Introduction

At presentation, 5-15% of the patients with primary colorectal cancer have developed metastases confined to the liver. Another 30-40% might develop liver metastases during the course of the disease. 1-2 Until now, surgery is the only available curative treatment for patients with colorectal liver metastases. Only 25% of the patients with hepatic metastases can be successfully treated with hepatic resection. The overall 5-year survival of patients surgically treated for curatively resectable liver metastases (solitary and multiple) varies, according to the different Duke stages, from 16-52%. 3-7 Curability of the patient depends, besides on the size, also on the amount and the localization of the metastases, and on the extent of the reached tumor-free margins after tumor resection. Additional treatment is desirable for patients with residual disease and for those with marginally tumor-free resection margins. So far chemotherapy has shown to be of only palliative value and there seems to be no role for conventional, fractionated external beam radiotherapy (EBRT) in the curative management of liver metastases following surgery. 1 The normal tissue tolerance of the adult liver for EBRT, in case of whole liver irradiation, is in the range of 25-30 Gy, far too low for giving a tumoricidal dose and although this dose might sterilize microscopical tumor no improvement in local control has been established. 8 Besides, radiation damage to intra abdominal structures adjacent to the liver which are often encompassed within the treatment field, can be severe. 9-13

By means of intraoperative radiotherapy (IORT) it is possible to deliver a high tumoricidal single dose of electron beam irradiation to the tumor or the resected tumor bed at the time of surgery. Radiosensitive normal tissues can be physically shielded or moved away from the beam path, thus minimizing unwanted radiation damage. Intraoperative radiotherapy of the liver theoretically offers the possibility to deliver a tumoricidal dose to the tumor area or the resection plane after non- or marginally curative surgery. In these cases, however, normal liver tissue will be included in the radiation field, possibly resulting in radiation damage, that may lead to postoperative complications and decreasing liver function even after a long period.

The present study was designed both to investigate the feasibility of delivering IORT to the liver and to define the tolerance dose of normal liver tissue to various high single doses of electron beam irradiation. The canine model was used to characterize both macroscopically and microscopically the short- and long term histological effects of IORT to the liver, for the purposes of applying dose-response experience to the human use of IORT.

Materials and methods

Experimental animals

To create a wound bed resembling that after resection of hepatic metastases 25 beagles underwent a partial liver resection. The liver of the beagle consists of 4 equally sized large lobes, 2 on the left and 2 on the right side, and of one to three smaller medially situated lobes. Partial resection of one of the large right lateral lobes was performed in all cases. The median age of the dogs was 14 months (range 12-16 months),...
IORT of the liver theoretically offers the possibility to deliver a tumoricidal dose to the resected tumor bed after non or marginally curative surgery. The radiation dose can be delivered precisely to the tumor by using the advantage of direct visualization. With different energies of electron beam irradiation a selection of the tissue penetration depth of the radiation dose is possible. This allows delivery of a high and thus tumoricidal radiation dose that can possibly result in increased local tumor control without increased radiation complications.

The use of IORT has been clinically investigated for various organs of the abdominal cavity. There is no experience with locoregional applied IORT to the partially resected liver. The current study was developed to study the tissue tolerance of normal and surgically manipulated canine liver to IORT.

The radiation dose can be delivered precisely to the tumor. Specific attention was paid to the tumor-free margins less than 1 cm. In case of non-curative resection no benefit in survival following additional treatment, consisting of chemotherapy or external beam radiotherapy (EBRT) is to be expected. Chemotherapy following non-curative resection has only a palliative role in improving disease free survival but has no effect on prolonging survival. External beam radiotherapy is limited to moderate, non tumoricidal doses by the tissue tolerance of the liver and the surrounding organs.

Histological alterations were minimal 3 months following the IORT procedure. Macroscopically a greyish spot was seen corresponding with the field of irradiation, occurring at all dose levels except for the control. Microscopically this presented as fibrous capsular thickening. Parenchymal changes were generally not present. One year following irradiation tissue alterations were more distinct. Macroscopically severe fibrosis with contraction of the liver tissue was seen (figure 3). Microscopically, capsular thickening, bile duct proliferation, liver cell atrophy and perportal fibrosis was seen (figure 4). Vascular structures, as within the portal zone and the central efferent vein remained largely unaffected and showed only slight signs of vascular proliferation or fibrosis. Although some of the specimen receiving the higher irradiation doses seemed to have more distinct histopathological changes, a dose effect relationship could not be observed.

The irradiated resection surface showed macroscopically much fibrotic scar tissue but had uncomplicatedly healed in both the 3 and the 12 month follow up group. Microscopically this scar tissue presented as severe fibrosis, bordered by architectural distorted liver parenchyma changing in to normal parenchyma.

Transmission electron microscope: Scattered through the parenchymal tissue degenerative changes like balloononed hepatocytes were seen (figure 6). The cytoplasm of such swollen and enlarged hepatocytes appeared to be less electron dense and swollen mitochondria and distended cisternae of the ER are diffusely seen accompanied by depletion of the glycogen particles. Most other hepatocytes show irregularly shaped nuclei although their organelles are clearly distinguishable and appear to be unaffected. Small fibre bundles lining the sinusoids are present through not as impressive as seen with SEM. For TEM as well as for SEM, no differences could be noted referring to the varying irradiation doses used.

### Discussion

Up to now surgery is the only available treatment modality that may cure patients with liver metastases for colorectal cancer. Patients left behind with microscopic residual tumor after hepatic resection, however, suffer impaired survival while patients with tumor-free margins less than 1 cm appear to have a worse prognosis over those with tumor free margins of more than 1 cm.

Transmission electron microscope: In the irradiated dogs distinct bundles of collagen like material lining the hepatocytes were seen, apparently more distinct in the dogs receiving 20 and 30 Gy, the sham irradiated dog showed no such changes. The bundles presented as a network of varying thickness (figure 5). Areas of severe destruction of hepatocytes exposing cytoplasm constituents alternated with larger areas showing normal intact hepatocytes.

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Tissue tolerance of normal and surgically manipulated canine liver to intra operative radiotherapy (IORT)

In the treatment of metastatic tumor to the liver following surgery, IORT theoretically has the advantage of treating localized areas of high risk possibly containing micrometastases and cellular appearance of the whole liver and adjacent structures. This experimental study has demonstrated that local irradiation following partial hepatectomy in the dog model can safely be performed. Although 1 year following IORT moderate parenchymal fibrosis and local hepatic atrophy of the irradiated area is found, liver function was not disturbed, indicating that doses up to 30 Gy are well tolerated.

References

In Chapter 3 the development and application of IORT are described. IORT is the application of a single high dose of (electron) radiation to an operationally exposed tumour or the surgical margins after tumour resection during an elective surgical procedure. Although the biological effectiveness (RBE) of a single dose is greater than that of fractionated therapy, the advantages of IORT are not so much based on radiobiological principles (see Chapter 2) as on physical principles: the irradiation can be applied very accurately and healthy tissues can be excluded from the treatment field.

IORT can also play a role in the treatment of tumour recurrence after conventional radiotherapy. IORT spares earlier irradiated normal tissues. In 1967, 12 years after the discovery of X-rays, the first description of IORT was published in connection with an inoperable stomach tumour. A historical overview is given of the development of radiotherapy from the first treatment for skin disorders to the present day, with current wide-ranging applications, such as external radiotherapy with 3-dimensional planning, brachytherapy, radioactive labelled antibodies and IORT. It speaks for itself that the results of animal experiments and clinical studies in combination with rapid technological progress have increased the popularity of radiotherapy over the past 100 years.

In the period from 1964 to 1976, the first clinical studies were performed in Japan on patients treated with IORT. Soon afterwards, studies were performed in the US, Spain and Germany. Since 1986, IORT has been used in clinical studies in the Netherlands (Groningen, Eindhoven) mainly for colorectal cancer. In many cases, a combination of surgery, external radiotherapy and IORT was used. These clinical studies were preceded by extensive animal experiments on the sensitivity of various tissues and organs to a single high dose of radiotherapy. The dog proved to be a reliable and comparable animal model to translate the results to the human situation.

At present, IORT is being applied to e.g. gastrointestinal tumours, breast cancer, sarcomas, pancreatic and biliary tumours and head and neck tumours. Although IORT has indicated a positive effect on survival in gastrointestinal cancer patients, similar effects have not yet been proven at other locations. Well-known problems are the difficulty of setting up prospective randomised trials and the need for multicentre studies: only a few centres are able to apply IORT, owing to the need for large infrastructural investments.

Chapter 4 describes the current treatment for colorectal liver metastases. The only treatment for liver metastases that has a chance of curing the patient is surgical resection. Increasing experience and improved diagnostics, indications, surgical techniques and perioperative care have resulted in a better cure rate for liver resections. Prognostic factors in the surgical treatment for liver metastases chiefly concern: number and size of the metastases, metastases outside the liver and the width of the tumour-free surgical margins. Treatment for liver metastases with chemotherapy, whether or not in combination with other treatment forms, still only has a palliative effect. Studies on different combinations of antitumour therapies applied according to different protocols showed no more than slight improvement in survival. One of the limiting factors was the severe side-effects of chemotherapy for the patient. Experimental techniques for the administration of antitumour medication, such as isolated liver perfusion or labelled antibodies, may help to solve this problem.

Tailored direct treatment for metastases, such as freezing (cryotherapy) or destroying them by means of heat (radiofrequency ablation and laser-induced thermotherapy), seems to have a favourable effect on inoperable metastases, although at present there are insufficient data.

In patients, radiation damage is chiefly expressed in a specific type of liver inflammation that can recover or ultimately cause organ failure. Generally, it can be concluded that fractionated radiotherapy (maximal 3 Gy fractions) with a total dose of 30 Gy can be applied to the whole liver without any clear functional damage.

Chapter 5 gives an overview of current knowledge on radiation damage to the liver. Animal studies and clinical studies have shown that the radiosensitivity of the liver varies depending on the physical parameters of the radiation, such as type of irradiation, dose, fractionation and treatment volume. In addition, the physical status of the patient and his/her liver are of importance. The use of toxic medication and surgery to the liver lead to greater radiosensitivity.

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