THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 7

REVIEW ARTICLE

A Review of Metastasis-Directed Therapy in Oligometastatic Gastrointestinal Cancers

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OPEN ACCESS

PUBLISHED
31 July 2024

CITATION
Dipko, K., Shrestha, S., Khandekar, R., et al., 2024. A Review of Metastasis-Directed Therapy in Oligometastatic Gastrointestinal Cancers. Medical Research Archives, [online] 12(7). https://doi.org/10.18103/mra.v12i7.5629

DOI
https://doi.org/10.18103/mra.v12i7.5629

ISSN
2375-1924

ABSTRACT

This review provides an overview of the current understanding regarding the role of metastasis-directed therapy (MDT) in patients with oligometastatic gastrointestinal cancers. A review of clinical data was conducted to describe patient outcomes associated with the use of local therapy alone or in combination with systemic therapy to gastrointestinal oligometastases. Included cancers were esophagus, liver, pancreas, colorectal, and anal canal. Radiotherapy was the most common MDT employed across studies although surgical resection and transarterial ablation were also used. Present data suggest that local therapies should be considered in the treatment of oligometastatic gastrointestinal malignancies for appropriate patients. MDT may be associated with improved overall survival, progression-free survival, particularly for esophageal and colorectal cancers. Enhanced disease control has also been seen for hepatocellular and pancreatic cancers with limited adverse events. The data highlight the increasing impact of locoregional management of oligometastatic disease through multiple treatment modalities. Targeted approaches involving radiotherapy and surgical resection can enhance clinical response to systemic therapy and improve patient outcomes. Future randomized clinical trials will further establish the role of MDT in patients with oligometastatic GI cancers.

Introduction

Gastrointestinal malignancies make up nearly 350,000 new cancer diagnoses worldwide and account for around 28.2% of deaths due to cancer each year[1]. Metastatic spread is one of the primary complications in gastrointestinal malignancies with nearly 35% of U.S. gastric cancer patients and 60% of new colorectal cancer (CRC) cases presenting with advanced disease[2,3]. The establishment of metastatic colonies is characterized by a series of steps undertaken by the primary tumor known as the invasion-metastasis cascade[4]. This process involves intravasation of cancer cells from the local tumor, survival and travel through the circulation, extravasation, and, finally, colonization at a distant site.

An emerging emphasis on addressing oligometastatic disease (OMD), an intermediate state between localized and disseminated illness, presents potential avenues to mitigate the burden incurred by disease spread and improve patient outcomes[5,6]. While the exact definition of OMD across fields remains heterogeneous, radiation oncology experts have defined it as 5 or less metastatic lesions[6]. While advances in systemic therapy continue to expand options for treatment, potential reseeding of tumor sites and development of resistance to systemic therapy has driven an increased interest in local consolidation using a multimodal approach. Trials investigating the role of MDT for various cancers has already shown encouraging results. In 2020, the SABR-COMET phase II trial demonstrated that local management of oligometastatic foci can increase overall survival (OS) rates as well as progression-free survival (PFS) in patients with myriad malignancies[7]. The CURB trial which assessed the impact of regional radiotherapy therapy for metastatic sites in patients with non-small cell lung carcinoma also demonstrated improvements in PFS[8]. Additionally, prolongation of systemic therapy efficacy has been shown for patients with castrate-resistant prostate cancer receiving MDT[9]. These data strengthen the notion that locoregional treatment of oligometastatic disease sites may improve clinical outcomes across a spectrum of malignancies. This review will aim to evaluate the role of local therapy in patients with various oligometastatic gastrointestinal cancers.

Biology

The concept of metastatic disease has undergone multiple evolutions over the last two centuries. The "seed and soil" hypothesis posited by Paget in 1889 compared tumor cells to seeds that circulate through the body and germinate in tissues that offer favorable growing conditions[10]. This was based on the observation that certain organ sites such as the liver and bone were more likely sites of metastases in advanced breast cancer. This concept was replaced by the theory that cancer is a truly systemic disease, and dissemination of disease is instead based on intrinsic characteristics of the tumor itself in addition to the anatomy of potential metastatic sites. In 1980, Fisher proposed that heterogeneity at the cellular level of malignancy is responsible for differences in therapeutic response[11]. This was pivotal in the standard management of breast cancer and led to an increased focus on chemotherapy and radiotherapy as opposed to radical resection. A more recent perspective submitted by Hellman and Weichselbaum asserts that tumor progression is more likely a product of host-disease interaction comprised of a combination of spread from the primary tumor and manifestation of systemic disease[12]. It is this hypothesis that has generated expanding interest in the oligometastatic condition, its influencing factors, and its effective management.

With growing understanding of how clinical and biological factors affect the course of malignant disease, the concept of metastasis continues to change. The ability of circulating tumor cells to re-seed primary lesions exemplifies this. Norton and Massagué originally proposed the concept hypothesizing that cancer cells could return to an original site through various mechanisms including local displacement and reattachment or through hematogenous travel[13]. Subsequent studies not

only confirmed the reality of this idea but demonstrated that reseeding of tumor sites can accelerate growth[14]. Analysis of tumor self-seeding patterns revealed that this phenomenon is selective for increasingly aggressive circulating tumor cells that possess enhanced ability to spread in comparison to parental cell populations. An additional focus on the molecular mechanism of malignancy spread has uncovered the existence of "oligomiRs," microRNAs that may be responsible for oligometastatic disease[15]. These have been found to be involved in key steps of the metastasis cascade such as adhesion, invasion, and migration[16,17]. This evidence supports the notion that prognosis and therapy for oligometastases can be guided by molecular identification of patient tumor types and strengthens the perspective favoring local management of metastatic disease.

Esophageal Carcinoma (EC)

Esophageal cancer is a relatively rare disease, and represents only about 1% of cancer diagnoses in the United States[18]. However, the burden of disease spread is evident in EC as the estimated 5-year survival rate for patients with metastatic disease drops nearly 41% when compared to survival rates in patients with localized disease[1]. Common sites of metastasis are the lungs, liver, bone, and distant lymph nodes.

Treatment modalities differ based on histology: squamous cell carcinoma (ESCC) versus adenocarcinoma (EACA). The current first-line systemic treatment for advanced ESCC is a platinum-fluoropyrimidine doublet with the addition of a programmed death 1 (PD-1) inhibitor. The phase III KEYNOTE-590 trial compared the addition of PD-1 inhibitor pembrolizumab to cisplatin-5-FU in treatment-naïve esophageal or gastroesophageal junction cancer. The immune checkpoint inhibitor yielded significant improvements in OS for both ESCC and EACA patients with the greatest increases in ESCC patients with elevated PD-L1 expression[19]. Second-line treatment consists of nivolumab[20].

A retrospective analysis of patients with advanced oligometastatic ESCC (≤ 3 metastases) compared chemotherapy alone to concurrent chemoradiotherapy (CCRT)[21]. The chemotherapy regimen consisted of paclitaxel 135 mg/m^2 on Day 1 and cisplatin 25 mg/m^2 on Days 1-3 repeated every four weeks. The radiation dose was 50Gy/25 fractions delivered over 5 weeks concurrent with two cycles of chemotherapy. Median PFS for the CCRT group was 8.7 months compared to 7.3 months for the CT group (not significant), and median OS was 16.8 months for the CCRT group compared to 14.8 months for the CT group (not significant).

Another retrospective study was conducted at the Mianyang Central Hospital in which the patient cohort was composed of individuals with oligometastatic EC and ≤ 5 oligometastatic lesions[22]. Patients were divided into a radiotherapy group (n=55) and a non-radiotherapy group (n=27). The radiotherapy group received a median dose of 60 Gy. Of the non-radiotherapy group, 19 received systemic therapy, 5 received apatinib anti-vascular targeted therapy, and 3 were provided with supportive care. The median OS differed significantly across treatment groups with the radiotherapy group achieving a median OS of 14 months versus 7 months for the non-radiotherapy group. Additionally, although not significant, there was a difference between radiotherapy patients who received ≥ 60 Gy and < 60 Gy with a median OS of 16 months and 10 months, respectively.

In 2020, Liu et al. conducted a prospective phase II trial that investigated whether stereotactic body radiation therapy (SBRT) for oligometastases followed by chemotherapy in ESCC patients resulted in favorable outcomes[23]. Patients had 3 or fewer metastases and controlled primary malignancy. The preferred radiotherapy schedule consisted of 48 Gy in 8-Gy fractions. A variety of first-line chemotherapy regimens were employed including cisplatin plus fluorouracil, paclitaxel plus cisplatin, paclitaxel plus carboplatin, or fluorouracil plus oxaliplatin. The median PFS was 13.3 months. Median

OS for the cohort was 24.6 months with 1 and 2-year OS rates being 76.2% and 58.0% respectively.

The ESO-Shanghai 13 trial compared whether PFS would be improved with the addition of local to standard of care systemic therapy in patients with oligometastatic ESCC[24]. OMD was defined as 4 or fewer metastases. Systemic therapy options were paclitaxel and cisplatin (first-line) and paclitaxel, docetaxel, and irinotecan (second-line). The use of anti-PD 1 antibodies was adopted as second-line therapy following changes in systemic therapy recommendations during the trial. Across both treatment arms, most patients had 1-2 sites of metastases. Around 43% of patients in the systemic and local therapy group had non-regional nodal metastases only, and 45% of patients in the systemic therapy group had only non-regional nodal metastases. The majority (89%) of patients receiving local therapy were delivered radiotherapy. SABR was administered to 20 patients at a dose range of 30-50 Gy and 3-6 fractions and was encouraged to be > 7Gy per fraction. Conventional intensity-modulated radiotherapy (IMRT) was delivered to 25 patients at a range of 45-61.2 Gy over 25-34 fractions. Two patients received hypofractionated radiotherapy at 45-60 Gy over 15-20 fractions. Abdominal lesions were dosed at 45-50Gy/25-28 fractions and 50-66Gy/25-34 fractions for cervical and thoracic lesions. Other treatment modalities for oligometastases included surgery, a combination of surgery and radiotherapy, and thermal ablation. Local management of oligometastases significantly increased PFS with 1 and 2-year PFS rates being 60.4% and 35.8% in the combined therapy group versus 27.5% and 9.8% in the systemic therapy group. Median PFS was 15.3 months for the combined therapy group versus 6.4 months for the systemic therapy group. Additionally, a significant increase in OS was seen in the combined therapy group.

Long-term analysis of the CROSS trial comparing chemoradiotherapy prior to surgery to surgery alone in patients with ESCC or EACA showed that combined therapy improved OS for patients with both histological malignancies[25]. However, patients with ESCC responded best to neoadjuvant therapy plus surgery with a 10-year OS of 46% compared to 36% in EACA.

An ongoing phase III trial (EA2183) aims to evaluate the role of radiotherapy on oligometastatic (≤ 3 metastases) esophageal and gastric adenocarcinoma in comparison with systemic therapy alone[26]. All patients will complete 4 months of systemic therapy after which they will be randomized to either radiotherapy to all disease sites followed by systemic therapy or systemic therapy alone. OS from the time of randomization is the primary endpoint of the study with secondary endpoints including PFS and safety and tolerability of radiotherapy. This prospective study has the potential to clarify the use of radiotherapy for locoregional management of oligometastases in esophageal cancers.

Hepatocellular Carcinoma (HCC)

HCC most commonly metastasizes to the lungs and intrahepatic sites as well as bone, and retroperitoneal lymph nodes. First-line management of advanced HCC is either a combination of atezolizumab and bevacizumab[27]. The phase III IMbrave150 trial was a multinational study that investigated the efficacy of atezolizumab plus bevacizumab versus sorafenib alone[28]. Patient OS for the atezolizumab-bevacizumab group was significantly higher with rates of 84.8% and 67.2% at 6 months and 12 months respectively. This was compared to the sorafenib group which showed OS rates of 72.7% and 54.6% at the same time points. PFS rates were also significantly higher in the treatment arm with a median PFS of 6.8 months versus 4.3 months. Other first-line options are durvalumab and tremelimumab. The HIMALAYA trial demonstrated that the STRIDE (Single Tremelimumab Regular Interval Durvalumab) regimen was superior to sorafenib in treating unresectable HCC[29]. On long-term follow-up, OS rates at 3 and 4 years were 30.7% and 25.2% respectively versus 19.8% and 15.1% for the sorafenib arm. Finally, the

PD 1 inhibitor, tislelizumab, is a recent first-line treatment option. In the RATIONALE-301 trial, it was noninferior to sorafenib[30].

A study involving 69 patients with oligometastatic HCC to the lung investigated the effects of local management of metastatic disease sites[31]. Of the 33 patients that received local therapy, 16 (48.5%) underwent surgical resection and 12 (36.4%) received radiotherapy. The 1-year and 2-year OS rates for the local treatment group were significantly higher than those in the systemic treatment alone group: 88.5% and 66.6% for local treatment and 63.6% and 31.2% for systemic therapy alone. PFS rates were also significant across treatment groups with the local treatment group demonstrating 1-year and 2-year PFS of 58.9% and 47.0% respectively. This was compared to 21.2% and 10.6% respective PFS rates in the systemic treatment group. The 2-year OS rates were also higher among the local treatment group with a rate of 70.7% versus 0% in patients with one pulmonary metastasis.

A multicenter retrospective analysis compared outcomes of hypofractionated radiotherapy for pulmonary oligometastases of HCC[32]. Oligometastatic disease was defined as ≤ 5 pulmonary metastases. A total of 58 patients were treated with helical tomotherapy (n=19), linear accelerator-based radiation therapy (n=35) and Cyberknife radiotherapy (n=4) with a dosing scheme that varied from 30-80 Gy in 3-10 fractions. A complete or partial response was obtained in 77.6% of patients (n=45) with 10.3% showing stable disease and 12.1% showing progressive disease. The median OS time was 16.3 months, and median PFS time was 4.9 months. After 1 year, the OS rate was 65.5% and the PFS rate was 22.4%. Factors influencing OS were the presence of an intrahepatic tumor, Child-Pugh class B, and short progression-free interval.

A recent meta-analysis investigated the role of locoregional treatment of HCC with oligometastases[33]. Pooled analysis of comparative studies involving local treatment of oligometastases versus systemic management produced an OR of 4.664. Pooled rates of OS rates at 1 and 2 years were 71.8% and 43.3% respectively.

A separate retrospective study focused on the effect of SBRT on HCC and hepatic oligometastases[34]. Nearly half of patients were diagnosed with HCC (49.1%) while the rest had OMD. The majority of oligometastatic sites (89.3%) were treated with SBRT alone. Others were treated with SBRT combined with surgery or radiofrequency ablation. Estimated 1 and 2-year local recurrence rates in the cohort were 91% and 74% respectively. For the OMD group, OS rates were 84% at 1 year and 67% at 2 years.

A retrospective study by the Korean Radiation Oncology Group (KROG) also investigated the role of radiotherapy in oligometastatic HCC[35]. Across five institutions, a total of 100 patient profiles were analyzed. All patients received SABR to all metastatic sites with the intent of maximizing local control. Radiation dose ranged between 30-60 Gy in 3-8 fractions. The most common sites of metastasis were bone and lung. The median OS was 16 months with a 2-year OS rate of 40%. Factors influencing OS were determined to be patient performance status, Child-Pugh class, control of primary tumor, and time interval of metastasis.

A phase II trial investigated the role of stereotactic ablative radiotherapy (SABR) in patients with oligometastatic HCC[36]. OMD was defined as ≤ 3 lesions in one organ and no more than 5 total. Patients received SABR with a dose of 48-60 Gy/4 fractions to the peripheral lung, 24 Gy/3 fractions to the spine, and 48-64 Gy/8 fractions to the central lung, lymph nodes, and adrenal gland. The 1 and 2-year OS rates were 88.9% and 80.0% respectively. PFS rates at the same time points were 21.2% and 0%. A complete response or partial response was achieved in 75.8% of lesions. Significant prognostic factors identified were Child-Pugh class level, AFP level, and time to OMD from the controlled primary tumor. Quality of life was also assessed and scores were found to be improved in the insomnia and social functioning

categories for patients that received SABR with no systemic therapy.

Another recent phase II study that considered SBRT plus anti-PD-1 antibody, sintilimab, in oligometastatic HCC yielded similarly positive results[37]. Inclusion criteria consisted of Child-Pugh class A, ECOG performance status of 0-1, between 1 and 5 lesions, and no prior history of radiotherapy. Patients received SBRT with sintilimab at a dose of 48-60 Gy/5-10 fractions 5 times a week and 200 mg intravenously once every 3 weeks for 12 months or until disease progression. The median PFS time was 19.7 months with 1 and 2-year PFS rates of 68% and 45.3% respectively. The median OS was 91.5% and 83.2% at 1 and 2 years with local control rates of 100% and 90.9% at the same time points. Of the 25 patients, 17 achieved complete remission and 7 achieved partial remission.

Results such as these are encouraging, and there are ongoing clinical trials continuing to investigate the effect of MDT on oligometastatic HCC. Yonsei University is conducting a phase II trial considering the role of SBRT on oligometastatic HCC (NCT05173610)[38]. Peking University is investigating the effect of SBRT in addition to immunotherapy (tislelizumab) and targeted therapy (regorafenib) in unresectable or oligometastatic HCC patients (NCT05917431)[39]. While the bulk of data remains largely retrospective, current evidence is promising for the role of radiotherapy in improving outcomes for patients with HCC. Results from prospective trials could better inform clinicians as to which patients are good candidates for aggressive local management of oligometastases.

Pancreatic Ductal Adenocarcinoma (PDAC)

PDAC commonly spreads to the liver, peritoneum, and lung. Survival rates for advanced PDAC are low with just 3% of patients achieving 5-year survival[1]. Current treatment guidelines for advanced disease indicate that gemcitabine and nab-paclitaxel or a combination of 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) are standard first-line options for unresectable disease[40,41]. Treatment decision-making is largely based on patient baseline performance status, comorbidities, support system, and patient preference. The PRODIGE trial demonstrated that FOLFIRINOX can achieve improved outcomes in OS when compared with gemcitabine alone[42]. However, patients in the FOLFIRINOX arm experienced greater toxicity rates. Current studies are ongoing to discover more effective, targeted therapies to treat PDAC such as poly ADP-ribose polymerase (PARP) inhibitors and human epidermal growth factor receptor 3 (HER3) blockers[43].

While systemic therapy is the current standard of care for advanced PDAC, the role of surgical resection of primary and metastatic tumors in oligometastatic PDAC is currently being investigated. A retrospective analysis from a high-volume pancreatic surgery center in China evaluated patient outcomes after synchronous resection of primary tumor and liver metastases. Yang et al. compared OS and among PDAC patients of the following cohorts: non-oligometastatic synchronous resection, oligometastatic synchronous resection, systemic chemotherapy only[44]. The median OS for the oligometastatic synchronous resection patients was significantly longer than the non-oligometastatic group at 16.1 months versus 6.4 months. Furthermore, in a matched analysis, the oligometastatic synchronous resection patients also demonstrated a longer OS than the systemic therapy patients with a median time of 16.1 months versus 7.6 months.

A retrospective study from France analyzed outcomes among patients who underwent various local treatment modalities for PDAC metastases[45]. Over half of metastatic sites occurred in the liver (57%) and over one quarter included lung (27%). Surgical resection was employed to manage 66% of oligometastases, 13% received radiation, and 21% other procedures. Median OS following local treatment was 36.5 months. Pathological components that reduced OS were the presence of

hepatic metastases, N2 status of the primary tumor, and synchronous metastases.

A recent, multicenter phase II trial, EXTEND, assessed the impact of adding MDT to standard systemic therapy in patients with PDAC[46]. OMD was defined as ≤ 5 sites of solid tumor metastases. PFS was significantly greater for patients in the MDT arm with a median PFS of 10.3 months versus 2.5 months. Additionally, patients in the radiotherapy treatment group demonstrated increased T-cell stimulatory cytokines, CD8+ T cell activation and proliferation, and T-cell receptor clonal expansion. There were no grade 3 adverse events associated with locoregional therapy.

One multicenter phase III trial run by Fudan University is considering the outcomes of synchronous resection of primary PDAC and liver oligometastases following induction chemotherapy[47]. The HOLIPANC phase II trial is a similar study investigating outcomes in PDAC with hepatic oligometastases that receive neoadjuvant NAPOX therapy followed by exploratory laparotomy and synchronous resection of primary and metastatic foci[48]. Researchers at Zhejiang University are conducting the HOPE-1 trial which is exploring thermal ablation of hepatic oligometastases in PDAC patients[49]. Following PDAC surgery, patients will be randomized to receive systemic chemotherapy alone or systemic chemotherapy plus liver thermal ablation.

A current phase II trial is investigating the role of SBRT in addition to standard chemotherapy for oligometastatic PDAC. Oligometastatic disease is defined as ≤ 5 sites of metastasis. Patients will receive SBRT once daily or every other day for 5 fractions. The primary endpoint of the study is the comparison of PFS between standard systemic therapy and SBRT plus standard therapy. Secondary endpoints are confirmed response rate, OS, adverse events, and longitudinal assessment of circulating tumor cells, and circulating tumor DNA. A prospective study, ScanPan1, is assessing multimodal treatment of oligometastatic PDAC. One cohort is composed of patients with hepatic metastases and the other is composed of patients with unilocular metastases that are amenable to SBRT, surgery, thermal ablation, or a combination of therapies[50]. These studies are important as they are some of the first prospective studies investigating MDT in the treatment of PDAC. Evidence from these trials could improve current understanding of the role of locoregional management of PDAC oligometastases and increase treatment options for patients with advanced disease.

Colorectal Cancer (CRC)

CRC is one of the most common cancers worldwide and accounts for over 50,000 deaths in the United States each year[51]. Development of metastases is common in CRC patients with 1/3 of patients either presenting with disseminated disease either at presentation or follow-up, and primary sites of distant disease being the liver or the lungs[52–54]. Determining the genetic composition of CRC tumors is important for guiding treatment options with mismatch repair (MMR) and microsatellite (MS) instability status generally obtained at diagnosis. Additional data suggests that loss of KRAS and SMAD4 mutations may contribute to the development of oligometastatic CRC[55,56]. In a study analyzing the genetics of hepatic metastases from CRC, researchers used molecular subtyping to categorize tumors into three classes[57]. The "canonical" subtype was characterized by decreased immune and stromal infiltration and increased E2F/MYC signaling and DNA damage, and cell cycle signaling pathways. The "immune" subtype was associated with upregulated immune and interferon signaling with increased NRAS, CDK12, and EBF1 mutations. The "stromal" subtype demonstrated enhanced stromal invasion with increased mutations in the KRAS, EMT, SMAD3, and angiogenesis pathways. OS was significantly impacted by subtype categorization of metastases with the "immune" subtype related with a 10-year OS of 64% compared to 37% (canonical) and 20% (stromal). Additionally, patients with low clinical risk scores and tumor

molecular subtypes of "canonical" or "immune" achieved a 10-year OS of nearly 95%. Further information regarding the genetic characteristics unique to OMD may present new opportunities for targeted local treatment.

Current treatment recommendations for unresectable MS stable or proficient MMR CRC consists of doublet chemotherapy (folinic acid, FU, oxaliplatin, or folinic acid, FU, and irinotecan). Pembrolizumab is offered first-line for MS instability-high or deficient MMR CRC. For individuals with RAS wild-type CRC, anti-epidermal growth factor receptor (EGFR) therapy in addition to doublet chemotherapy is standard of care[58].

As many as 50% of CRC patients will develop liver metastases either at presentation or through recurrence[59]. Currently, surgical resection is the standard of care for resectable disease, but 80%-90% of patients are not surgical candidates indicating the need to employ other treatment modalities to manage disease. Goodman et al. considered local control rates, response, and survival time for patients with hepatic metastases who received SBRT[60]. In this study, 67% of patients had CRC, 13.6% had non-CRC gastrointestinal cancer, 7.4% breast, 3.7% ovarian, 3.7% non-small cell lung cancer, and 4.9% other cancers. All patients had 1-3 liver metastases. SBRT was administered in 3-5 fractions at a range of 8-20 Gy per fraction with a median total dose of 54 Gy. Estimated OS rates at 1, 3, and 4 years were 89.9%, 44.0%, and 28.0% respectively. Estimates of PFS at 1, 3, and 4 years were 37.1%, 22.3%, and 18.6% respectively.

A systematic review by Kobiela et al. on the use of SBRT in oligometastatic CRC also demonstrated favorable patient outcomes[61]. For hepatic metastases, local control rates at 1 and 2-year marks ranged between 50%-100% and 32%-91% respectively. Median OS ranged between 53%-100% at 1 year and 26%-83% at 2 years. For lung metastases, local control rates ranged between 62%-92% after 1 year and 53%-92% after 2 years. The median OS range was 65%-76% at 2 years. Furthermore, Hitchcock et al. reported in their review of local management for CRC metastases that SABR is an effective treatment modality for pulmonary metastases with 1-year local control rates ranging between 80-90%[62–64]. Another phase II study evaluated the efficacy of SBRT on liver metastases from various gastrointestinal and other cancers[65]. A total of 89 patients received a median radiation dose of 40Gy. Local control rates at 1 and 3 years were 71.9% and 61.2% respectively. The median OS rates at 1, 2, and 3 years were 66.3%, 35.9%, and 20.8%. Significant prognostic factors decreasing local control rates were the presence of KRAS and TP53 mutations. The improvement in survival outcomes is suggestive that SBRT can benefit CRC patients with unresectable liver metastases, although evaluation for the tumor genetic profile may be warranted. Per current guidelines for managing metastatic CRC, administration of SBRT should be considered for patients with unresectable liver metastases[58].

In addition to SBRT, transarterial therapies can be employed to manage liver CRC metastases. One single-center trial compared degradable starch microspheres (DSM) to ethiodized oil (conventional) in the transarterial chemoembolization (TACE) of liver metastases[66]. After completing systemic therapy, patients were randomized to receive DSM-TACE or conventional TACE. Results demonstrated a significant reduction in tumor volume for the DSM-TACE arm, although, no significant difference was noted in median survival. A phase III trial involving CRC patients with liver metastasis were randomized to TACE with irinotecan drug-eluting beads or 5-FU plus irinotecan intravenous chemotherapy[67]. The median OS for the TACE arm was increased to 22 months versus 15 months for the intravenous arm.

The Finnish RAXO trial which investigated outcomes in metastatic CRC patients based on repeated evaluation of tumor resectability supports the implementation of recurring evaluation of local metastases throughout treatment. Initial evaluation of 1086 patients

classified 29% as resectable upfront, 16% as borderline, and 55% as unresectable. Ultimately, 399 patients (37%) underwent curative intent procedure with resection and/or local ablative therapy (thermoablation or SBRT). The median OS for patients that underwent procedures was 71.5 months versus 20.4 months in those that did not. After 5 years, OS rates were 61% and 6% respectively. There was no significant difference between median OS for patients that were classified as upfront resectable or that were converted resectable with a median OS of 82.8 months and 80.4 months respectively. However, for patients that were classified as resectable but received systemic therapy alone, median OS was significantly lower at 23.5 months and similar to those that were never resectable and received systemic therapy alone (median OS 20.6 months)[68].

A prospective study comparing local treatment of unresectable colorectal liver metastases to systemic treatment alone reported long-term outcomes in their patients. CRC patients with non-resectable liver metastases and no extrahepatic burden were randomized to two groups. One received the current standard of care systemic therapy alone which consists of 5 FU/LV/oxaliplatin with the later addition of bevacizumab. The other treatment arm received the same systemic therapy with additional radiofrequency ablation. In both groups, if tumor burden was later deemed amenable to resection, resection was completed. The randomized phase II trial had previously demonstrated that the primary endpoint of 30-month OS was exceeded in both the combined treatment and systemic treatment alone arms of the trial at 61.7% and 57.6% respectively[69]. Additionally, PFS differed significantly across treatment arms with a median PFS of 16.8 months in the combined treatment arm compared to 9.9 months in the systemic treatment arm. On long-term follow-up, 3, 5, and 8-year PFS rates for the combined treatment group were 27.7%, 16.9%, and 24.2% respectively. This compared to 11.9%, 5.9%, and 2.0% in the systemic treatment arm[70]. OS rates at 3, 5, and 8-years differed significantly only at the 8-year mark with a rate of 30.3% in the combined treatment arm versus 8.9% in the systemic treatment arm.

The ongoing ERASur phase III study evaluates the efficacy of MDT in comparison with standard systemic therapy for patients with BRAF wild-type and MS stable disease. Inclusion criteria consists of no more than 4 sites of metastatic disease as determined by imaging, no liver-only metastatic disease, and disease sites that are amenable to total ablative therapy. Upon completion of 16-26 weeks of first-line standard of care systemic therapy, patients are randomized to either undergo total ablative therapy comprised of surgical resection, microwave ablation, and/or SABR or to continue systemic therapy. The primary endpoint of the study is OS with secondary endpoints being event-free survival, adverse events profile, and time to local recurrence with exploratory biomarker analysis[71].

Anal Squamous Cell Carcinoma (ASCC)

Around 13% of new ASCC cases have metastatic disease at diagnosis[2]. Treatment options for advanced disease include surgery, radiation, and chemotherapy with or without radiotherapy[72]. While there is no prospective data, the relative sensitivity of ASCC to radiotherapy has made total consolidation a preferred strategy. The InterAAct phase II trial compared cisplatin plus fluorouracil to carboplatin plus paclitaxel in the management of treatment-naïve metastatic anal cancer[73]. Objective response rates were similar across both cohorts, however, median PFS differed significantly with a PFS of 8.1 months for the carboplatin plus paclitaxel group versus 5.7 months for the cisplatin plus FU group. Median OS also favored the carboplatin plus paclitaxel group at 20 months versus 12.3 months.

The data is sparse regarding local management of metastatic foci in ASCC. One series considered multiple organ-directed treatment modalities to manage advanced disease[74]. Therapies included

surgery, stereotactic radiotherapy, and radiofrequency ablation. The median OS was 31 months, and median PFS was 5 months. Another retrospective study evaluated outcomes in 77 patients with ASCC[75]. Of these, 42.8% underwent locoregional management of metastatic disease sites following systemic chemotherapy. Surgical resection or radiofrequency ablation was employed for 58%, and chemoradiation for 42%. Compared to patients who did not receive additional MDT, median PFS was significantly longer at 16 months compared to 5 months. Median OS also differed significantly at 53 months and 17 months respectively.

A retrospective analysis investigated the impact of definitive IMRT for patients with metastatic ASCC[76]. The majority of patients had no more than 2 metastatic lesions, and lesions were most commonly localized to non-regional lymph nodes or the liver, and the lung. Patients received a median dose of 56 Gy in a median of 28 fractions. Nearly half of patients received induction chemotherapy; all patients received concurrent chemotherapy. At 3 years, the local control rate was 81%, PFS was 27%, and OS was 53%. What little data exists is suggestive that further investigation is merited into metastasis-directed treatment in ASCC.

Conclusion

OMD is common among various gastrointestinal cancers, and the continually growing data focused on locoregional management of advanced disease sites holds promise for future treatment options. Current studies demonstrate the importance of interdisciplinary collaboration needed to implement myriad therapeutic modalities for managing oligometastatic sites in patients with gastrointestinal cancer. Preliminary data suggests that metastasis-directed therapy can improve PFS and OS with low rates of toxicity, however, further larger scale trials are needed.

Conflict of Interest:

None.

Funding:

None.

Acknowledgements:

None.

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