Surgical treatment of liver and lung metastasis. New techniques and outcomes
Mutsaerts, E.L.A.R.

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General discussion
The major obstacles in curing cancer are the inability to prevent and the difficulty to treat metastatic disease. Metastases occur after completion of a cascade consisting of several steps. The process is selective and the surviving metastatic subclones (0.01%) have heterogeneous phenotypic properties. The effectiveness and growth potential of metastases depend on interactions between the tumour cells and the host.

It can be stated that systemic therapy should be treatment of first choice in disseminated disease, but unfortunately the current systemic therapies have only minor impact on the ultimate outcome. A multidisciplinary approach in principle is expected to be more effective. In some malignancies the occurrence of metastases is limited in number and spread is initially sometimes only to a single organ. Here, local treatment options like complete surgical removal may lead to long lasting palliation and sometimes even cure and this approach has therefore been widely successfully for years. The challenge now arises to identify preoperatively the patient who will most likely benefit from resection of haematogenous metastases.

**Morbidity and mortality of liver metastasectomy**
Guidelines for selecting a patient for surgical removal of liver metastases are: medical fit to tolerate the planned procedure, adequate post-resection organ reserve, complete resectability possible and no evidence of uncontrollable disease elsewhere. Further, surgery can only be justified if operative mortality remains substantially below anticipated 5-year survival rates with reasonable morbidity. Prognostic risk factors for postoperative morbidity as analysed in a number of series are: extent of resection, vena cava resection, concomitant colon and hepatic resection, blood loss, perioperative blood transfusion and operative time. In our study (chapter 2) in patients who underwent liver resection for metastatic cancer, we found duration of surgery and amount of perioperative blood transfusion to be the only independent and significant prognostic factors for morbidity and mortality. An interesting issue that emerged from this study is the evidence of a relationship between extended right hemihepatectomy and bile duct problems with prolonged jaundice. This finding could not be confirmed in the literature. This relationship could be explained by high risk surgical procedures in the area of the hepatic hilum (anterior segmentectomy, central bisegmentectomy, or total caudate lobectomy), damage of the remaining left bile duct, underdevelopment of the left liver lobe with a small sized left bile duct, and patients with liver cirrhosis. The importance to minimize flow inhibition (portal vein / hepatic artery) and a careful parenchyma dissection technique to prevent blood loss and bile leakage has to be underlined. We could however, not determine a perioperative factor to be exclusionary when considering a patient for resection. After hepatic metastasectomy postoperative morbidity and mortality are 27% and 2% respectively (chapter 2). Resection of hepatic metastases thus can be achieved with acceptable morbidity and such a low mortality that the operation is justified in most patients who meet the general eligibility criteria.
Survival of liver metastasectomy

Liver metastasectomy may be considered a safe procedure but not every patient is deemed suitable. Over the years, numerous factors have been considered to be contraindications due to poor outcome. For hepatic resection of metastases of colorectal origin the following factors are mentioned to be predictors of poor long term results: node-positive primary, short disease free interval from primary to metastases, more than three hepatic lesions, size of largest hepatic lesion > 5 cm, positive resection margins, extra-hepatic disease and CEA level >200 ng/ml. Our data (chapter 3) suggest that the chances for long term survival decrease with increasing number of metastases found on Computed Tomography (CT). We did not find any other factor to be significantly related to survival. Particularly not the number of metastases found in the specimen, removed and histologically confirmed was related to survival. Generally lesions can be found in the specimen that are smaller than the smallest visible on CT. Therefore our finding is rather unexpected since it sounds more logical that not the number of lesions on CT scan but the number found in the resected specimen is a predictor of outcome. An explanation for this unexpected result of our study could be the fact that the outcome of patients with more lesions found in the specimen than visualized on CT scan was relatively better than the outcome of patients with more lesions on CT scan than found in the specimen. Further it should be noted that most of the patients had besides a conventional CT, a so-called Computed Tomographic Arterial Portography (CTAP). CTAP is considered more sensitive as conventional CT. According to our protocol patients with more than four lesions were excluded for surgery. Therefore, there may be a selection bias in our patient population towards a small number (less than 5) of metastases due to the use of CTAP in the great majority of patients.

The question arises if the number of lesions on CT will change as a predictor of outcome with the introduction of the new generation of CT scans. The sensitivity of the current preoperative radiological work-up is superior to that available a decade ago. Helical CT screening and positron emission tomography may identify nodules in the 2-3 mm range, instead of the slices of minimally 7 mm which were made in the early nineties. Where the difference in number of lesions found on CT or in the surgical specimen will decrease, the prognostic impact of the number of lesions on CT might be expected to diminish.

Estimated overall survival after liver resection for hepatic metastases from colorectal origin at two year is 71% and at five year 29%.

Even patients with a recurrence in the liver after a first resection may benefit, provided comparable good patient selection is applied, with similar morbidity and mortality rates compared to a first liver resection (chapter 3).

In highly selected patients who underwent resection of non-colorectal liver metastases the 5-year overall survival was 35%, which is comparable to that of patients in whom metastasectomy for metastatic spread of colorectal origin is carried out (chapter 4). This finding is surprising because colorectal liver metastases are considered by many as regional spread through the portal system, whereas non-colorectal liver metastases are most often spread through the systemic circulation. These favourable results may be explained by
certain tumour biologic characteristics, for example long doubling time, liver as predominant site of spread, intrahepatic distribution pattern and uninvolve ment of major vessels or large bile ducts. Hepatic resection for non-colorectal metastases may also increase the efficacy of the immune response of the host due to the cytoreductive effect and render systemic chemotherapy more effective 16-18.

Minimal invasive techniques in liver and lung metastasectomy
In the past few years, new minimal invasive techniques for local management of hepatic and pulmonary malignancies have become available. Techniques for local ablation of tumours in the liver include ethanol injection, thermo-ablation with cryoprobes, interstitial laser coagulation and recently, radiofrequency ablation (RFA). In our study (chapter 5) we describe the initial multi-centre experience with radiofrequency ablation for hepatic tumours in the Netherlands. This study shows a morbidity and mortality rate of 26% and 2%, respectively, which is comparable to the risk of morbidity and mortality in series of surgical resection. Of all complications, three (6%) had a probable relationship to the RFA technique. Twenty-six patients (63%) developed a recurrence of which three at the RFA site after 6 to 12 months. Although RFA is an elegant minimal invasive technique, it has its limitations. First, it is a local treatment with all its restrictions; tumour destruction might be incomplete what can be explained by difficulties in achieving complete ablation by overlapping fields in larger tumours. This in turn may be due to hyperechoic blurring of the ultrasound image during the RFA procedure by air bubbles. The second limitation relates to the tumour localization. In our study several complications were related to the proximity of the low flow major bile ducts where RFA may result in heat induced fibrosis and stenosis. A third limitation is related to its percutaneous use; it does not allow adequate inspection of the abdominal cavity for unexpected additional extrahepatic disease. Several questions need to be addressed regarding RFA application in the treatment of hepatic tumours. First, will RFA be able to replace surgical resection of hepatic metastases? The combination of surgery for resectable liver tumours and RFA for locally unresectable lesions holds promise as a treatment with curative intent. Whether this combination improves survival is yet to be proven. It is clear that in our initial experience, adding resection to RFA brings the morbidity rate to the level of resection only. Second, up to now the golden standard for unresectable lesions is chemotherapy. Estimated one-, two-, and three-year survival rates after RFA are 93%, 69%, and 46% respectively, unrelated to the number of treated metastases 19. The long-term outcome of RFA has to be proven. At this moment a new study is launched by the European Organisation for Research and Treatment of Cancer (EORTC): Chemotherapy combined with LOcal ablation Contra Chemotherapy alone (CLOC C trial) to evaluate the role of RFA in unresectable colorectal liver metastases. In comparison with other interstitial techniques RFA has the following advantages: tumours up to 5 cm in diameter can be ablated (ethanol or acetic acid injection is only effective in tumours smaller than 3 cm in diameter), the technique is relatively cheap (interstitial laser photocoagulation
and microwave ablation is much more expensive) and in selected cases it can be carried out percutaneously (where cryoablation has the inconvenience of an obligatory laparotomy / laparoscopy, the potential complications of the cryoshock phenomenon and bleeding) 20-22.

In the last decades a growing enthusiasm with minimally invasive techniques has resulted in the emergence of a new therapeutic modality in thoracic surgical practice, the thoracoscopic resection of pulmonary lesions. Five year survival rates after pulmonary metastasectomy may be as high as 30% 23-26. The advantages of thoracoscopic removal of solitary metastases are the limited surgical trauma, which results in an improved postoperative recovery, shorter hospital stay, and decreased long-term morbidity 27-29. In chapter 6 we discuss the feasibility and accuracy of this technique for metastatic lesions and conclude that a thoracoscopic resection followed by a “wait and see” policy can be considered as a viable treatment option for patients with a solitary metastasis smaller than 3 cm and located in the periphery of the lung. The retrospective comparison of metastasectomy by thoracoscopic wedge resection and open thoracotomy is described in chapter 7. The results of this study suggest that thoracoscopic resection of peripherally located metastasis is a potentially curative procedure with an outcome that is comparable with that after resection by thoracotomy. However, from an oncological point of view the adequacy of using the minimal invasive thoracoscopic technique is questioned. CT scans may underestimate surgical findings (thoracotomy) in 42% of the patients 30. Thoracoscopy limits tactile examination of the lung, in contrast to thoracotomy, which makes palpation possible. This limitation may result in missing some nodules and consequently in reduced long-term survival 31. In our series however, the incidence of pulmonary recurrence, giving an impression of the accuracy of either method, was comparable for the two different techniques, open and closed. It is suggested that missed lesions by the thoracoscopic approach will not have influence on survival, as time to pulmonary recurrence is not a main determinant for survival, particularly in case of multiple metastases which is a poor prognostic factor. Long-term survival is uncommon when more than three metastases are found preoperatively 23,32. Patients with pulmonary recurrences after a complete lung metastasectomy by minimal invasive thoracoscopy may benefit from a second metastasectomy, either by thoracoscopy or thoracotomy. Repeated metastasectomies may prolong survival in some patients 32. Further, the current generation of helical CT screening and positron emission tomography may identify nodules in the 2-3 mm range and could be helpful to identify metastases more accurately 33-35. Another limitation relates to the tumour localization. Conversion to thoracotomy is necessary when the lesion identified on preoperative CT scan cannot be found or when thoracoscopy poses technical problems. In general conversion is necessary in 35% of patients (chapter 6). Special attention to prevent port-site metastasis is warranted. These events may occur, albeit rarely (chapter 8).

Based on our results in metastatic liver and lung disease, it seems plausible to extend the indication for metastasectomy to patients with metastases in both liver and lung. Six patients with limited number synchronous hepatic and pulmonary metastases of colorectal origin
were treated in this way. Although no long-term survivors were seen yet, we suggest considering carefully the possibility of metastasectomy in these cases since survival by this treatment option in selected patients seems to be better than after treatment with chemotherapy alone (chapter 9).

**Concluding remarks**

At the moment, surgical resection is the only approach that offers a chance of long-term survival and cure in patients with hepatic and pulmonary metastases due to lack of effective chemotherapy regimens. In the last decades several technical improvements and development of new surgical techniques have had a major impact on operative morbidity and mortality rates. With improved safety and favourable results of survival, the indications for resection of liver and lung metastases have expanded. Further improvements in imaging techniques for detection of metastatic disease will lead to a better patient selection. More clinical studies are needed to prove the survival benefit of radiofrequency ablation of liver metastases and thoracoscopic resection of pulmonary metastases. Further studies are also warranted to search for new chemotherapeutic agents and multimodality treatment schedules consisting of surgical resection and/or ablation and chemotherapy.

**References**

12. Moran BJ, O’Rourke N, Plant GR, Rees M. Computed tomographic portography in preoperative imaging of