Review Article on Oligometastasis- Fallacy or Real Deal?

The multidisciplinary management of oligometastases from colorectal cancer: a narrative review

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Contributions: (I) Conception and design: ETJ Chandy; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: In the United States of America, almost 150,000 people are estimated to be diagnosed with colorectal cancer in 2020 and up to 35% of those are expected to present with oligometastatic disease. The term 'oligometastasis' was first used in 1995, however surgical literature describing liver resection for colorectal cancer dates back to the 1940s. Five-year survival rates of up to 42% with surgery alone for solitary lesions are reported. Modern trials have demonstrated median overall survival rates of over 80 months for patients with colorectal liver metastases treated with perioperative chemotherapy. Colorectal liver metastases have accordingly been described as 'proof of concept' for the oligometastatic theory.

Keywords: Radiofrequency ablation (RFA); liver resection; stereotactic ablative body radiotherapy (SABR); transarterial chemotherapy (TACE); selective internal radiotherapy (SIRT)

Submitted Apr 09, 2020. Accepted for publication Aug 05, 2020.
doi: 10.21037/apm-20-919
View this article at: http://dx.doi.org/10.21037/apm-20-919

In this review, we discuss management options for oligometastatic colorectal cancer, including an overview of surgical concepts, the current literature on local ablative techniques including stereotactic ablative body radiotherapy (SABR), thermal ablation, selective internal radiotherapy (SIRT), transarterial chemo-embolization (TACE) and systemic therapy as an adjunct to local treatment strategies. We discuss the role of modern imaging techniques in selecting suitable patients for radical treatment.

We also outline the role of the oncology multidisciplinary team meeting, which has become a key component in the care management pathway to ensure that the increasingly complex treatment strategies available are appropriately selected and combined for each individual patient. We review the available literature on the impact on quality of life that each treatment modality affords, recognizing the importance of embracing advances in medical technology whilst maintaining patient well-being as the center of focus.

Introduction

Oligometastatic colorectal cancer (OCRC) is generally defined as up to 5 lesions in no more than 3 metastatic sites which typically involve the liver, lung, peritoneum, lymph nodes and ovary (1). The terms 'synchronous' and 'metachronous' are used respectively to define OCRC where metastases present within, or beyond, the first 6 months of the diagnosis of the primary. Almost 150,000 Americans will be diagnosed with CRC in 2020 (2). Of those, 20% will present with metastatic disease and a further 35% will develop metastatic disease after upfront treatment for localized disease (3). Whereas 5–35% of patients are expected to present with oligometastatic disease (4), less than 10% of patients with metastatic colorectal cancer (MCRC) will present with resectable disease.

While some fields of oncology are focusing on de-escalation of treatment in lower risk tumors (5,6), the introduction of the oligometastatic paradigm has, conversely, led clinicians to study more radical strategies for

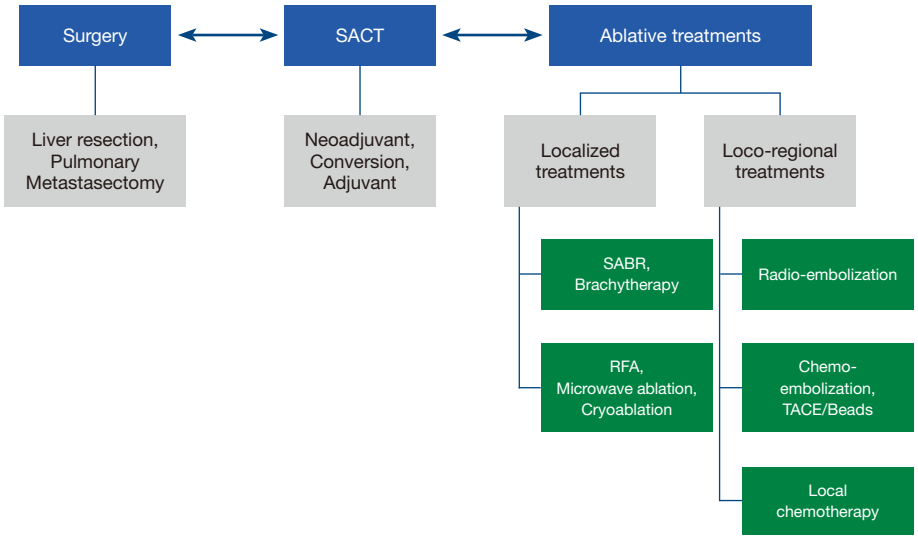

Figure 1 Treatment modalities in oligometastatic colorectal cancer. The complexity of combining the manifold treatment possibilities requires discussion by an expert multi-disciplinary team representing experts in each of these therapeutic disciplines. RFA, radiofrequency ablation; SABR, stereotactic ablative radiotherapy; SACT, systemic anti-cancer body therapy; TACE, transarterial chemo-embolization. Adapted from (1).

disease states that traditionally were deemed suitable only for 'palliative' management. Written into the concept of the oligometastatic state is the premise that curative treatment paradigms may result in long term survival (7). The term 'oligometastasis' was first used in 1995 (8), however surgical literature describing liver resection for colorectal cancer (CRC) dates back to the 1940s (9,10) and 5 year survival rates of up to 42% with surgery alone for solitary lesions are reported (11). Colorectal liver metastases have accordingly been described as a 'proof of concept' for the oligometastatic theory (12).

In this narrative review, we will discuss management options for oligometastatic colorectal cancer, focusing on contemporary treatment paradigms including an overview of surgical concepts, the current literature on local ablative techniques including SABR, SIRT, TACE and the role of systemic therapy as an adjunct to local treatment strategies. We discuss the role of modern imaging techniques in selecting suitable patients for radical treatment. We also outline the role of the oncology multi-disciplinary team meeting, which has become a key component in the care management pathway. We specifically discuss the available literature on the impact on quality of life of each reviewed therapy.

Methods

A literature search was performed on Jan 09, 2020 in PubMed using the search terms [(colorectal) and (oligomet*)]. Only papers in English, and in humans only were included. Papers were considered regardless of year of publication. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/apm-20-919).

The role of the MDT

Given the complexity of decision making, the manifold therapeutic strategies (*Figure 1*), and the sub-specialty expertise required to appropriately manage OCRC; treatment decisions require the input from a multi-disciplinary team (MDT) at tumor board meetings in specialist cancer centers (13). The ideal MDT includes colorectal, hepatobiliary, and thoracic surgeons, radiation and medical oncologists, pathologists, diagnostic and interventional radiologists, and cancer nurse specialists. The MDT's role includes registering patients in local and national cancer registries, ensuring thorough initial diagnostic work-up, guiding therapeutic decision making,

identifying patients as eligible for appropriate clinical trials, and evaluating treatment response (1,14). The first management decision is to deem whether patients have currently, potentially, or never resectable disease. If not resectable, then disease amenable to radical, ablative treatment strategies can be identified and the most suitable ablative strategy can be selected.

Imaging

Reliable and timely identification of OCRC with multimodal imaging is essential. Following treatment, imaging is used to assess disease response using the RECIST criteria (15) and subsequently, in conjunction with serum biomarkers [e.g., carcinogenic embryonic antigen (CEA)], to herald early recurrence of disease to allow further radical treatment and maximize the window of therapeutic opportunity.

Contrast enhanced CT is generally employed initially to image the whole body (chest, abdomen and pelvis +/– brain) because of its widespread availability and relatively low cost. Dual energy CT is being increasingly used as it can provide better image contrast (16). MRI is routinely used to image the liver and the brain as it offers superior soft tissue definition compared to CT. Whole body MRI is available in some centers and has advantages over standard imaging pathways (17). Fluorodeoxyglucose-positron emission tomography (FDG PET), in combination with CT, is recommended in expert consensus guidelines (18) to stage colorectal oligometastatic disease. It improves patient selection for hepatic resection and reduces the number of futile laparotomies (19,20). Its main advantage is in detecting extrahepatic lesions occult on CT alone (21).

Beyond the traditional uses of imaging described above, novel imaging biomarkers to guide management of OCRC have been extensively researched. Radiology can provide prognostic information such as the presence of vascular invasion, a fibrous capsule and details of the tumor-liver interface (16). Functional imaging, e.g., perfusion CT and dynamic contrast-enhanced MRI, can reveal information about biomarkers associated with tumor angiogenesis (22) that correlate with outcome (23,24). These techniques are not yet standardly used in the clinical setting.

Surgery

The widely agreed definition of resectable hepatic disease is where complete macroscopic resection is possible whilst maintaining sufficient functional liver volume (25). Specialist hepatic surgical input is essential to decide which patients are technically resectable and will benefit from liver resection in the long term. Oncological (or prognostic) criteria include the number of lesions, the presence of extra-hepatic disease and the time interval between the development of primary and secondary tumors, although there are no internationally agreed guidelines (1).

Hepatic resection is safe and effective in the management of colorectal of liver metastases (CRCLM) and 5-year survival rates of 30–50% can be expected. Despite its long-established efficacy, there are no randomized trials comparing it to other treatment modalities, yet it remains the gold standard treatment where technically and oncologically appropriate (26). However, serious peri-operative morbidity and a mortality rate of up to 9% secondary to hepatic failure are recognized and are a function of the extent of resection and the presence of coexisting liver disease (27). Possible complications include hemorrhage, bile leak, intrabdominal sepsis and cardiopulmonary dysfunction, and can occur in up to 21% of patients (27). Nonetheless, studies have shown that overall quality of life can be improved by hepatic resection for malignant tumors (28).

In 1999, Fong *et al.* reviewed the outcome data for 1,001 patients who underwent liver resection for colorectal metastases. The survival rate for these patients was 37% at 5 years and 22% at 10 years. The surgical mortality rate was low at less than 5%. A clinical risk score (CRS) was derived from these data to aid the appropriate selection of patients for liver resection. Clinical risk factors were defined as more than one tumor, carcinoembryonic antigen (CEA) >200 ng/mL, metastasis >5 cm, node positive primary, and a disease-free interval <12 months. Fong *et al.* concluded that patients with a CRS of 0–2 have a favorable outcome and hepatic resection should be considered. Patients with a CRS of 3–5 have a poorer prognosis and liver resection should be considered in combination with neoadjuvant or adjuvant therapy (29) (see below).

Minor hepatic resection involves no more than two Couinaud segments being removed and major resection is defined as the removal of three or more segments. Minor laparoscopic liver resection (LLR) is now common practice but remains in an assessment phase (30). Certain outcomes including postoperative complications and length of stay are superior for laparoscopic procedures compared to open procedures, and no clinical outcomes are thought to be inferior. Unfortunately, the quality of studies consensus is

Table 1 Summary of commonly used systemic agents in oligometastatic colorectal cancer

Agent	Mechanism of action	Typical adverse effects	Evidence in oligometastatic colorectal cancer
5-Fluourouracil	Pyrimidine analogue, irreversible inhibitor of thymidylate synthase	Alopecia, anorexia, nausea, vomiting, diarrhea. Beware DPD deficiency	Resectable liver metastases [EPOC (36), New EPOC (37)]
Folinic acid	Thymidylate synthase inhibitor (enhances effect of 5-Flourouracil)	Fever, anaphylactoid reaction, insomnia, gastrointestinal upset (all rare)	Resectable liver metastases [EPOC (36), New EPOC (37)]
Capecitabine	Orally administered pre-cursor of 5-Flourouracil	Asthenia, diarrhea, PPE	Resectable liver metastases [Gruenberger *et al.* (38)]
Oxaliplatin	Cytotoxic platinum agent	Neutropenia, thrombocytopenia, hepatic enzyme derangement, peripheral sensory neuropathy	Resectable liver metastases [EPOC (36), New EPOC (37)]
Irinotecan	Topoisomerase 1 inhibition	Acute cholinergic syndrome, anemia, neutropenia, severe diarrhea. UGT1A1*28 allele is associated with increased toxicity	Unresectable liver metastases [CELIM (39)]
Cetuximab	Chimeric monoclonal IgG_1 antibody to EGFR	Rash, diarrhea, hypomagnesemia, conjunctivitis	Unresectable liver metastases [CELIM (39), New EPOC (37)]
Bevacizumab	VEGF inhibitor	Asthenia, epistaxis, hypertension, proteinuria, impaired wound healing, proteinuria	Unresectable liver metastases [OLIVIA (40)]

Note both the CELIM and OLIVIA trials used the addition of the biological agents Cetuximab and Bevacizumab respectively in both arms and thus do not demonstrate additional benefit of these agents above cytotoxic chemotherapy in this context. DPD, dihydropyrimidine dehydrogenase; PPE, palmar-plantar erythrodysesthesia; VEGF, vascular endothelial growth factor.

based upon is generally low. Major LLR is not routinely performed laparoscopically. Available literature indicates that length of stay is superior to open procedures and other outcomes are not inferior, although the quality of studies is generally low and further evidence is required (30).

There is uncertainty on the sequence of surgery in synchronous OCRC. However, an international consensus panel on the management of synchronous CRCLM recommends that simultaneous surgery to the primary resection be performed if a minor resection is planned. If a major hepatic resection is required, then this should be performed as a separate procedure to the primary resection (31).

Pre-operative portal vein embolization (PVE) has been used to increase the feasibility of major hepatic resections by converting potentially unresectable lesions to resectable and reduce the risk of postoperative liver insufficiency or failure. PVE interrupts the portal vein flow to the region of the liver containing metastatic disease. This causes atrophy of the diseased liver and subsequent hypertrophy of healthy liver (i.e., the future liver remnant) via the release of hormones and growth factors. PVE is recommended when the future remnant liver is expected to be ≤20% in normal liver or ≤30% in diseased liver (32).

Pulmonary metastasectomy for colorectal metastases is well established and retrospective cohort studies have suggested that in highly selected patients, survival can be similar to patients undergoing hepatic resection for CRC (33). However, there is no randomized evidence to support this practice. The Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial was designed to investigate whether active monitoring of colorectal lung metastases results in similar OS to pulmonary metastasectomy. Unfortunately, the trial was stopped early due to poor recruitment and the statistical end points were not met. Long term survival has also been recorded following resection of CRC splenic and adrenal metastases (34), though there are only scanty data to support surgery in this context.

Systemic anti-cancer treatment

International guidelines state that in most cases of OCRC, systemic treatment remains the standard of care and should be considered as the initial treatment strategy regardless of local treatment modality (1,31,35). See *Table 1* and *Figure 2*.

In patients with favorable surgical and oncological characteristics, the role of peri-operative chemotherapy is less clear since the EPOC trial showed no difference in overall survival (OS) when peri-operative chemotherapy

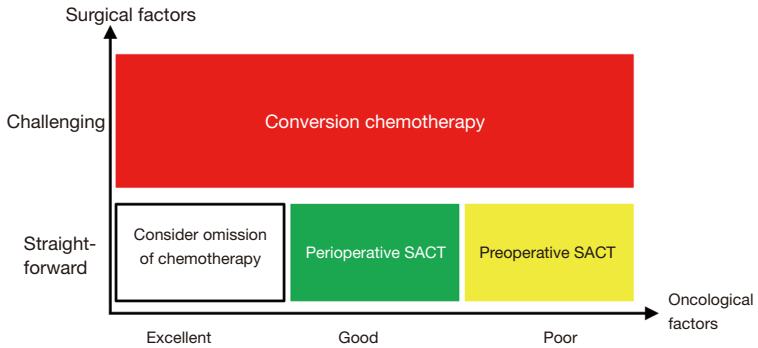

Figure 2 Chemotherapy strategy according to surgical/technical and oncological categorization of patients. Adapted from ESMO consensus guidelines for the management of patients with metastatic colorectal cancer (1).

was given to patients with initially resectable CRC liver metastases. This randomized controlled phase 3 study recruited 362 patients from 78 international hospitals with up to 4 liver metastases and assigned them (1:1) to 12 weeks of FOLFOX (Folinic acid, 5-Fluorouracil and Oxaliplatin) chemotherapy before and after surgery, or surgery alone. Progression-free survival was increased by 8.1% at 3 years with the addition of chemotherapy (36). Median OS was 61.3 months in the FOLFOX arm and 54.3 months in the surgery alone arm, though was not statistically significantly different. The New EPOC trial randomized patients with KRAS exon 2 wild-type resectable or suboptimally resectable CRC liver metastases between peri-operative chemotherapy with or without Cetuximab [a monoclonal antibody to EGFR with known benefit in KRAS wild type advanced CRC (41)] and found that progression-free survival was shortened with the addition of the antibody.

However, in patients with anything less than excellent prognostic features (including all patients presenting with synchronous disease), peri-operative chemotherapy is recommended. This is usually as FOLFOX, without additional biological agents. In patients with poor prognostic features, FOLFOX or FOLFOXIRI (Folinic acid, 5-Fluorouracil, Oxaliplatin and Irinotecan), with or without Bevacizumab, are recommended (1). For patients with unfavorable prognostic features, despite the lack of randomized evidence, consensus guidelines suggest adjuvant chemotherapy is warranted in patients who have not had previous chemotherapy for metastatic disease. FOLFOX or CAPOX (Capecitabine and Oxaliplatin) are recommended unless adjuvant oxaliplatin has recently been administered for locally advanced disease (1).

Conversion chemotherapy is used to challenge patients with unresectable disease with the expectation that the disease may become operable. Currently there do not exist good biomarkers to identify which patients with limited inoperable metastatic disease will most benefit from this strategy. It is estimated that 12.5% of patients with unresectable disease may become eligible for surgery with modern chemotherapy (42). These patients can expect to have survival rates similar to patients who have initially resectable disease (43). All metastatic patients should be imaged after 2 months of treatment, and again after a further 4 months of systemic treatment to ensure that any window for local treatment is not missed (1).

CELIM was a randomized phase 2 trial of 114 patients across 17 centers with non-resectable or >5 liver metastases. It compared Cetuximab treatment with FOLFOX or FOLFIRI (Folinic Acid, 5-Fluorouracil and Irinotecan). R0 (margin-negative) resection was subsequently achieved in 38% and 30% of patients in the two respective arms. The OLIVIA trial compared Bevacizumab with FOLFOX or FOLFOXORI in patients with unresectable liver metastases. The overall resection rate was 61% and 45% with R0 resection rates of 49% and 23% in the two respective arms. There are to date insufficient clinical data on the role of systemic treatment in OCRC in non-hepatic sites to reliably inform treatment decisions (44).

Stereotactic ablative body radiotherapy (SABR)

SABR enables a very high dose of radiotherapy to be delivered with high precision to a target. It is delivered in either a single or small number (<8) of fractions, and planned to ensure a very steep dose fall off from the target (*Table 2*). This enables a high biological equivalent

Table 2 Recommended SABR dose/fractionations to treat oligometastases

Site of metastases	Dose (Gy)/fractionation (#)
Liver	45 Gy/3#
	55–60 Gy/5#
	60 Gy/8#
Lung	54 Gy/3#
	55 Gy/5#
	60 Gy/8#
Adrenal	30–36 Gy/3#
Spine	24–27 Gy/3#
Bone	30–40 Gy/3#
Lymph node	30–40 Gy/3#
Re-irradiation	Up to 30 Gy (depending on previous dose)

Although timings vary between centers, individual fractions are generally delivered on alternate days (i.e., three fractions per week). Adapted from (45).

dose (BED) to be delivered to the target. SABR is highly conformal to the target volume which reduces normal tissue toxicity and therefore the risk of adverse effects (46). It has many advantages over surgical resection, being non-invasive, delivered as an outpatient, and well-tolerated, in even very infirm patients. It is routinely used in patients who are medically inoperable (47,48). In addition to treating lung and liver oligometastases, SABR is used to treat bone, lymph node and other soft tissue metastases (49).

There is some evidence that metastases from CRC have a relatively radioresistant phenotype and may require dose escalation to achieve adequate local control (50-53). However, several studies have demonstrated high rates of local control with SABR at current doses to OCRC. In 2018, Franzese *et al.* reviewed the outcomes of 437 oligometastases treated in 270 patients with colorectal cancer. 48.5% of metastases were pulmonary, 36.4% hepatic, 12.4% lymphatic and the remaining 2.7% were adrenal, bone or pancreatic. Local control rates of 95% at 1 year and 73% at 5 years were achieved. The OS rates were 88.5% and 37.2% at 1 and 5 years respectively. This study did not report treatment-related toxicity or patient reported quality of life (54). A systematic review of 18 studies encompassing 656 patients with colorectal liver oligometastases (1–2 metastases in almost all patients) published in 2018 demonstrated a local control rate of 67% and 59.3% at 1 and 2 years. The pooled OS rate was 67.18% and 56.5% at 1 year and 2 years respectively. Grade 1–2 liver toxicity was reported in 30.7% and grade 3–4 liver toxicity in 8.7%. Three treatment related deaths were reported (0.004%) (55).

In 2017, Kobiela *et al.* performed a systematic review into the treatment of CRC liver and lung oligometastases with SABR. Fifteen studies were included comprising 593 patients with 856 oligometastases. The hepatic local control rates ranged from 50–100% and 32–91% at 1 and 2 years, respectively. The pulmonary local control rates were 62–92% and 53–92% at 1 and 2 years. In the lung SABR studies, the rate of grade ≥3 toxicity was 0.7%. In the liver studies, the rate of grade ≥3 toxicities was 2.3% (56).

SABR-COMET, an international phase 2 study, was the first randomized trial to assess OS in patients with oligometastatic disease who received either SABR to all metastatic lesions or the palliative standard of care (57); 99 patients were enrolled at ten centers; 33 were randomly assigned to the control group and 66 to the SABR group. 18/99 patients had a primary colorectal cancer. Most patients had 1–3 metastases. Patients with breast and prostate cancer were over-represented in the treatment group accounting for 41% of patients receiving SABR, but only 21% of the control group. Nonetheless the addition of SABR increased the 5-year OS from 17.7% to 42.3%, (P=0.006) (58). A 4.5% treatment related mortality rate was observed in the SABR arm due to deaths from radiation pneumonitis (n=1), pulmonary abscess (n=1), and subdural hemorrhage after surgery to repair a SABR-related perforated gastric ulcer (n=1).

Quality of Life (QoL) was measured using a general tool, FACT-G (59) which includes 4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. A 5-point decline in the total FACT-G scale, or a 2-point decline on a subscale, is generally considered a clinically meaningful change. In the whole cohort, QoL declined, though minimally, over time after randomization as a result of decline in physical and functional subscales. There were no reported declines in social and emotional subscales. Comparison between arms showed no differences in QoL between the SABR and SOC arms in total or subscale scores (60).

Across all studies, patients with non-lung metastases, tumors larger than 30 mm, and those heavily pre-treated with systemic therapies generally have worse OS after SABR. A lower BED to the planned target volume is associated with higher rates of local failure after treatment

with SABR (46,49).

There are technical challenges with delivering SABR, particularly due to organ motion and visualizing oligometastases on cone-beam CT (CBCT) scans prior and during treatment. With recent improvements in CBCT and the advent of the MR-linac, which enables superior soft tissue visualization and is able to track the target or a surrogate marker in real time during treatment, these difficulties may be reduced or overcome (61). SABR-COMET hints at the promise of ablative radiotherapy in oligometastatic disease but larger phase 3 trials are underway to establish its survival benefit, safety, and the limits of metastatic burden that warrant radical treatment (62). Ideally, trials looking specifically at the use of SABR in OCRC are required in order to establish the radiosensitivity of colorectal metastases and the adjacent organs at risk.

Brachytherapy

CT-guided brachytherapy has demonstrated safety and efficacy in the treatment of non-operable colorectal liver metastases. Brachytherapy catheters are inserted into the liver metastases under fluoroscopic CT guidance. This technique enables the delivery of high dose rate interstitial irradiation and has the benefit over SABR that it is independent of patient and organ motion. It is possible to treat lesions over 5 cm in size and lesions close to at risk structures that could not be treated with radiofrequency ablation (63). In a single center study in Germany assessing CT-guided brachytherapy to treat 199 colorectal liver metastases with a median follow up of 15.2 months, no local recurrences were observed if a minimum dose to the target exceeded 24 Gy (64).

Thermal ablation

Thermal ablation is a widely accepted treatment option for oligometastases within the liver and lung. The different modalities include radiofrequency ablation (RFA), microwave ablation, cryoablation and electroporation. Each technique involves insertion of a needle applicator directly into a target tumor under image guidance. RFA and microwave ablation involve focal administration of extreme heat (70 to >100 ℃) to destroy malignant tissue. Cryoablation relies on controlled, local freezing to induce focal cell death (65). Electroporation involves the delivery of unipolar electrical pulses that increase tumor cell transmembrane potential resulting in cell destruction (66,67).

RFA is the most commonly used and reported of the thermal ablative techniques. Thermal ablation is a parenchymal-sparing strategy that can be used either alone, or in combination with resection, to maximize residual healthy tissue. In 2013 a consensus paper reported a mean 31% 5-year survival post-ablation in selected patients with a total sample size of 1,613 patients, mostly with unresectable CRCLM (68).

The CLOCC trial (69) randomized patients with unresectable liver-only metastatic colorectal carcinoma to either systemic treatment alone or in combination with RFA with or without surgery. One hundred and nineteen patients were recruited, and though initial analysis showed no significant difference in OS, long-term follow up showed a significant increase in 8-year OS from 8.9% to 35.9% (HR 0.58). Progression-free survival benefit was also evident with improvement from 10.6% to 27.6% at 3 years. This phase 2 trial provided the first randomized evidence for OS benefit from treatment of unresectable liver metastases from colorectal cancer with RFA.

There is evidence that liver metastases >3 cm have poorer outcomes (70) with RFA. Likewise, a larger number of metastases has been found repeatedly to be a poor prognostic factor (71,72). Gillams *et al.* recommend treating five or fewer lesions routinely, and up to nine tumors in selected cases (68). The location of the tumor within the liver can also affect the safety and efficacy of RFA. Tumors immediately adjacent to larger blood vessels (≥3 mm diameter) have an increased incomplete treatment rate due to the heat-sink effect (unwanted cooling by adjacent hepatic blood flow), reported at 23% in a case series of 227 RFA treatments (73). Thermal ablation also carries the risk of injury to vulnerable neighboring structures such as the bile duct or colon, therefore it may not be the preferential treatment modality for tumors in these locations (68).

Percutaneous RFA rarely causes major complications (<2.5%) and mortality is rare (68). In the CLOCC trial, the authors found that QoL was transiently impaired following RFA but recovered back to baseline by 8 weeks (74). Evrard *et al.* found that QoL appeared to improve as treatment progressed (75).

While there have been no randomized comparisons of surgery versus thermal ablation in CRC lung metastases, survival and local control outcomes appear to be similar. Schlijper *et al.* (76) conducted a meta-analysis of 27 studies of the use of RFA or surgery in lung metastases secondary

to colorectal cancer, and found 2- and 5-year survival rates of 64–73% and 34.9–45% for RFA, and 64–88% and 29–71.2% for surgery, respectively. The RAPTURE study was a prospective multicenter non-randomized study and demonstrated that patients with colorectal lung metastases treated with RFA had 1- and 2-year survival rates of 89% and 66%, respectively. It also showed that pulmonary function is preserved after RFA for primary or secondary lung cancer (77).

Extrapulmonary disease is known to be a poor prognostic factor for patients with pulmonary metastases from any primary (78-80). Pulmonary RFA carries a low rate of significant morbidity but pneumothorax is the commonest complication. It is reported at a rate between 16–67% although grade 3 or greater toxicity occurs only rarely at 0–1% (78,79,81). In the RAPTURE study the authors found no change in QoL scores in the 12 months following RFA (77). Furthermore, hospital stay is short for the majority (78).

There is growing interest in microwave ablation, which may have some physical advantages over RFA (82). Local hepatic tumor progression rates have been reported between 9.6–14.5% (83), although local tumor recurrence was found to be significantly increased compared to surgery (risk ratio 2.49, P=0.016) despite greater safety (84). Yuan *et al.* analyzed 53 studies comparing RFA and microwave ablation for primary and secondary lung cancer and suggested that median OS was inferior for microwave than for RFA in pulmonary metastases. Cryosurgery and electroporation are much less commonly reported.

Transcatheter arterial chemo-embolization (TACE)

The liver's unique vascular architecture can be exploited in the treatment of malignant liver disease. The hepatic portal vein is responsible for 75% of blood flow to the liver (85), although primary and secondary liver tumor angiogenesis relies almost exclusively on the hepatic arterial system (86). Since the 1960s, surgical ligation of the hepatic artery (87) was known to produce objective clinical responses in liver metastases. By the 1970s, this had been combined with placement of an infusion catheter distal to the ligated artery to allow chemotherapy to be delivered locally via the hepatic arterial system for up to 5 weeks post-operatively to enhance response (88).

These principles have evolved and TACE now has an excellent evidence base in hepatocellular carcinoma, and is used in up to 20% of patients with the disease (89). It has also been utilized in CRC liver disease. TACE is usually performed by an interventional radiologist via femoral artery catheterization under local anaesthetic. Using the Seldinger technique, the catheter is guided into the hepatic artery and chemotherapeutic embolization material is injected down the catheter before the latter is removed. The patient remains on bed-rest until the following day and can then be discharged home in the absence of any complications. Post-embolization syndrome (PES) is a well-recognized inflammatory complication of TACE, characterized by fever, right upper quadrant pain and nausea and vomiting, and occurs in up to half of patients (90).

There are two drug carrier platforms used to deliver TACE to the hepatic arterial circulation. Lipiodol-based (conventional) delivery is comprised of a radio-opaque emulsion of oil and water derived from poppy seed oil admixed with a chemotherapeutic agent. To date, this platform has demonstrated benefit only in primary liver tumors (91). Drug-eluting microspheres (DEMs, also known as drug-eluting beads) were introduced in 2006. DEMs can load a variety of drugs via ion-exchange or absorption and are infused directly into tumors to release drugs over a sustained period of time to minimize systemic drug delivery (92). They significantly reduce the rate (odds ratio 0.44) of PES compared to conventional TACE delivery systems (89). The best studied use of this platform in metastatic CRC is DEBIRI; drug eluting beads loaded with Irinotecan (93).

Martin *et al.* (94) randomly assigned 60 chemotherapy-naive patients with liver-dominant metastases from CRC that were not amenable to a curative paradigm, in a phase 2 trial. The treatment arms were FOLFOX and Bevacizumab, with and without 2 cycles of DEBIRI. Grade 3/4 adverse events were similar in both arms and both arms received similar number of chemotherapy cycles. Overall response rates were greater in the DEBIRI treatment arm using modified RECIST (94) criteria (though not with RECIST 1.1). At 6 months, there was a non-significant improvement in overall response in the DEBIRI treatment arm.

Fiorentini *et al.* (95) reported a phase 3, multi-institutional study of 74 patients randomized to DEBIRI (2 cycles) or FOLFIRI (8 cycles). All patients had unresectable CRCLM occupying <50% of the liver parenchyma and had no other sites of disease. All patients had received at least 2 lines of prior systemic therapy. Median survival was 22 and 15 months for DEBIRI and FOLFIRI respectively, though statistical significance was not reported. Toxicity was generally more favorable in the DEBIRI than the FOLFIRI

arm, however grade 2/3 pain and fever was significantly higher in the DEBIRI arm. Quality of life assessment showed improved physical function at 1 and 3 months and that the decline in quality of life was slower with the local treatment. A recent review by Gill *et al.* (4) concludes that these two studies do not provide sufficient evidence for DEBIRI. For now, patients being treated with OCRC should be considered for other treatment modalities.

Selective internal radiotherapy

Radioembolization or Selective Internal Radiotherapy (SIRT) uses glass or resin microspheres with a diameter of 20–35 μm. The beads release the β-emitter ^{90}Yttrium (^{90}Y), which has a half-life of 64 hours and has a low linear energy transfer to target liver metastases. Up to 80 million resin microspheres or 2 million glass microspheres are injected into the appropriate hepatic artery or one of its main branches, equivalent to approximately 1–3 GBq of radiation dose. The procedure is similar to TACE described above but requires a preliminary procedure 2–3 weeks prior to the treatment to identify and embolize vessels which may shunt arterial blood from liver to lung or upper gastro-intestinal tissue (96).

The FOXFIRE, SIRFLOX and FOXFIRE-Global randomized, phase 3 clinical trials were designed to study whether the addition of SIRT to FOLFOX alone would improve OS in first-line treatment for MCRC. Patient eligibility was similar across the 3 trials and criteria included histologically confirmed CRC with liver-only or liver-dominant metastases in patients with a WHO performance status of 0 or 1, and limited extra-hepatic disease. 1,103 patients were enrolled. Median survival was 22.6 in the SIRT/FOLFOX arm and 23.3 months in the FOLFOX alone arm (P=0.61). Progression-free survival was also not statistically significantly different between the two arms. The cumulative incidence of first progression in the liver was lower in the FOLFOX plus SIRT group than the FOLFOX alone group, demonstrating some local efficacy with SIRT, however the rates of subsequent hepatic resection were not significantly different across the two treatment arms. The odds of grade 3 or worse adverse event were higher in SIRT/FOLFOX arm than in the FOLFOX alone arm (odds ratio 1.42); 11 (1%) of 844 total deaths were treatment related; 8 of these were in the SIRT/FOLFOX group. Three deaths were due to radiation-induced liver disease, two due to complications of surgery, one due to liver failure, one due to drug-induced pneumonitis and one due to off-target delivery of the microspheres. Two further deaths were secondary to long term liver toxicity. EQ-5D-3L quality of life scores were not significantly different across the two arms of treatment (97).

As with TACE, unless specific sub-populations of patients with OCRC can be identified as benefitting from arterial embolization treatments, or these treatment paradigms can be further refined to improve efficacy, there is as yet no standard role for SIRT if other treatment modalities are available.

Discussion

While surgery remains the gold standard in liver-limited, technically resectable, favorable-prognosis disease, there remain opportunities to refine management of more challenging treatment scenarios. High quality, randomized data is required to ensure patients are only offered treatments supported by good evidence.

Improved detection of occult metastatic disease could be achieved by advances in imaging at diagnosis, and the development of biochemical tests, including circulating free tumor DNA or circulating tumor cells (98) to more precisely define which patients are likely to benefit from radical treatment. Similarly, earlier detection of disease recurrence widens the window of opportunity for surgical or ablative re-treatment. Further improvement of ablative technologies would allow patients who do not want, or are not fit for surgery, to receive optimal treatment. Especially in this patient cohort, where the chance of long-term cure is modest, minimizing morbidity and maximizing quality of life is essential. Greater understanding of the radiobiological tolerance of normal liver (99), improved motion management strategies, for instance with MR-based radiotherapy (100), and the clinical development of novel technology such as intensity modulated proton therapy, could all help build on the clinical success of SABR in this context (101). As well as refining the individual technologies, a greater knowledge of how to exploit their combination (for example, the synergy of immunotherapy with SABR) is required (102).

Conclusions

In order to continue to improve outcomes in OCRC, investment in basic, translational and clinical studies is required. It is important that at all stages of research it is

recognized that colon cancer has a distinct biology from other tumor types and that colon cancer itself is an umbrella term comprising a group of molecular genotypes that have their own clinical characteristics (103,104). In the future, biological tests may help to select patients with OCRC most likely to benefit from radical treatment. Furthermore, validated quality of life assessments, ideally in the form of patient-reported outcomes (105), should be built into future clinical trials to demonstrate the value for patients. As our treatment strategies become more complex, the patients' needs must remain the priority for the skilled professionals of the MDT, and our evolving technologies must continue to serve their welfare.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Simon Lo, Michael Milano, Tithi Biswas, Charles Simone) for the series "Oligometastasis-Fallacy or Real Deal?" published in *Annals of Palliative Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the NARRATIVE REVIEW reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-919

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-919). The series "Oligometastasis-Fallacy or Real Deal?" was commissioned by the editorial office without any funding or sponsorship. RAS is an employee of Varian. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Chandy ETJ, Saxby HJ, Pang JW, Sharma RA. The multidisciplinary management of oligometastases from colorectal cancer: a narrative review. Ann Palliat Med 2021;10(5):5988-6001. doi: 10.21037/apm-20-919

