESCC patients, and Numb knockdown via siRNA could enhance tumor cell apoptosis and inhibit cell growth [35].

2.2. Metastasis-associated biomarkers

Twist1 is involved in epithelial-mesenchymal transition (EMT), which is closely related to tumor progression. Twist1 expression is indicated to be upregulated in ESCC, and thus, Twist1 can be used as a diagnostic and prognostic biomarker [36]. Tumor angiogenesis is one of the most notable features of malignant neoplasms and metastases. The endothelial cell-derived peptide endothelin (ET) axis, including ET-1 and its two receptors, ETAR and ETBR, may enhance neovascularisation and venous invasion. ETBR is overexpressed in ESCC tissues compared with noncancer tissues and is significantly associated with tumor differentiation, tumor size, lymph node metastasis, and venous invasion via immunohistochemistry analysis. On the other hand, survival analysis has also demonstrated that high ETBR expression is an independent risk factor for ESCC patients [37].

2.3. Noncoding RNA

Noncoding RNA (ncRNA) refers to RNA that does not encode protein and exerts important biological functions at the RNA level. Among them, microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are well known today. miRNAs (usually 21–25 nt) and lncRNAs (over 200 nt) are stable in tissue and blood samples of patients and reflect the biology of the tumor, making them candidates for prognostic biological markers. By analyzing RNA-seq data of miRNA expression in TCGA-ESCA, overexpression of miR-421 was proven to be independently associated with shorter overall survival (OS) and poorer prognosis of EAC patients [38]. A miRNA array using serum samples from 101 ESCC patients indicated that only the circulating miR-1246 is an independent risk factor for poor survival [39]. Another study demonstrated that elevated miR-142–3p is associated with poor prognosis in ESCC patients [40]. Xu et al. found that miR-196b expression is upregulated and that miR-196b promotes tumor development by targeting suppressor of cytokine signaling 2 (SOCS2) in ESCC. In view of this negative correlation between miR-196b and SOCS2, their combined expression has the potential to become a valuable diagnostic biomarker for ESCC patients with poor outcomes [41]. LncRNA CCAT2 overexpression has been suggested to be associated with poor survival by promoting tumor invasion and metastasis in ESCC patients [42]. Previous studies have shown that 3- or 7- lncRNA expression signatures can predict survival and help in the choice of the appropriate treatment for ESCC patients [43,44].

2.4. Tumor-immune-related biomarkers

There is a growing appreciation for the tumor microenvironment, which is increasingly believed to play key roles in the development and progression of tumors. Wang et al. demonstrated that stimulator of interferon genes (STING) and macrophage migration inhibitory factor (MIF) in tumor infiltrating lymphocytes (TILs) can predict the survival of ESCC patients, and the combined overexpression of STING and MIF is dramatically related to reduced patient survival [45]. The polymeric immunoglobulin receptor (PIGR), a member of the immunoglobulin superfamily, exerts its biological effects mainly through transferring immunoglobulin A (IgA) onto mucosal surfaces. PIGR is often considered to correlate with tumor progression, and a recent study based on the TMA technique has shown that high PIGR expression in upper gastrointestinal adenocarcinoma is independently associated with a decreased recurrence rate and better prognosis [46].

2.5. Other biomarkers

Achaete scute-like 2 (ASCL2), an intestinal stem cell marker, is a downstream target of the Wnt signaling pathway and plays an important role in the carcinogenesis and progression of EAC [47, 48]. The immunohistochemistry results show that high ASCL2 protein expression is an independent prognostic factor and predicts negative outcomes for surgically resected EAC patients. Advances in metabolomics technologies have enabled the extraction of more information from blood, tumor tissue, and body fluids. In human metabolism, mannose plays a pivotal role in glycosylation of proteins. A recent study revealed that elevated levels of serum D-mannose are associated with favorable outcomes [49]. Cyclo-oxygenase (COX), also named prostaglandin endoperoxide synthase, is involved in catalyzing the conversion of arachidonic acid (AA) to prostaglandin (PG). The activity of COX-2 in normal tissue is extremely low, and when induced by certain external and/or internal factors, COX-2 expression is well enhanced, eventually resulting in an inflammatory response and tissue destruction. Foley et al. suggested that a combination of PET image features and COX-2 expression is an important prognostic biomarker in EAC [50]. Protein tyrosine phosphatases (PTPs) are recognized as tumor suppressors because of their roles in regulating tyrosine phosphorylation and acting as antagonists of tyrosine kinase (TK) signaling. Cao et al. showed that the protein expression of PTPN12, which belongs to the PTP family, could be an independent predictor of ESCC patient survival [51]. C-X-C chemokine receptor 4 (CXCR4), a G-protein coupled receptor, is frequently upregulated in a variety of gastrointestinal (GI) tumors including esophageal, gastric and colorectal cancer. Furthermore, overexpression of CXCR4 is suggested as a prognostic biomarker for poor outcomes in the above GI tumors [52]. The epigenetic inactivation of RASSF5A is frequently detected in ESCC tissues, and RASSF5A may serve as a favorable prognostic biomarker for ESCC [53].

3. Palliative treatment for ECBM

The therapeutic strategy for bone metastasis should focus on relieving existing symptoms and avoiding or slowing the progression of skeletal-related events (SREs). Accordingly, given its unique role in relieving bone pain, external beam radiotherapy (EBRT) is often recommended when bone metastases are localized to one or limited anatomical sites [54]. The great majority of patients with bone metastases can achieve partial or complete pain relief after radiation therapy, but some experience a temporary increase in pain, which is a potential side effect of radiation therapy. This usually occurs days after radiation therapy and lasts for 1–2 days. According to this latest retrospective study, 536 patients with 751 predominantly osteolytic bone metastatic lesions were investigated. Among them, a total of 15 lesions originating from esophageal cancer were classified into the unfavorable group. Patients with higher EBRT doses (biologically effective dose, BED_{10}<39.0 Gy) and drug administration of bone-modifying agents (BMAs)/antineoplastic agents after EBRT were better controlled locally of bone metastases [55].

Major advances in radiation therapy techniques have been achieved since Roentgen's 1895 discovery of X-rays. Currently, conventionally fractionated radiotherapy has evolved to include conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), proton beam therapy (PBT), carbon ion radiotherapy (CIRT), etc. [56–59]. A single-center retrospective analysis showed that esophageal cancer commonly metastasizes to bones (31 cases, 37.8 %), followed by

lung (24 cases, 29.3 %), others (17 cases, 20.7 %), and liver (10 cases, 12.2 %). Meanwhile, IMRT has proven to be a feasible and positive approach for metachronous oligometastatic EC patients, and the radiation dose that would be received with a BED10 $\geq$ 60 Gy was shown to increase survival time [60]. These modern radiotherapy techniques allow for high-dose radiation to the target volume while decreasing effects on normal tissue and adjacent organs. Moreover, fractionated doses of irradiation can split the total radiation dose into several fractions that go hand in hand with chemotherapy to increase the lethality of tumors and improve patient survival. Recently, Matsuoka et al. reported that people with cutis, bone and adrenal gland metastases from esophageal adenosquamous carcinoma obtained favorable survival outcomes after the use of docetaxel combined with concurrent irradiation therapy [61]. Therefore, in comparison to EBRT, SBRT seems to be suitable for patients with esophageal cancer which is understood to have a poor prognosis and unfavorable survival rates. To my knowledge, few studies have separately described SBRT for skeletal metastases from esophageal cancer in any detail.

Bone pain as a result of bone metastases is the most common cancer-associated pain that can lead to a sharp decline in quality of life (QOL) [62]. Once esophageal cancer with bone metastasis is diagnosed, it is already advanced, and the corresponding treatment should change from radical to palliative approaches, including analgesia, radiotherapy, chemotherapy, hormones, and bisphosphonates [63]. The goals of treatment should focus on relieving the patient's bone pain and debilitating effects [64]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and stronger opioids as first options are the most commonly used analgesic drugs in most patients. As the distribution of metastatic bone lesions increases with the total number of lesions, persistent intake of analgesic medication is bound to accelerate drug resistance, which attenuates the analgesic effect. Moreover, in addition to their powerful analgesic properties, these drugs have a multitude of side effects and complications, including sedation, nausea, respiratory depression and physical dependence, and overdose can be dangerous [65]. Therefore, further treatment options such as radiation therapy (EBRT or SBRT) effectively compensate for the deficiency of drugs. The use of local external radiotherapy is appropriate for localized metastatic lesions, while hemibody irradiation is recommended when the metastatic lesion extends to large areas of the body. If bone pain persists or recurs after external beam radiation, treatment options are recommended, including fractionated radiation therapy (especially since the initial treatment was a single external beam), stereotactic radiation therapy, image-guided local thermal ablation, and radiopharmaceuticals. Additionally, for patients with widespread painful bone involvement, bone-seeking radiopharmaceuticals may offer a promising method of controlling pain. Bone-seeking radioisotopes can act directly on osteoblast-associated tissue and are suitable for patients with bone pain mainly caused by osteoblastic bone metastases. A wide range of radioisotopes found in the earth, including strontium-89, samarium-153, rhenium-186, and rhenium-186, are well absorbed in bone structure and cover a broader systemic distribution with a superior pain reduction effect [66–69]. Moreover, radionuclide therapy has a relatively low level of toxicity and few long-term side effects. For example, in the thyroid field, ^{131}I is a well-known and widely used radionuclide [70–72]. An increasing number of radiolabeled agents are starting to be reported in treating different types of tumors, and many of these radionuclides have entered clinical trials [72]. One report of esophageal cancer with bone metastasis in which repeated administration of strontium-89 five times every 3 months effectively relieved pain [73]. The reality is, however, that cases reported of esophageal cancer with bone metastasis that have been treated by nuclear medicine therapy are scarce. More and further studies about radionuclide-targeted therapy are needed to include esophagus-derived bone metastases in research.

Metastatic spinal cord compression (MSCC) generally occurs in patients who are diagnosed with metastatic bone tumors with pathological fractures [74]. Surgical treatment is regarded as the most common and effective means of releasing spinal cord compression, correcting spinal deformity and restoring spinal stability [75]. Meanwhile, surgery plus postoperative RT allows patients with MSCC to obtain more health gains. However, a previous study has shown that surgery plus RT may not necessarily be more effective than RT alone [76]. RT alone applies to primary tumors that are extremely sensitive to radiotherapy. Compared to other radiotherapy options, SBRT can safely administer a higher dose to the target to reach lasting local control [77]. Local recurrence and vertebral compression fractures (VCFs) might represent important limitations of SBRT within the field of MSCC [78–81].

4. Radiotherapy combined with chemotherapy for ECBM

Chemotherapy and radiotherapy are the most commonly used palliative treatments. Previous literature indicated that preoperative radiotherapy combined with chemotherapy can improve overall survival for esophageal cancer patients, especially those with lung and liver metastases [82–85]. Qi et al. (2019) showed that concurrent paclitaxel/carboplatin/nimotuzumab-based neoadjuvant CRT could improve overall survival time and pathological response with tolerable toxicities [86]. The study mentioned above reports an extremely rare case of recurrent esophageal adenosquamous carcinoma with widespread skeletal and visceral metastases [61]. After neoadjuvant chemotherapy with FP (2 cycles), esophagectomy and mediastinal and celiac lymph node dissection, chemotherapy with docetaxel (27 cycles), and irradiation therapy (linac 36 Gy/16Fr), the patient achieved long-term complete remission of over 8 years. A detailed study based on the SEER database in 2022 suggested that esophageal cancer patients with bone metastasis who received radiotherapy and chemotherapy had a 7-month improvement in median survival time and better prognostic benefits [19]. In contrast, Makino et al. found that the survival difference between the CRT group and the surgery group was not statistically significant [26]. Thus, it is difficult to ascertain the usefulness of CRT and more prospective studies are needed.

Although radiotherapy is one of the most common treatments for pain palliation in BM patients, several deleterious side effects must be mentioned and considered. Esophageal cancer patients commonly suffer from hematologic toxicity (HT) during vertebral body (VB) irradiation [87]. Patients with HT often present with leukopenia, anemia and thrombocytopenia. The clinical presentation of HT after VB irradiation can be asymptomatic or symptomatic. Some patients will develop clinical symptoms, including dizziness, hyperdynamics, numbness, poor sleep quality, fever, hepatomegaly, thrombocytopenia, and bleeding tendency, especially in the setting of bacterial infection. Fortunately, these symptoms are easily cured after symptomatic treatment. The current study shows a

close correlation between increasing low dose and mean radiation dose to the VB and the low rate of HT in esophageal cancer patients receiving CRT. Compared to 3DCRT, IMRT and SBRT, PBT has a better low dose distribution and mean radiation dose (5–15 Gy), so the incidence of HT was lower [88]. In general, achieving bone marrow dose constraints is vital to minimize the risk of HT. In addition, other RT-induced side effects of esophageal cancer with bone metastases (e.g., acute cutaneous skin reactions, VCFs, myelopathy) have not been investigated in detail due to the overall small number of patients.

5. Conclusions and future directions

The first and most difficult point is early identification of ECBM. With the development of detection technology, the assessment of biomarkers in body fluids or tissues, can help us determine prognosis and guide a suitable treatment option for cancer patients. The simple fluid and tissue test could be generalized and considered to monitoring status of ESCC and following-up after operation. However, part of problems still remain. The most important point is to validate these biomarkers clinically. Furthermore, the biological functions and mechanisms behind these biomarkers remain to be addressed.

Although radiotherapy technology is advancing at a rapid rate, there is much room for progress to improve the quality of patients' life. First of all, photon radiotherapy should be considered to exert a positive effect against pain, even when the bone metastasis is not extensive. Compared with conventional radiation therapy, photon radiotherapy can allow for irradiating tumors with higher doses while simultaneously keeping surrounding normal tissues from being exposed to a high dose. The strength of a photon lies in its biological role of causing initial DNA damage by directly breaking double-strand DNA [89]. Secondly, given the synergistic anti-tumor effect of immunotherapy and radiotherapy, a combination therapy of two may improve overall survival compared with each method alone [90,91]. In the end, it is well known that sensitivity to radiotherapy is a determining factor for prognosis. Hence, via integrated analysis of multi-omics, we further identify the patient's sensitivity to radiotherapy to assess the feasibility of radiation therapy. In total, there are some novel perspectives in RT that we have offered indicating that it is a promising tool for EC patients with bone metastases. Better understanding and using RT technology will help drive future promising therapeutic interventions for ECBM patients to improve their quality of life and extend their lives.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Xiaofeng Yuan: Writing – original draft, Conceptualization. **Jun Chen:** Writing – review & editing, Writing – original draft. **Dingsen Shi:** Writing – review & editing, Writing – original draft. **Jiaxun Song:** Writing – review & editing. **Pu Wang:** Writing – review & editing. **Dong Cheng:** Writing – review & editing. **Cheng Yang:** Writing – review & editing. **Xubin Qiu:** Writing – review & editing, Visualization, Conceptualization. **Chenjun Zhai:** Writing – review & editing, Visualization, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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