Current Colorectal Cancer Reports (2022) 18:45–53
https://doi.org/10.1007/s11888-022-00477-y

RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (PP LEE AND AC RALDOW, SECTION EDITORS)

Local Therapies for Colorectal Cancer Oligometastases to the Lung

Eric M. Chung[1] · Jun Gong[2] · Karen Zaghiyan[3] · Mitchell Kamrava[1] · Katelyn M. Atkins[1]

Accepted: 13 April 2022 / Published online: 10 June 2022

Abstract

Purpose of Review There is a growing consensus that oligometastatic disease-directed treatment is associated with improved oncologic outcomes in patients with colorectal cancer; however,the optimal local management of pulmonary oligometastases remains controversial.

Recent Findings While surgery has traditionally been recognized as the gold standard local treatment for pulmonary metastases, there is no prospective data supporting a significant benefit of pulmonary metastasectomy (PME) compared to other local treatment modalities, such as stereotactic ablative radiotherapy (SABR) or radiofrequency ablation (RFA). There has been increasing utilization of SABR for pulmonary oligometastases—particularly for patients who are not candidates for PME, with comparable survival, local control, and toxicity observed.

Summary There remains an unmet need for high-quality prospective data to optimally guide patient selection for local treatment modalities of pulmonary oligometastases. Given the evolving complexity of oligometastatic disease states and multitude of local and systemic treatment factors, multidisciplinary clinical discussion is essential.

Keywords Colorectal cancer · Oligometastasis · SABR · SBRT · Pulmonary metastasectomy · RFA

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with 1.8 million diagnoses in 2018 alone [1]. At the time of diagnosis, nearly one fourth of patients with CRC harbor metastatic disease, while more than half will develop metastases over their lifetime—most commonly to the liver and lung [2, 3]. Notably, 10–15% of all CRC patients will develop pulmonary metastases, while CRC remains the second most common cause of pulmonary secondary tumors overall [4, 5], highlighting the clinical need for effective therapeutic strategies in this setting.

Historically, the standard treatment for metastatic disease has been systemic therapy [6]. However, CRC often presents with solitary metastases or oligometastatic disease, and there is now growing evidence to support aggressive local management with improvement in oncological outcomes in patients with these disease states [7–10]. Further, compared to other distant metastatic sites, lung metastases from CRC may be associated with improved survival [11].

While complete surgical excision (pulmonary metastasectomy (PME)) has generally been acknowledged as a standard upfront treatment for patients with oligometastatic disease [12], more recently, non-invasive techniques have emerged as safe and efficacious strategies for patients with pulmonary oligometastases, including stereotactic body radiotherapy (SBRT)—also known as stereotactic ablative radiotherapy (SABR)—and radiofrequency ablation (RFA) [13, 14], which have been gaining popularity in use. In this review, we will discuss local management options for CRC with pulmonary oligometastases, including a review of recent literature on PME, local ablative techniques including SABR

This article is part of the Topical Collection on *Radiation Therapy and Radiation Therapy Innovations in Colorectal Cancer*

✉ Katelyn M. Atkins
Katelyn.atkins@cshs.org

[1] Department of Radiation Oncology, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA

[2] Department of Medical Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

[3] Division of Colon and Rectal Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA

and RFA, as well as the role of perioperative (or periablative) chemotherapy and the sequence of therapy.

Classification of Metastases

Classically, lung metastases have been classified as synchronous (discovered during the initial diagnostic work-up) or metachronous (discovered after diagnostic examinations). Further, lung metastases can be defined as "isolated" or "non-isolated," depending on whether it is accompanied by additional extra-pulmonary metastases. Notably, one fourth of patients present initially with synchronous metastases, while 25% subsequently develop metachronous metastases, and only 2% present with isolated lung metastases [4]. "Initial" versus "non-initial" lung metastasis refers to the sequence of metastatic spread where the lungs are the first site of metastasis—with initial accounting for 74.4% of all CRC lung metastases [15]. Of these patients, 37.7–44.5% have isolated lung metastases, of which only 21.1–32.5% are PME candidates [16].

In current practice, we often assess whether disease is "oligometastatic." Notably, oligometastatic disease was first described by Hellman and Weichselbaum as a distinct cancer clinical state between locoregional and widespread metastatic disease—which has classically been defined as fewer than five lesions in three or less metastatic sites [17]. More recently, European Society for Radiotherapy and Oncology (ESTRO) and American Society for Radiation Oncology (ASTRO) consensus guidelines have been introduced that define oligometastatic disease as 1–5 metastatic lesions, a controlled primary tumor being optional, where all metastatic sites can safely be treated with curative intent metastasis-directed therapy. The authors further acknowledge that there is no biological evidence to support the maximum number or size of metastases to confer clinical benefit with metastasis-directed therapy, and there was consensus that the maximum number of lesions that can safely be treated can vary on a case-by-case basis, with no specific limitation number of lesions [18•]. Moreover, ESTRO and the European Organisation for Research and Treatment of Cancer (EORTC) further nuanced this nomenclature and classification to propose several oligometastatic disease states in a consensus statement. The first stratification (induced vs genuine metastatic disease) is based on the presence or absence of a history of polymetastatic disease. Genuine oligometastatic disease was further sub-classified into repeat and de-novo oligometastatic disease, while de novo could be further divided into synchronous and metachronous states. Lastly, oligorecurrence, oligoprogresssion, and oligoresistance was defined based on whether oligometastatic disease was diagnosed during a treatment-free interval, during active systemic therapy, or whether radiographically progressing [19•]. Importantly, this classification model awaits prospective validation and assessment before routine clinical implementation.

Pulmonary Metastectomy

Surgery has traditionally been recognized as the most effective local treatment for pulmonary metastases and is an established treatment option for metastatic CRC. Patients undergoing PME have reported 5-year survival rates ranging from 40 to 68% [20]—however, this data is largely based on retrospective case series. Moreover, this improvement in survival is commonly attributed to advances in surgical technique, increased availability of pulmonary metastectomy, multimodality treatment strategies, and the introduction of novel ablative therapies such as SABR and radiofrequency ablation [21–24]. Generally, the first choice for resection of lung metastases is a sublobar resection, such as a wedge resection or segmental resection of the lung. Additionally, several criteria should be met before patients are considered for this treatment: a complete (R0) resection is technically feasible, patients can functionally tolerate pulmonary resection, the primary tumor is controlled, and the absence of other extra-thoracic metastases (except for resectable liver metastases) [25–27].

It has been reported that postoperative mortality rates for PME are between 0 and 2% and overall complication rates range between 0 and 23%, with the most common postoperative complications being infection, pneumonia, air leakage, and atelectasis [28–30]. Given this, it is important to determine which patients will benefit the most from surgery. Several risk factors have been identified that predict for poor survival following PME: short disease-free interval between colorectal cancer and lung metastases, multiple (> 2 or more) lung metastases, thoracic mediastinal/hilar lymph node involvement, and elevated pre-operative CEA level [31]. These criteria should be considered pre-operatively and discussed in a multidisciplinary setting to assess if a patient is a good candidate for PME.

While retrospective studies have demonstrated that PME is associated with longer survival compared to chemotherapy alone, with reported 5-year survival rates ranging from 41 to 68% versus 20% [20, 32]—to date, there have been no prospective data to support this theory. Moreover, several systematic reviews and meta-analyses have failed to demonstrate the effectiveness of PME on oncological outcomes [33, 34]. In a systematic review that included 50 studies published in 2010, the authors were unable to identify any meaningful conclusions of the effectiveness of surgical metastectomy, mainly due to the poor quality of evidence identified. Indeed, all studies were single arm with no controlled trials. Similarly, another 2013 systematic review of

25 studies was also unable to confirm the benefit of surgical resection, also due to lack of high-quality evidence [35].

To address this issue, the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial was performed. This trial was a prospective multicenter study that randomized 65 patients between 2010 and 2016 to surgical metastasectomy or active clinical monitoring. However, the study ended early due to poor accrual and was underpowered. Notably, there was no significant difference in 5-year survival (38% vs. 29% respectively, HR 0.82, 95% CI: 0.43–1.56) in patients treated with metastasectomy or active clinical monitoring [36•]. The PulMiCC trial published an update in 2020, including 93 patients and reporting similar results with median survival following metastasectomy of 3.5 (95% CI: 3.1–6.6) years compared with 3.8 (95% CI: 3.1–4.6) years for controls with hazard ratio for death within 5 years of 0.93 (95% CI: 0.56–1.56) [37•]. Thus, the benefit of PME remains unclear in the absence of an adequately powered randomized trial. Additionally, the long survival of patients treated with active monitoring in this study suggests that CRC survival is indeed multifactorial and further investigations are needed to determine which patients with oligometastatic disease will benefit the most from aggressive local therapy [38].

Stereotactic Ablative Radiotherapy

Over the last decade, the use of stereotactic ablative radiotherapy (SABR) in patients with pulmonary metastases has been shown to be safe, effective [13, 14], and associated with improved survival and oncological outcomes [7–9]. As a result, there has been increasing utilization of SABR as a local treatment modality for pulmonary oligometastases [39]—particularly for patients who are not candidates for metastasectomy due to tumor location and/or tumor size. Compared to surgery, SABR has several advantages, including convenience, lower morbidity, good immediate tolerance, ability to treat central lesions, and no need for general anesthesia [40].

In a 2018 meta-analysis of 15 studies and 686 pulmonary metastases treated with SABR, local control (LC), which was defined as absence of growth within the irradiated site, was 81% at 1 year, 66% at 2 years, and 60% at 3 years. Three-year overall survival and progression-free survival rates were 52% and 13%, respectively. Radiation doses ranged from 30 to 60 Gy delivered in 1–8 fractions. Furthermore, there were no periprocedural mortalities and low incidence of severe toxicities with grade 3 toxicities ranging from 1.5 to 2.3%. The most common morbidities included fatigue, chest pain, and pneumonitis [41•].

There is now growing evidence that pulmonary metastases with colorectal origin have lower local control when treated with SABR compared to other tumor histologies [42, 43]. In the same 2018 meta-analysis, they reported LC was significantly worse for CRC pulmonary metastases compared to non-colorectal histologies (HR, 2.93; 95% confidence interval (CI), 1.93–4.45; $P < 0.001$). Additionally, gene expression analyses suggest that colorectal pulmonary metastases have intrinsic radioresistance and increased doses of SABR may be needed to achieve LC [44, 45]. However, despite worse LC, OS for CRC pulmonary metastases was higher compared to non-colorectal histologies [41•].

Several prognostic factors have been identified that help predict outcomes following SBRT for pulmonary metastases. Tanadini-Lang et al. developed a nomogram that found that survival after SBRT was influenced by size of the pulmonary lesion, whether synchronous metastases were present, and whether the primary lesion was controlled [46]. Other studies have also demonstrated the lesion size and the presence of synchronous metastases are important prognostic factors. Additional factors that predict for higher local recurrence following SABR include increased number of lesions and lower SABR dosage [47–49]. In fact, multiple studies have demonstrated that higher SABR dose (including biological effective dose (BED)) is associated with improved oncologic outcomes.

A 2019 single-institution retrospective review of 118 patients with 202 pulmonary oligometastases treated with SABR demonstrated 3- and 5-year LC rates of 81% and 77%, with 3- and 5-year OS rates of 55% and 36%, respectively. Furthermore, the authors reported that higher SABR dose ($BED_{10} > 100$ Gy vs. $BED_{10} < 100$ Gy) was associated with improved LC and OS—5-year LC 84% vs. 57% and 5-year OS 38% vs. 25%, respectively [50•]. Consistent with the above series, the impact of BED has been observed at the meta-analysis and multi-institutional level. A 2018 meta-analysis of 8 studies including 478 patients found improved LC with $BED_{10} > 100$ Gy (OR 0.16, 95% CI: 0.09–0.28, $P < 0.001$) [51•]. Additionally, in one of the largest series to date, a 2020 multicenter retrospective review of 330 patients with 371 pulmonary oligometastases from CRC treated with SABR, 3-year LC, 3-year PFS, and 3-year OS were 64.9%, 34.9%, and 63.4%, respectively. In this study, Yamamoto et al. stratified SABR dose into three subgroups, $BED_{10} < 106$ Gy, BED_{10} 106–150 Gy, and $BED_{10} > 150$ Gy, with 3-year LC of 57.0%, 65.3%, and 77.7%, respectively. In their MVA, $BED_{10} \geq 115$ Gy was associated with improved LC (HR: 0.55, 95% CI: 0.30–0.98, $P = 0.04$), RFS (HR: 0.67, 95% CI: 0.47–0.97, $P = 0.03$, and OS (HR: 0.48, 95% CI: 0.27–0.86), $P = 0.01$ [52•]. Furthermore, limited toxicity was seen even at these escalated doses with ≥ grade 2 and ≥ grade 3 toxicities of 10% and 1.5%, respectively.

Importantly, most data in the setting of SABR for CRC pulmonary metastases are retrospective series except for a few phase II studies investigating lung oligometastases [53, 54]. Notably, the 2020 the Stereotactic Ablative

Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers (SABR-COMET) multicenter phase II study was the first randomized trial to assess SABR for oligometastatic disease. In this trial, 18/99 patients had CRC primary tumors and with 89/191 metastatic lesions arising from the lung. The trial found an increase in median OS from 28 months with standard of care systemic therapy to 41 months with standard of care with SABR to all metastatic lesions [55].

Additionally, until recently, there has been no high-level evidence or consensus on the optimal dose and fractionation schedule for SABR in oligometastatic disease. The recently published Single-Fraction vs. Multifraction Stereotactic Ablative Body Radiotherapy for Pulmonary Oligometastases (SAFRON II) tested whether single-fraction or multifraction SABR is more effective for the treatment of patients with pulmonary oligometastases from any non-hematologic tumor located away from the central airways. This was a phase II trial that randomized 87 patients (47% with CRC primary) with 133 pulmonary oligometastases to receive a single fraction of 28 Gy or 4 fractions of 12 Gy to each oligometastasis. There was no significant difference observed between the arms for freedom-from local failure at 1 year (95% vs 93%) and 3 years (80% vs 64%), OS at 1 year (93% vs 95%) and 3 years (67% vs 81%), or grade 3 or higher treatment-related adverse events [56•].

Evidence for PME vs SABR

Systematic reviews, consensus statements, and clinical practice guidelines have supported pulmonary PME as the first-choice treatment for patients with CRC pulmonary metastases as PME has been associated with improvements in DFS and OS [20, 32, 33]. However, most of this evidence is based on retrospective and non-randomized data. By contrast, SABR has been traditionally reserved for patients with CRC and pulmonary metastases who are not candidates for surgical treatment and is considered an effective and less invasive alternative to surgery. However, there is now increasing evidence that SABR can provide similar outcomes to surgery, with high local control and comparable toxicity profiles.

Studies comparing PME vs. SABR are rare, and largely retrospective, single-institution data subject to selection bias—as patients treated with SABR often represent older patients with poorer performance status, reduced pulmonary function, increased comorbidities, and higher metastatic burdens compared to patients who undergo surgery [57]. In Widder et al., the authors compared metastasectomy vs. SABR for 110 patients with CRC pulmonary metastases [40]. Surgery was the treatment of choice and patients with favorable prognoses were offered metastasectomy, while SABR was reserved for those who were not offered or declined surgery. Despite this, OS was comparable between the two groups with 1-, 3-, and 5-year OS rates of 87%, 62%, and 41% for metastasectomy, and 98%, 60%, and 49% for SABR, respectively. In another single-institution retrospective review published in 2016, 170 patients with CRC pulmonary oligometastases, the 2-year OS was 82% following surgery and 77% following SBRT [57].

More recently, in a 2018 retrospective review of 51 patients with 1–3 pulmonary metastases who underwent PME vs SABR, there was no difference in survival with 1-year OS and 2-year OS of 95.0 vs 79.5% and 81.8 vs 68.2% for PME and SABR, respectively [58•]. PFS was significantly longer with PME compared to SABR (2-year PFS 46.0% vs 11.9%). However, this PFS improvement has several caveats: the median tumor size in the SABR group was double the PME group (2.5 vs 1.25 cm) and patents with synchronous metastases (known negative prognostic factor) were more likely to be treated with SABR. Furthermore, the PME group was more likely to receive adjuvant systemic treatment. Lastly, there was no difference in local control between the two groups with 1-year LC and 2-year LC of 96.6% vs 83.5% and 91.5% vs 75.2% for PME and SABR, respectively. On multivariate analysis, tumor size was the most significant prognostic factor.

Radiofrequency Ablation

Radiofrequency ablation (RFA) has recently emerged as a non-surgical strategy for the management of pulmonary metastases [59]. RFA is a minimally invasive procedure that involves a high-frequency electric current delivered through an electrode that heats the area of the lung parenchyma and subsequently causes focal necrosis of tumor tissue. The advantages of RFA are its minimally invasive nature with exceedingly low mortality rate of 0–0.4%. However, complications are not uncommon—with the most common toxicities including pneumothorax (33–66% of all cases) [60]. Less commonly, bleeding, hemoptysis, pleural effusion, and infection can occur, although grade 3 or greater toxicities are exceedingly rare at 0–1% [61]. Tumor size is a limitation for RFA with data suggesting that local control is worse tumors > 3 cm. In a single-institution retrospective series of 153 patients, 2-year LC for tumors ≤ 3 cm and > 3 cm was 64% vs 25%, respectively [62]. In another retrospective multicenter study of 87 patients, local recurrence was 11.5% at 1 year, 18.3% at 2 years, and 21.1% at 3 years [63]. Tumor size was the only significant factor associated with a local failure rate, with tumors > 2 cm in size being approximately 3 times more likely to recur.

While no randomized data exists to compare surgery or SABR to RFA for CRC lung metastases, survival, and local control appear comparable. In one of the largest series to date, a 2015 retrospective review of 566 patients who

underwent RFA from 2002 to 2010, 3-year OS was 67.7% and the 5-year OS was 51.5%. Max tumor size was 4 cm and the median tumor diameter was 1.5 cm, with 70% of patients with tumors ≤ 2 cm. Local tumor progression rates were 11% at 4 years. Additionally, the authors noted that tumor size > 2 cm was associated with worse OS (HR 2.10, $P = 0.003$). Postprocedural complications were common, with pneumothorax occurring in 67% of cases, of which 50% required chest tube placement [59].

Recently, a prospective multicenter study published in 2020 that included 70 patients with 100 lesions all < 3 cm, treated with RFA from 2008 to 2014 in Japan, reported a 3-year OS of 84% and 3-year local progression of 9%. The 30-day mortality was 1.4%, where 1 of 88 patients died due to a large hemothorax. Pneumothorax was common (43%), of which 60% required treatment with chest tube placement. Factors found to be associated with worse survival included rectal rather than colon location, positive CEA, and absence of previous chemotherapy [64•]. Although these 3-year results are promising and comparable to PME and SABR, the data regarding RFA is largely limited to retrospective review with limited randomized controlled trials.

Role of Perioperative Chemotherapy

International and National Comprehensive Cancer Network NCCN guidelines state that in patients with CRC with resectable oligometastases, systemic therapy remains standard of care and should be considered as the initial treatment strategy regardless of local treatment modality and favor a course of systemic therapy totaling a perioperative treatment time of 6 months [65] that can occur before, between, or after resections. Significant improvements in survival outcomes have been demonstrated with perioperative chemotherapy in CRC patients receiving PME via meta-analyses [66]. If PME occurs first, adjuvant chemotherapy for 6 months (fluoropyrimidine and oxaliplatin) confers a survival advantage as well after resection of metastases from CRC [67]. The advantages of such an approach with perioperative chemotherapy is multifold: to facilitate earlier treatment of micrometastatic disease, to allow assessment of disease biology or responsiveness to therapy for prognostication, and to avoid local therapy in those with early disease progression. Specifically, it can help determine whether the disease reflects an induced oligometastatic state vs oligo-progressive or oligo-resistant disease [19•]. The choice of regimens has included both doublet combinations of either fluoropyrimidine and oxaliplatin or irinotecan, but in select patients, a triplet of all three (FOLFOXIRI) is acceptable—particularly in those with permissible performance status and for whom a more aggressive tumor response would be beneficial [65].

Although the evidence for systemic chemotherapy in CRC patients with lung metastases has historically reflected patients undergoing PME, evidence has been accumulating to support the benefit of systemic chemotherapy with non-surgical locoregional therapies such as SABR and RFA [68•]. Here, in patients with oligometastases treated with standard combination cytotoxic therapy, patients who received locoregional therapy with curative intent during first-line chemotherapy reported longer PFS (23.9 versus 10.6 months; HR: 0.41, 95% CI: 0.31–0.53, $P < 0.001$) and OS (52.6 versus 28.0 months; HR: 0.34, 95% CI: 0.24–0.48; $P < 0.001$) compared with those who did not. Additionally, patients with oligometastatic CRC and low tumor burden who received non-curative intent locoregional therapy during first-line chemotherapy also experienced longer OS.

Importantly, however, it remains unclear whether local ablative therapy should be offered upfront proceeding systemic therapy or as consolidative therapy following initial systemic therapy. Upfront local therapy may prevent further metastatic seeding from initial oligometastatic sites. However, local consolidative therapy allows for response and disease biology assessment before consideration of additional localized treatment, but can be more challenging to deliver if there is significant response to systemic therapy making the tumor more difficult to target [69]. Indeed, most published series regarding the timing of local therapy is derived from the non-small cell lung cancer oligometastatic setting and demonstrate both upfront and consolidative local therapy appear to be safe and efficacious, however, future RCTs directly comparing upfront vs. consolidative therapy are needed.

Although further study is warranted on SABR or RFA in oligometastatic disease-directed treatment in CRC, locoregional therapies should be highly considered in these patients, not only during first-line systemic therapy for advanced CRC, but also at later stages of treatment history in select patients. Most importantly, decisions on perioperative chemotherapy and locoregional therapy for CRC with oligometastases to the lung or elsewhere should always take place in the context of multidisciplinary discussion.

Conclusion

There is a growing consensus that aggressive local therapy for CRC patients with oligometastases can improve oncologic outcomes; however, the optimal management of pulmonary oligometastases remains controversial. While PME remains first-line therapy, no studies have been powered to demonstrate a significant benefit of PME vs other local treatment modalities. Notably, patients who are not suitable for PME have comparable survival and local control following SABR, with very low risk of periprocedural toxicity. And

while RFA has emerged as a promising option, long-term follow-up data is still limited. Thus, there remains an unmet need for high-quality prospective data to optimally guide appropriate patient selection for these treatment modalities as well as further investigate potential synergy and toxicity with targeted and immune therapies in the context of specific oligometastatic disease states. Additionally, given the evolving complexity of oligometastatic disease states combined with the multitude of patient and treatment factors that may impact outcomes, it is essential that clinical management be discussed in a robust multidisciplinary setting.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Eric M. Chung, Jun Gong, Karen Zaghiyan, and Mitchell Kamrava each declare no potential conflicts of interest. Katelyn M. Atkins has received honorarium from OncLive.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians. 2020;70(1):7–30. https://doi.org/10.3322/caac.21590.
2. Taylor I. Liver metastases from colorectal cancer: Lessons from past and present clinical studies. Br J Surg. 1996;83(4):456–60. https://doi.org/10.1002/bjs.1800830406.
3. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ, Pemberton JH, Wolff BG. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surgery, Gynecology & Obstetrics 1992;174 (1), 27–32. https://pubmed.ncbi.nlm.nih.gov/1729745/
4. Mitry E, Guiu B, Cosconea S, Jooste V, Faivre J, Bouvier A-M. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. Gut. 2010;59(10):1383–8. https://doi.org/10.1136/gut.2010.211557.
5. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Scientific Reports. 2016; 6(1). https://doi.org/10.1038/srep29765
6. Gloeckler Ries LA. Cancer Survival and Incidence from the Surveillance, Epidemiology, and End Results (SEER) program. Oncologist. 2003;8(6):541–52. https://doi.org/10.1634/theoncologist.8-6-541.
7. Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, Huddart RA, Nutting CM, Ostler PJ, van As NJ. Stereotactic body radiotherapy for oligometastases. Lancet Oncol. 2013;14(1):e28-37. https://doi.org/10.1016/S1470-2045(12)70510-7.
8. Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, Karam JA, Kavanagh BD, Tang C, Komaki R, Louie AV, Palma DA, Tsao AS, Sepesi B, William WN, Zhang J. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672–82. https://doi.org/10.1016/S1470-2045(16)30532-0.
9. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, Dowell JE, Cheedella N, Nedzi L, Westover KD, Pulipparacharuvil S, Choy H, Timmerman RD. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol. 2018;4(1):e173501. https://doi.org/10.1001/jamaoncol.2017.3501.
10. Sauter ER, Bolton JS, Willis GW, Farr GH, Sardi A. Improved survival after pulmonary resection of metastatic colorectal carcinoma. J Surg Oncol. 1990;43(3):135–8. https://doi.org/10.1002/jso.2930430303.
11. Prasanna T, Karapetis CS, Roder D, Tie J, Padbury R, Price T, Wong R, Shapiro J, Nott L, Lee M, Chua YJ, Craft P, Piantadosi C, Sorich M, Gibbs P, Yip D. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. Acta Oncologica (Stockholm, Sweden). 2018;57(11):1438–44. https://doi.org/10.1080/0284186X.2018.1487581.
12. Timmerman RD, Bizekis CS, Pass HI, Fong Y, Dupuy DE, Dawson LA, Lu D. Local surgical, ablative, and radiation treatment of metastases. CA A Cancer J Clin. 2009;59(3):145–70.
13. Navarria P, Ascolese AM, Tomatis S, Cozzi L, De Rose F, Mancosu P, Alongi F, Clerici E, Lobefalo F, Tozzi A, Reggiori G, Fogliata A, Scorsetti M. Stereotactic body radiotherapy (sbrt) in lung oligometastatic patients: role of local treatments. Radiation Oncology. 2004;9(1). https://doi.org/10.1186/1748-717x-9-91
14. Ricardi U, Filippi AR, Guarneri A, Ragona R, Mantovani C, Giglioli F, Botticella A, Ciammella P, Iftode C, Buffoni L, Ruffini E, Scagliotti GV. Stereotactic body radiation therapy for lung metastases. Lung Cancer (Amsterdam, Netherlands). 2012;75(1):77–81. https://doi.org/10.1016/j.lungcan.2011.04.021.
15. Wang Z, Wang X, Yuan J, Zhang X, Zhou J, Lu M, Liu D, Li J, Shen L. Survival benefit of palliative local treatments and efficacy of different pharmacotherapies in colorectal cancer with lung metastasis: results from a large retrospective study. Clin Colorectal Cancer. 2018;17(2):e233–55. https://doi.org/10.1016/j.clcc.2017.12.005.
16. Tampellini M, Ottone A, Bellini E, Alabiso I, Baratelli C, Bitossi R, Brizzi MP, Ferrero A, Sperti E, Leone F, Miraglia S, Forti L, Bertona E, Ardissone F, Berruti A, Alabiso O, Aglietta M, Scagliotti GV. The role of lung metastasis resection in improving outcome of colorectal cancer patients: results from a large retrospective study. Oncologist. 2012;17(11):1430–8. https://doi.org/10.1634/theoncologist.2012-0142.
17. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard J-Y, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386–422. https://doi.org/10.1093/annonc/mdw235.
18.• Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, Méndez Romero A, Nevens D, Palma D, Park C, Ricardi U, Scorsetti M, Yu J, Woodward WA. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology

and Oncology. 2020;148:157–66. https://doi.org/10.1016/j.radonc.2020.04.003. (**ESTRO and ASTRO consensus definitions for oligometastatic disease. Defined OMD as 1-5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable.**)

19.• Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, Dingemans A-MC, Fournier B, Hurkmans C, Lecouvet FE, Meattini I, Méndez Romero A, Ricardi U, Russell NS, Schanne DH, Scorsetti M, Tombal B, Verellen D, Verfaillie C, Ost P. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21(1):e18–28. https://doi.org/10.1016/S1470-2045(19)30718-1. (**. ESTRO/EORTC proposal for new classification system for oligometastatic disease. Proposed classification system including 9 different oligometastatic "states" based on history of polymetastatic disease, repeat vs. de-novo oligometastatic disease, synchronous vs. metachronous oligometastatic disease, and oligorecurrence vs. oligoprogression vs. oligopersistent disease.**)

20. Pfannschmidt J, Hoffmann H, Dienemann H. Reported outcome factors for pulmonary resection in metastatic colorectal cancer. J Thor Oncol. 2010;5(6 Suppl 2):S172-178. https://doi.org/10.1097/JTO.0b013e3181dca330.

21. Comito T, Cozzi L, Clerici E, Campisi MC, Liardo RLE, Navarria P, Ascolese A, Tozzi A, Iftode C, De Rose F, Villa E, Personeni N, Rimassa L, Santoro A, Fogliata A, Mancosu P, Tomatis S, Scorsetti M. Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach. BMC Cancer. 2014;14:619. https://doi.org/10.1186/1471-2407-14-619.

22. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg. 2007;84(1):324–38. https://doi.org/10.1016/j.athoracsur.2007.02.093.

23. Riquet M, Foucault C, Cazes A, Mitry E, Dujon A, Le Pimpec Barthes F, Médioni J, Rougier P. Pulmonary resection for metastases of colorectal adenocarcinoma. Ann Thorac Surg. 2010;89(2):375–80. https://doi.org/10.1016/j.athoracsur.2009.10.005.

24. Watanabe K, Nagai K, Kobayashi A, Sugito M, Saito N. Factors influencing survival after complete resection of pulmonary metastases from colorectal cancer. Br J Surg. 2009;96(9):1058–65. https://doi.org/10.1002/bjs.6682.

25. Gonzalez M, Ris HB, Krueger T, Gervaz P. Colorectal cancer and thoracic surgeons: close encounters of the third kind. Expert Rev Anticancer Ther. 2012;12(4):495–503. https://doi.org/10.1586/era.12.21.

26. National Comprehensive Cancer Network. (2019). *Colon cancer (version 2.2019)*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

27. Erhunmwunsee L, Tong BC. Preoperative evaluation and indications for pulmonary metastasectomy. Thorac Cardiovasc Surg. 2016;26(1):7–12. https://doi.org/10.1016/j.thorsurg.2015.09.002.

28. Londero F, Grossi W, Morelli A, Parise O, Masullo G, Tetta C, Livi U, Maessen JG, Gelsomino S. Surgery versus stereotactic radiotherapy for treatment of pulmonary metastases A systematic review of literature. Future Science OA. 2020;6(5):FSO471. https://doi.org/10.2144/fsoa-2019-0120.

29. Rodríguez-Fuster A, Belda-Sanchis J, Aguiló R, Embun R, Mojal S, Call S, Molins L, Rivas de Andrés JJ. Morbidity and mortality in a large series of surgical patients with pulmonary metastases of colorectal carcinoma: a prospective multicentre Spanish study (GECMP-CCR-SEPAR). Eur J Cardio-Thor Surg. 2014;45(4):671–6. https://doi.org/10.1093/ejcts/ezt459.

30. Fukada M, Matsuhashi N, Takahashi T, Tanaka Y, Okumura N, Yamamoto H, Shirahashi K, Iwata H, Doi K, Yoshida K. Prognostic factors in pulmonary metastasectomy and efficacy of repeat pulmonary metastasectomy from colorectal cancer. World J Surg Oncol. 2020;18(1):314. https://doi.org/10.1186/s12957-020-02076-3.

31. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S-E, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes H-G. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1065–75. https://doi.org/10.1016/s1470-2045(14)70330-4.

32. Cunningham D, Atkin W, Lenz H-J, Lynch HT, Minsky B, Nordlinger B, Starling N. Colorectal cancer. Lancet (London, England). 2010;375(9719):1030–47. https://doi.org/10.1016/S0140-6736(10)60353-4.

33. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol. 2013;20(2):572–9. https://doi.org/10.1245/s10434-012-2726-3.

34. Fiorentino F, Hunt I, Teoh K, Treasure T, Utley M. Pulmonary metastasectomy in colorectal cancer: a systematic review and quantitative synthesis. J R Soc Med. 2010;103(2):60–6. https://doi.org/10.1258/jrsm.2009.090299.

35. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol. 2013;20(2):572–9. https://doi.org/10.1245/s10434-012-2726-3.

36.• Treasure T, Farewell V, Macbeth F, Monson K, Williams NR, Brew-Graves C, Lees B, Grigg O, Fallowfield L, PulMiCC Trial Group. Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. Trials. 2019;20(1):718. https://doi.org/10.1186/s13063-019-3837-y. (**Multi-center randomized controlled trial published in 2019, randomized 65 patients to either surgical metastasectomy or active clinical monitoring. The study had difficulty enrolling patients and was underpowered. There was no significant 5-year survival difference (38% vs 29%, HR 0.82, 95% CI: 0.43-1.56)**)

37.• Milosevic M, Edwards J, Tsang D, Dunning J, Shackcloth M, Batchelor T, Coonar A, Hasan J, Davidson B, Marchbank A, Grumett S, Williams NR, Macbeth F, Farewell V, Treasure T. Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients – control survival is much better than previously assumed. Colorectal Dis. 2020;22(10):1314–24. https://doi.org/10.1111/codi.15113. (**Updated analysis of PulMiCC trial that included 93 patients, reported similar results with no significant difference in survival with median OS 3.8 years for control arm vs 3.5 years for PME arm.**)

38. Jawed I, Wilkerson J, Prasad V, Duffy AG, Fojo T. Colorectal Cancer Survival Gains and Novel Treatment Regimens. JAMA Oncol. 2015;1(6):787. https://doi.org/10.1001/jamaoncol.2015.1790.

39. Dahele M, Hatton M, Slotman B, Guckenberger M. Stereotactic body radiotherapy: A survey of contemporary practice in six selected European countries. Acta Oncologica (Stockholm, Sweden). 2015;54(8):1237–41. https://doi.org/10.3109/0284186X.2014.1003961.

40. Widder J, Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJM, Langendijk JA. Pulmonary oligometastases: Metastasectomy or stereotactic ablative radiotherapy? Radiother Oncol. 2013;107(3):409–13. https://doi.org/10.1016/j.radonc.2013.05.024.

41.• Cao C, Wang D, Tian DH, Wilson-Smith A, Huang J, Rimner A. A systematic review and meta-analysis of stereotactic body radiation therapy for colorectal pulmonary metastases. J Thor Dis. 2019;11(12):5187–98. https://doi.org/10.21037/jtd.2019.12.12. (**2018 meta-analysis of 15 studies and 686 pulmonary metastases, treated with SABR. LC for CRC pulmonary metastases treated by SABR at 1-, 2-, and 3-year were estimated to be 81%, 66%, and 60%, respectively. OS and PFS at 3-year were 52% and 13%, respectively. Patients with CRC pulmonary metastases were associated with significantly lower LC compared to non-CRC pulmonary metastases, but higher OS.•**)

42. Binkley MS, Trakul N, Jacobs LR, von Eyben R, Le Q-T, Maxim PG, Loo BW, Shultz DB, Diehn M. Colorectal histology is associated with an increased risk of local failure in lung metastases treated with stereotactic ablative radiation therapy. Int J Radiat Oncol Biol Phys. 2015;92(5):1044–52. https://doi.org/10.1016/j.ijrobp.2015.04.004.

43. Wang X, Zamdborg L, Ye H, Grills IS, Yan D. A matched-pair analysis of stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer versus early stage non-small cell lung cancer. BMC Cancer. 2018;18(1). https://doi.org/10.1186/s12885-018-4865-9

44. Ahmed KA, Fulp WJ, Berglund AE, Hoffe SE, Dilling TJ, Eschrich SA, Shridhar R, Torres-Roca JF. Differences between colon cancer primaries and metastases using a molecular assay for tumor radiation sensitivity suggest implications for potential oligometastatic SBRT patient selection. Int J Radiat Oncol Biol Phys. 2015;92(4):837–42. https://doi.org/10.1016/j.ijrobp.2015.01.036.

45. Ahmed KA, Scott JG, Arrington JA, Naghavi AO, Grass GD, Perez BA, Caudell JJ, Berglund AE, Welsh EA, Eschrich SA, Dilling TJ, Torres-Roca JF. Radiosensitivity of lung metastases by primary histology and implications for stereotactic body radiation therapy using the genomically adjusted radiation dose. J Thorac Oncol. 2018;13(8):1121–7. https://doi.org/10.1016/j.jtho.2018.04.027.

46. Tanadini-Lang S, Rieber J, Filippi AR, Fode MM, Streblow J, Adebahr S, Andratschke N, Blanck O, Boda-Heggemann J, Duma M, Eble MJ, Ernst I, Flentje M, Gerum S, Hass P, Henkenberens C, Hildebrandt G, Imhoff D, Kahl H, Klass ND. Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease. Radiother Oncol. 2017;123(2):182–8. https://doi.org/10.1016/j.radonc.2017.01.003.

47. Jingu K, Matsuo Y, Onishi H, Yamamoto T, Aoki M, Murakami Y, Yamashita H, Kakuhara H, Nemoto K, Sakayauchi T, Okamoto M, Niibe Y, Nagata Y, Ogawa K. Dose escalation improves outcome in stereotactic body radiotherapy for pulmonary oligometastases from colorectal cancer. Anticancer Res. 2017;37(5):2709–13.

48. Kinj R, Bondiau P-Y, François E, Gérard J-P, Naghavi AO, Leysalle A, Chamorey E, Evesque L, Padovani B, Ianessi A, Benezery K, Doyen J. Radiosensitivity of colon and rectal lung oligometastasis treated with stereotactic ablative radiotherapy. Clin Colorectal Cancer. 2017;16(3):e211–20. https://doi.org/10.1016/j.clcc.2016.08.003.

49. Sharma A, Duijm M, Oomen-de Hoop E, Aerts JG, Verhoef C, Hoogeman M, Nuyttens JJ. Factors affecting local control of pulmonary oligometastases treated with stereotactic body radiotherapy. Acta Oncologica (Stockholm, Sweden). 2018;57(8):1031–7. https://doi.org/10.1080/0284186X.2018.1445285.

50.• Sharma A, Baker S, Duijm M, Oomen-de Hoop E, Cornelissen R, Verhoef C, Hoogeman M, Jan Nuyttens J. Prognostic factors for local control and survival for inoperable pulmonary colorectal oligometastases treated with stereotactic body radiotherapy. Radiother Oncol. 2020;144:23–9. https://doi.org/10.1016/j.radonc.2019.10.004. (**2019 single-institution retrospective review of 118 pts with 202 pulmonary mets treated with SABR. 3- and 5-year LC rates of 81% and 77%, respectively. 3- and 5-year OS of 55% and 36%, respectively. Higher SABR dose (BED10 > 100 Gy vs. BED10 < 100Gy) associated with improved LC and OS.**)

51.• Jingu K, Matsushita H, Yamamoto T, Umezawa R, Ishikawa Y, Takahashi N, Katagiri Y, Takeda K, Kadoya N. Stereotactic radiotherapy for pulmonary oligometastases from colorectal cancer: a systematic review and meta-analysis. Technol Cancer Res Treat. 2018;17:1533033818794936. https://doi.org/10.1177/1533033818794936. (**2018 meta-analysis of 18 studies and 1920 patients with pulmonary oligomets. The local control rate in patients with pulmonary oligometastases from colorectal cancer was significantly lower than that in patients with pulmonary oligometastases from other cancers. Subset analysis of 8 studies and 478 pts found improved LC with BED10 > 100Gy (OR 0.16, 95% CI: 0.09-0.28, P < .001)**)

52.• Yamamoto T, Niibe Y, Matsumoto Y, Onishi H, Aoki M, Nishikawa A, Oh R-J, Shintani T, Yahara K, Ozaki M, Manabe Y, Jingu K. Analyses of local control and survival after stereotactic body radiotherapy for pulmonary oligometastases from colorectal adenocarcinoma. J Radiat Res. 2020;61(6):935–44. https://doi.org/10.1093/jrr/rraa071. (**2020 multicenter retrospective review of 330 pts with 371 pulmonary oligometastases from CRC treated with SABR. 3-yr LC, 3-yr PFS, and 3-yr OS 64.9%, 34.9%, and 63.4%, respectively. The results of multivariate analyses showed that a higher LC rate was associated with no history of local therapy for oligometastases (P = 0.01), SBRT without concurrent chemotherapy (P < 0.01), type B calculation algorithm (P < 0.01) and higher biological effective radiation doses (≥115 Gy, P = 0.04). A longer OS was associated with no history of local therapy for oligometastases (P = 0.04), a more recent period of SBRT (2010–15, P = 0.02), tumor located in the upper or middle lobe (P < 0.01) and higher biological effective radiation doses (≥115 Gy, P = 0.01).**)

53. Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenes H, Chidel MA, Pugh TJ, Kane M, Gaspar LE, Schefter TE. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol. 2009;27(10):1579–84. https://doi.org/10.1200/JCO.2008.19.6386.

54. Nuyttens JJ, van der Voort van Zyp CNMG, Verhoef C, Maat A, van Klaveren RJ, van der Holt B, Aerts J, Hoogeman M. Stereotactic body radiation therapy for oligometastases to the lung: a phase 2 study. Int J Radiat Oncol, Biol, Phys. 2015;91(2):337–43. https://doi.org/10.1016/j.ijrobp.2014.10.021.

55. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, Schellenberg D, Ahmad B, Senthi S, Swaminath A, Kopek N, Liu M, Moore K, Currie S, Schlijper R, Bauman GS. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol. 2020;38(25):2830–8. https://doi.org/10.1200/JCO.20.00818.

56.• Siva S, Bressel M, Mai T, Le H, Vinod S, de Silva H, Macdonald S, Skala M, Hardcastle N, Rezo A, Pryor D, Gill S, Higgs B, Wagenfuehr K, Montgomery R, Awad R, Chesson B, Eade T,

Wong W, Sasso G. Single-Fraction vs Multifraction Stereotactic Ablative Body Radiotherapy for Pulmonary Oligometastases (SAFRON II): the Trans Tasman Radiation Oncology Group 1301 Phase 2 Randomized Clinical Trial. JAMA Oncol. 2021. https://doi.org/10.1001/jamaoncol.2021.2939. (**Phase II RCT of 87 pts (47% with CRC primary) and 133 pulmonary oligometastases that randomized patients to single fraction of 28Gy or 4x12Gy. The primary end point of severe toxicity was no different in the single-fraction arm (5%) than in the multifraction arm (3%). The secondary end points of efficacy, survival, and quality of life were also not different between the study arms.●**)

57. Filippi AR, Guerrera F, Badellino S, Ceccarelli M, Castiglione A, Guarneri A, Spadi R, Racca P, Ciccone G, Ricardi U, Ruffini E. Exploratory analysis on overall survival after either surgery or stereotactic radiotherapy for lung oligometastases from colorectal cancer. Clin Oncol. 2016;28(8):505–12. https://doi.org/10.1016/j.clon.2016.02.001.

58.● Lee YH, Kang KM, Choi H-S, Ha IB, Jeong H, Song JH, Jang I-S, Kim SH, Lee JW, Rhee DY, Jeong BK. Comparison of stereotactic body radiotherapy versus metastasectomy outcomes in patients with pulmonary metastases. Thoracic Cancer. 2018;9(12):1671–9. https://doi.org/10.1111/1759-7714.12880. (**2018 retrospective review of 51 pts with 1-3 pulmonary metastases who underwent PME vs SABR. There was no significant difference in the local control rates of the treatment groups (P = 0.163). Progression-free survival (PFS) was longer in the metastasectomy than in the SBRT group (P = 0.02), with one and two-year PFS rates of 51.1% and 46% versus 23.8% and 11.9%, respectively. The one and two-year overall survival (OS) rates were 95% and 81.8% in the metastasectomy group and 79.5% and 68.2%, in the SBRT group, respectively.**)

59. de Baère T, Aupérin A, Deschamps F, Chevallier P, Gaubert Y, Boige V, Fonck M, Escudier B, Palussiére J. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol. 2015;26(5):987–91. https://doi.org/10.1093/annonc/mdv037.

60. Moorcraft SY, Ladas G, Bowcock A, Chau I. Management of resectable colorectal lung metastases. Clin Exp Metas. 2016;33(3):285–96. https://doi.org/10.1007/s10585-015-9774-6.

61. Akhan O, Güler E, Akıncı D, Çiftçi T, Köse IÇ. Radiofrequency ablation for lung tumors: outcomes, effects on survival, and prognostic factors. Diagn Interv Radiol. 2016;22(1):65–71. https://doi.org/10.5152/dir.2015.14378.

62. Simon CJ, Dupuy DE, DiPetrillo TA, Safran HP, Grieco CA, Ng T, Mayo-Smith WW. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. Radiology. 2007;243(1):268–75. https://doi.org/10.1148/radiol.2431060088.

63. Palussière J, Catena V, Buy X. Percutaneous thermal ablation of lung tumors – Radiofrequency, microwave and cryotherapy: Where are we going? Diagn Interv Imaging. 2017;98(9):619–25. https://doi.org/10.1016/j.diii.2017.07.003.

64.● Hasegawa T, Takaki H, Kodama H, Yamanaka T, Nakatsuka A, Sato Y, Takao M, Katayama Y, Fukai I, Kato T, Tokui T, Tempaku H, Adachi K, Matsushima Y, Inaba Y, Yamakado K. Three-year survival rate after radiofrequency ablation for surgically resectable colorectal lung metastases: a prospective multicenter study. Radiology. 2020;294(3):686–95. https://doi.org/10.1148/radiol.2020191272. (**2020 prospective multi-center study that included 70 pts with 100 lesions, all <3cm, treated with RFA from 2008-2014. 3-yr OS of 84% and 3-yr local progression of 9%. 30-day mortality was 1.4%.**)

65. National Comprehensive Cancer Network. (2021). *Colon cancer (version 3.2021)*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

66. Li Y, Qin Y. Peri-operative chemotherapy for resectable colorectal lung metastasis: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2020;146(3):545–53. https://doi.org/10.1007/s00432-020-03142-9.

67. Brandi G. Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis. World J Gastroenterol. 2016;22(2):519. https://doi.org/10.3748/wjg.v22.i2.519.

68. Moretto R, Rossini D, Zucchelli G, Lonardi S, Bergamo F, Santini D, Cupini S, Tomasello G, Caponnetto S, Zaniboni A, Antoniotti C, Pietrantonio F, Buonadonna A, Marmorino F, Bordonaro R, Fea E, Tamburini E, Boccaccino A, Grande R, Aprile G. Oligometastatic colorectal cancer: prognosis role of locoregional treatments and impact of first-line chemotherapy-a pooled analysis of TRIBE and TRIBE2 studies by Gruppo Oncologico del Nord Ovest. Eur J Cancer (Oxford, England: 1990). 2020;139:81–9.

69. Tjong MC, Louie AV, Iyengar P, Solomon BJ, Palma DA, Siva S. Local ablative therapies in oligometastatic NSCLC-upfront or outback?—a narrative review. Transl Lung Cancer Res. 2021;10(7):3446–56.