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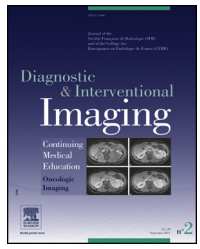

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Interventional oncology for liver and lung metastases from colorectal cancer: The current state of the art

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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.

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 CLOCC 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