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Interventional oncology for liver and lung metastases from colorectal cancer: The current state of the art


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Colorectal cancer; Metastases; Radiofrequency; Chemotherapy; Image-guided surgery

Abstract  Interventional oncology is developing rapidly as a result of advances in imaging and medical devices. Although the treatments offered are recent and not yet fully validated in the guidelines, they allow non-invasive curative treatments to be offered to a growing number of patients. When it is used in a highly selected patients with less than three metastases under 2–3 cm in size, percutaneous tumor ablation offers local efficacy similar to excision surgery with considerable sparing of the parenchyma, both for lung and liver metastases. Hepatic intra-arterial therapies (chemotherapy, radioembolization, and chemoembolization) are now ”salvage” methods after chemotherapy has failed and are being assessed in earlier lines of treatment.

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Interventional oncology (interventional radiology to treat cancer) is a rapidly advancing specialty and in the near future will probably represent the fourth pillar of cancer care alongside medical oncology, surgery and radiotherapy. Interventional oncology allows new image-guided treatments, which are relatively non-invasive to treat localized malignant disease through a potent local treatment effect (drug concentration, thermal damage), at the same time reducing potential side effects, either in the same organ or remotely. Local malignant disease is increasingly being found because of early detection, routine monitoring of patients with known cancer and the large reduction in tumor volumes as a result of new classes of systemic therapies.

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For colorectal cancer, interventional oncology has a major role for the treatment of metastatic liver and lung disease through percutaneous tumor destruction, and in metastatic liver disease with intra-arterial treatments.

Percutaneous ablation

Principle

Percutaneous ablation is based primarily on thermal destruction, exposing the targeted tumor cells to temperatures of over +60 °C [1] or less than −40 °C [2] causing near-immediate irreversible cell death. The first thermal ablation technique to be used was radiofrequency ablation (RFA) in which tissues are heated with a sinusoidal current (400 to 500 KHz) by ionic friction from electrodes inserted into the tissue. Other thermal ablation technologies such as microwave and cryoablation have been developed more recently for percutaneous use, in an attempt to circumvent the limitations of RFA by firstly increasing ablation size using different energies and the possible use of several simultaneous applicators, and secondly by providing faster treatment, and reducing the sensitivity of ablation to thermal convention, particularly in contact with large diameter vessels [3,4]. Some techniques also provide for more straightforward follow-up imaging [5]. The advantages of these new technologies have been demonstrated in preclinical studies but need to be confirmed in clinical trials. A non-thermal destruction method, irreversible electroporation (IRE) has also recently been introduced [6] and is currently under early stage clinical assessment for the liver and other organs [7,8]. At present, RFA remains the reference technique for percutaneous ablation as it is a mature technique with many reported publications. As a result, only the RFA results will be considered below.

Liver metastases

The main factor influencing the results of thermal ablation is the size of the target metastasis and there is hard evidence that better results are achieved after RFA for metastases of <3 cm in size. The incomplete ablation rate in a now old publication was 21.6% for the 37 metastases ≥30 mm, compared to 2.6% for 190 metastases <30 mm [9]. More recently, 9, 26.5 and 45% incomplete ablation rates have been reported for 290 liver metastases from colorectal cancer treated by RFA, measuring 0–3, 3–5 and >5 cm, in size respectively [10]. The risk of incomplete ablation increases by 22% for each 5 mm increase in diameter of the tumor and falls by 46% for each 5 mm increase in the depth of the ablation margin [11]. Apart from size, the blocks to complete ablation are proximity to large vessels, as the fluid passing through the heated tissue causes cooling through convention, which is responsible for the “heat sink effect”, and causes difficulties in ablating tissue close to vessels which are 3 mm or over in diameter [12–14]. The incomplete treatment rate for metastases close to vessels of ≥3 mm has been reported to be 23% compared to 3% for metastases remote from these vessels [9]. This difference disappears with percutaneous balloon occlusion of the vessel involved [15]. The local efficacy of RFA has been reported to be equivalent to that of atypical excision for small metastases, with incomplete local treatment rates of 5.7 and 7.1% for 227 RFA and 99 atypical excisions, respectively [9]. Analysis of two EORTC studies on RFA in the CLOC trial [16] and excision of metastases ≤4 cm in the EPOC trial [17], reported a local recurrence rate of 5.5% compared to 6.0% as a result of metastases and 7.4% compared to 14.5% per patient for excision and RFA respectively, leaving patients with more advanced disease in the RFA group [18] The local recurrence rate after RFA for 30 mm or smaller metastases was 2.9% (21.4% for metastases over 30 mm) and 6.2% after excision of 30 mm or smaller metastases [18]. The local recurrence rate after RFA is considerably higher than after surgery for 20 mm or larger tumors, whereas no significant difference is seen for tumors under 20 mm in size [19]. The recurrence rate in patients who had previously undergone hepatectomy is reported as 18% for metastases with an average diameter of 2.3 cm, including 6% for metastases ≤3 cm, and 52% for metastases >3 cm [20]. The hepatic recurrence rate in 6025 patients undergoing surgery with or without radiofrequency ablation for malignant liver metastases from colorectal cancer was 45.4%, including 9.6, 12 and 18.3% early recurrence after anatomical resection, atypical resection and RFA respectively. Only anatomical excision was better than RFA and no significant difference was found between RFA and atypical resection. In addition no difference in survival was found between the anatomical excision, RFA and atypical resection groups [21]. An important factor for successful ablation which is rarely reported is good visualization of the target tumor. Sofocleous et al. reported a 94% complete ablation rate (67/71) for liver metastases from colorectal cancer developing in the residual liver after hepatectomy; three of the four failures were attributed to poor visualization of the tumor, resulting in suboptimal targeting [22].

No randomized studies have compared surgery to thermal ablation and the available series are retrospective and contain obvious bias, comparing surgery in candidates for surgery and thermal ablation in patients not candidates for surgery [23,24], although after stratifying by extra-hepatic extension, general health and extent of advancement of the disease, this difference usually disappears [24]. This bias is highlighted in the conclusions of a Cochrane meta-analysis: ’’The imbalance between characteristics of patients in the allocated groups appears to be the main concern’’ [25,26]. Patients who are not candidates for surgery are generally not the ideal candidates for thermal ablation either, as the factors which make a tumor inoperable (size, proximity to major blood vessels or biliary tract) also make it difficult to treat with percutaneous ablation and RFA is therefore usually reserved for patients who are potential surgery candidates but cannot have surgery because of comorbidities or if the malignant disease is deemed to be too aggressive (extra-hepatic disease, recurrence after surgery, etc.). These selection bias issues impact on overall survival with median and 5-year survival rates of 4.3 years and 48.7% after RFA in 64 technically operable patients, compared to 2.2 years and 18.4% in 37 RFA in 137 patients who were technically inoperable [27]. Otto et al. reported that only a small subset of candidates to surgery are amenable to RFA [28]. A retrospective review has examined 2123 cases of surgery for liver metastases from colorectal cancer and compared 141 patients treated with bilateral
surgical excision to 95 patients treated with thermal ablation [thermal ablation only (n = 9); thermal ablation combined with excision (n = 86)] and reported an overall 5-year survival rate of 56% for ablation and 49% for excision (P = 0.16), despite a higher clinical risk score (lymph node invasion, disease free interval (DFI) significantly number and size of metastases, CEA level) in the thermal ablation group [29]. The use of preoperative RFA as a complement to surgery in 15% of 168 surgical cases [30] and 24 of 174 surgical cases [31] was not associated with reduced overall survival compared to surgery without ablation.

Ideally the comparison between surgery and RFA should include prognostic indicators for surgery (stage of the primary cancer, DFI and number and size of metastases, lymph node invasion, CEA, age, excision margin, response to and number of lines of chemotherapy) [32–34] and prognostic indicators for RFA (lymph node invasion at the time of surgery for the primary cancer, DFI and number and size of metastases) which when combined into a prognostic score separates patients with a 2-year survival after RFA of 74% compared to 42% [18,22].

Apart from RFA in potential candidates for surgery, the role of RFA in a more palliative situation needs to be examined. There is currently only one study, which describes randomization of 120 patients between RFA combined with systemic chemotherapy compared to chemotherapy alone in patients with inoperable colorectal liver metastases.

Progression-free survival at 3 years was 27% in the RFA plus chemotherapy group and was significantly higher than the 10.6% figure for the chemotherapy alone group. Overall mortality at 30 months was not significantly different between the groups although the survival curves continued to separate over longer-term follow-up, with overall survival rates of 47% compared to 36% at 4 years and 40% compared to 30% at 5 years [16].

Lung metastases

Organ specific differences favoring RFA are seen for the lung. Firstly, the same amount of energy produces a larger ablation volume in lungs than in soft tissues and kidneys, probably because of the thermal and electrical insulation provided by the air-filled lung parenchyma surrounding the targeted metastasis [35]. Secondly, pulmonary RFA is always performed under CT guidance, which provides excellent visualization because of the large differences in density between the metal of the needle, the metastatic tissue and the air-filled lung, and by the accurate targeting which can be optimally assessed on multiplanar reconstructions. This accurate targeting is essential for good treatment results. The local efficacy of RFA in treating lung metastases has been proven with a 100% histological necrosis rate in 10 of the 10 metastases treated by RFA and then excised surgically [36].

The largest series published to date included 566 consecutive patients with 1037 lung metastases of colonic (34%), rectal (18%), renal (12%), sarcomatous (9%) or other (28%) origins. Overall survival was 62 months and the 3- and 5-year survival rates were 67.7% and 51.5% respectively [37]. The disease variables which were associated with overall survival in a multivariate analysis were the site of the primary cancer other than colon or kidney, DFI of <1 year, size >2 cm and number of metastases >3. Local tumor progression at the RFA site was also associated with shorter survival [37]. Earlier series showed slightly longer overall survival of 51 months in 148 patients [38], 41 months in 122 patients [39] and 34.9 months in 84 patients [40]. The better results in the Bergonie/Gustave-Roussy series can be explained by restricted inclusion criteria resulting in a population with better predictive indicators such as a median diameter of metastases of 15 mm, whereas the tumors were over 40 mm in diameter in 40% of the cases reported by Chua et al. [38] and were up to 90 mm in size (mean ± standard deviation = 23 ± 14 mm) for Hamada et al. [40]. In addition, the average number of metastases present per patient was 1.8 for de Baere et al., compared to 3.3 for Gillams et al. [39]. Twenty-one percent of the patients in the series of de Baere et al. also had a DFI of under 12 months [37], compared to 12 and 52% for Chua et al. and Gillams et al., respectively [38,39].

The 5-year survival rate of 51% with a median overall survival of 62 months reported for RFA compares well with the best results reported for surgery for lung metastases. These describe a 5-year survival rate of 53.5% and median survival of 69.5 months in a multicenter register of lung metastasectomies from colorectal cancer [41], a 5-year survival rate of 27% to 68% and overall survival of 33 to 72 months in a meta-analysis [42], and a 5-year survival rate of 32.7% to 56% and overall survival of 37 to 47 months in a literature review of 11 publications which included 1307 patients, and also reported a 5-year survival rate of 39.1 to 67.8% for R0 resection [43]. The predictive indicators for overall survival after RFA described above are similar to those for lung metastasectomies and are the origin of the primary cancer, number of metastases, R0 resection, pre-resection ACE level and histological lymph node invasion [41,42,44]. The use of minimally invasive techniques for local treatment of lung metastases is not associated with differences in local recurrence or overall survival [45], although obviously RFA does not provide regional control of the disease and specifically does not provide control of lymph nodes. The possible benefit of surgical lymphadenectomy, however, is not proven [46,47] and curettage is usually not performed in lung metastasectomies. RFA for lung metastases can be repeated if needed. As it is relatively non-invasive and spares the healthy lung parenchyma, if changes in respiratory function are not present after RFA [48,49], 24% of patients treated initially can be retreated with RFA up to 4 times, with a 44.1% control rate reported for metastatic lung disease at 4 years compared to a 4-year PFS rate before repeat treatment of 20.3% [37].

RFA for lung metastases is a treatment option for metastases under 2–3 cm in diameter and is widely used in patients who are not candidates for surgery, or if surgery requires extensive resection. RFA for lung metastases in candidates for surgical candidates is an option which needs to be discussed in a multidisciplinary team meeting, as its results are superimposable on those of surgery itself.

**Intra-arterial treatments**

Hepatic intra-arterial treatment benefits from the fact that liver tumors are preferentially and almost exclusively supplied by the hepatic artery, whereas the healthy liver
parenchyma is vascularized 30% from the hepatic arterial system and 70% from the portal system.

Hepatic intra-arterial chemotherapy (HIAC) initially used 5-FU and FUDR because of the high liver extraction rates, of 19—51% and 94—99%, respectively [50]. Many randomized trials with these drugs have reported better response to HIAC than IV therapy, although only two studies have shown a benefit on survival with HIAC [51,52], probably because most of the trials allowed crossover and the actual numbers of HIAC performed were low.

More recently, combined HIAC and FUDR with oxaliplatin and systemic irinotecan achieved an objective response rate of 90% and a 47% conversion rate to surgery in initially inoperable patients [53]. HIAC with oxaliplatin achieved an overall response rate of 62% and a 20% conversion rate to surgery in patients who had already been extensively treated with systemic therapies and had already received oxaliplatin (n = 34), irinotecan (n = 37) or both agents (n = 28) [54]. Used first line, HIAC with oxaliplatin combined with systemic 5-FU and cetuximab achieved a 90% objective response rate, 100% control of the disease and time to progression of 20 months with a 48% surgical conversion rate [55]. It should be noted that the magnitude of the response and complete pathological response rate (confirmed on surgical excision) increased by a factor of 9.33 (1.59—54.7) when oxaliplatin was given intra-arterially compared to systemically [56]. In the same study, the complete disease response was associated with an increase in overall survival of 114 months compared to 42 months.

The precise role of HIAC in inoperable liver metastases is still being debated between first line therapy, intensification after a poor response to first line therapy and salvage or adjuvant treatment [57,58], although its feasibility has considerably increased as a result of the possibility of percutaneous implantation of catheters and ports, providing permanent access to the hepatic artery. The technical success rate of percutaneous insertion through a femoral approach is 94 to 99% [59—61]. A comparison of percutaneous and surgical approaches showed equivalent primary patency (4.80 courses compared to 4.82 courses) with higher secondary patency rates after repeat percutaneous intervention with percutaneous implantation (9.18 compared to 5.95 courses, P = 0.004) [59,62]. The migration and obstruction rates for catheters implanted percutaneously are in the region of 3 to 10%, with a 30% extra-hepatic infusion rate requiring regular imaging monitoring of catheter function. Repeat percutaneous procedures are performed if necessary either to obstruct an extra-hepatic artery or for fibrinolysis of a partially obstructed catheter or to change a completely obstructive catheter [63]. Only obstruction of the hepatic artery, a very rare event, is usually irreversible. Overall the HIAC dropout rate due to malfunction of the chamber/port system is 21% after percutaneous implantation and 34% after surgical implantation [64], casting some doubt on surgical implantation, even if the surgery itself is performed for other reasons [65].

Chemoembolization has recently been examined in colorectal metastases using drug elution beads laden with irinotecan (DEBIRI). In preclinical studies, DEBIRI improved the pharmacokinetics of irinotecan with 27, 18.3 and 174.4 ng of irinotecan per 200 mg of tumor, 24 hours after IV, HIAC and DEBIRI injection of irinotecan respectively [66], 90% of the irinotecan being released in the first hour and 98% after 2 hours [67]. One study on 55 patients who had failed first line treatment with FOLFOX-bevacizumab (n = 55), second line therapy with FOLFOX-cetuximab (n = 14) and third line therapy (n = 24), reported a 75% objective response rate at 12 months with overall survival of 19 months and time to progression after DEBIRI of 11 months [68]. A randomized study on 74 patients which compared DEBIRI and FOLFIRI IV reported a long overall survival with DEBIRI of 22 months (95% confidence interval (CI) = 21—23) for DEBIRI and 15 months (95% CI = 12—18) for FOLFIRI [69]. The times to progression-free survivals were 7 months (95% CI = 3—11) for DEBIRI compared to 4 months (95% CI = 3—5) for FOLFIRI (P = 0.006, log-rank). Early toxicity was greater with DEBIRI (70%) compared to FOLFIRI (25%) and late toxicity was higher with FOLFIRI (80%) than DEBIRI (20%). The toxicity profiles of DEBIRI and FOLFIRI were different, with grade 3 neutropenia in 4 and 44% of cases, diarrhea in 6 and 18% of cases and mucitis in 1 and 20% of cases respectively. The costs of DEBIRI were significantly lower than those of FOLFIRI (€ 8000 for two courses compared to € 26,000 for 8 courses).

Radioembolization involves a hepatic intra-arterial injection of non-degradable microspheres bound to 90yttrium, which is a β emitting isotope. The microspheres remain trapped in the tumor and are unable to pass through the hepatic vascular system and deliver irradiation with an average penetration of 2.5 mm into tissues (maximum 1 cm). The dose delivered to the tissue is over 120 Gy [70,71] and does not cause major toxicity to the normal liver which has limited tolerance to ionizing irradiation (in the region of 35 Gy [72]). Two types of 90yttrium microspheres are available: glass, which have been approved since 1999 to treat hepatocellular carcinoma and resin microspheres approved by the FDA in 2002 to treat hepatic metastases from colorectal cancer. Two vascular procedures are needed for this treatment: The first "skeletilizes" the hepatic artery by occluding extra-hepatic blood vessels to non-target organs (gastrointestinal tract, skin, lung and gallbladder). During this initial procedure the future distribution of the 90yttrium microspheres is modeled by scintigraphic imaging after injecting macro-aggregates of 99technecium-labeled albumin. A few days later the 90yttrium microspheres are injected in a second procedure after the dose has been calculated according to the distribution of the injection of macro-aggregates of albumin labeled with 99technecium.

Radioembolization has been studied as an early line of treatment in a randomized phase III study which compared radioembolization combined with HIAC with FUDR compared to HIAC with FUDR alone and included 70 patients with bilobar, inoperable metastases from colorectal cancer, and 60 of whom were previously untreated with chemotherapy. The objective response rate and medium time to progression of disease were significantly longer in the FUDR plus radioembolization group, with figures of 44% compared to 17.6% and 15.9 compared to 9.7 months respectively [73]. At least three prospective studies have examined the role of radioembolization combined with systemic chemotherapy [74]. Used first line, radioembolization combined with systemic 5-FU was compared to systemic 5-FU alone and demonstrated significant increases in the objective response rate (73% compared to 0%), time to progression (18.6 compared to 3.6 months), progression-free
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Survival (11.5 compared to 4.6 months) and overall survival (29.4 compared to 12.8 months) [75]. Prospective studies have assessed RE in combination with more recent chemotherapy including FOLFIRI4 in the first line treatment of 25 patients and reported a 90% objective response rate [76], or with irinotecan in 25 patients who were previously untreated with the drug and had failed previous chemotherapy and reported 48% objective response and 39% stable disease rates [77].

In more advanced lines of therapy, one prospective, multicenter, phase II study included 50 patients with isolated or predominantly liver metastases who had progressive progression after at least three lines of systemic chemotherapy including oxaliplatin and irinotecan. The disease control rate was 24% with a PFS of 3.7 months, median survival of 12.6 months and 1- and 2-year survival rates of 50.4 and 19.6% respectively [78]. Another, prospective, randomized multicenter phase III study in 46 inoperable patients who were refractory to chemotherapy compared systemic 5-FU to 5-FU plus radioembolization [79] and found a significantly longer median time to liver progression in the combination group (5.5 compared to 2.1 months respectively), with no increase in toxicity in the radio-chemotherapy group, but no significant benefit in overall survival (10.0 compared to 7.3). It should be noted that crossover was permitted in this study and that 10 patients included initially in the chemotherapy only group progressed and were treated with radioembolization. Recently, a prospective cohort study on 302 patients suffering from inoperable liver metastases from colorectal cancer and treated with radioembolization reported survival of 10.5 months and four predictive indicators, the number of lines of chemotherapy, tumor volume, radiological response and hemoglobin concentration [80]. A large retrospective comparative cohort study of 339 patients with liver metastases which were refractory to chemotherapy and were treated with radioembolization reported a median overall survival of 12 months which was significantly longer than the 6.3 months in a control group of 51 patients who did not undergo radioembolization and were treated with standard therapy [81].

The side effects of radioembolization mostly occurred during the first week after treatment and involved moderate abdominal pain, fever, nausea and hepatic dysfunction. Most of the serious adverse events are associated with injection of 90Yttrium microspheres into extra-hepatic branches of vessels and include gastritis or radiation ulcer (5–10%), radiation pancreatitis (<1%) and cholecystitis (<1%) and are usually avoided by good preparation of the arterial bed [74]. The most serious and relatively unpredictable complication is radiation-induced liver disease due to the direct toxicity of the irradiation on the non-malignant liver. This rare complication affects approximately 4% of patients, occurs late, from 4–8 weeks after radioembolization and is characterized histologically by sinusoidal obstruction. The clinical features are jaundice, ascites and hepatocellular failure [82,83] and the predictive factors are bilobar treatments, large tumor volume, high radiation dose, previous chemotherapies and pretreatment liver profile abnormalities.

At present, outside of the prospective studies, the main role of RE is as a “salvage” therapy and it has some benefit and advantages in disease which is refractory to chemotherapy when the liver tumor burden is >25%, two or more lines of chemotherapy have failed or the CEA level is greatly raised [84]. Radioembolization is now recommended in the ESMO guidelines for patients suffering from limited liver disease [85]. Results from the large prospective trials including SIRFLOX [86] and the worldwide FOXFIRE [87] are expected shortly and should establish the role of renewable energies in the treatment of liver metastases of colorectal cancer in early lines of therapy.

**Conclusion and future trends**

The treatment of colorectal liver metastases is now multimodal and includes surgery, chemotherapy and percutaneous ablation. Percutaneous ablation is a recent therapy and offers an additional curative treatment option for inoperable metastases or for patients who are not candidates for surgery.

Percutaneous ablation has been shown to offer equivalent local efficacy to surgery in both liver and lung, is far less invasive and spares the parenchyma in selected patients, particularly in terms of tumor size. Candidates for surgery with 1 to 3 metastases under 2–3 cm in size which are fully visible and can be targeted on imaging should be discussed in an MDT to consider percutaneous ablation for either lung or liver, possibly in the same session. Because of the limitations and the contraindications of percutaneous ablation, the proportion of patients who can actually receive the technique is small compared to the initial number of potential candidates. Clearly, pre-ablation imaging should be the same as a pre-surgical assessment including a minimum of chest, abdominal and pelvic CT and ideally PET-CT, which has been shown to change the treatment plan in 26% of patients intended for percutaneous ablation [88]. Increased imaging sensitivity in the future should allow an increasingly exhaustive assessment of the disease avoiding preoperative discoveries and increasing the role of percutaneous ablation for small paucimetastatic tumors. Prognostic indicators and scores for both liver [22] and lung [37] will help to select patients liable to benefit from percutaneous treatment alone and those who are potential candidates for ablation treatment combined with neoadjuvant or adjuvant therapy because of a high risk of recurrence. Advances in molecular biology will help to better define individualized strategies and the possibility of carrying out a biopsy at the time of percutaneous ablation will need to be used more widely for this purpose. The undisputed advantages of percutaneous ablation are that it is minimally invasive, and carries a low morbidity, properties which should be capitalized on in the future to enable sequential or combined treatments with systemic chemotherapy, targeted therapy or immunotherapy. Although ablation is primarily used at present as an independent technique, with the main aim of completely destroying tumor cells in the target volume, combination treatment strategies remain to be designed and assessed to reduce both the local and remote recurrence of the tumor. As an example, an increase in ablation volume and efficacy has been demonstrated in animals pre-treated with sorafenib [89] and percutaneous ablation produces rises in plasma IL-6 of up to 54 times normal values [90] which could be used beneficially to optimize the immunotherapy.
treatments which are currently being developed for cancer.

If patients are not initially candidates for surgery or ablation, hepatic intra-arterial chemotherapy achieves good response rates, in turn contributing to high subsequent surgical excision or percutaneous ablation response rates. The feasibility of hepatic intra-arterial chemotherapy is continually improving and percutaneous catheter/ chamber implantation is avoiding the need for surgery. TACE (transcatheter arterial embolization) and radioembolization are still currently salvage therapies pending the results of large studies [86].

Take-home messages
- Percutaneous destruction of liver and lung metastases under 2 to 3 cm in size is over 90%.
- Overall survival rates after radiofrequency ablation of lung metastases are similar to those obtained after surgical metastasectomy.
- Hepatic intra-arterial chemotherapy for colorectal metastases achieves response rates in the region of 90% and surgical conversion rates of over 40%.
- Radioembolization is currently recommended by ESMO as a salvage therapy for colorectal metastases with limited invasion.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

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