Local ablative therapies for colorectal liver metastases and the immune system

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Chapter 9

General Discussion

Prospects of application of local ablative therapies

As colorectal carcinoma is one of the most common cancers in the Western world and its prognosis is limited, the need for improved or new therapeutic modalities is high[1-4]. Metastasis of colorectal carcinoma to the liver occurs eventually in over 50% of patients[5,6]. When metastases are confined to the liver, curation may still be achieved by surgical resection[7,8]. At this moment, resection is the gold standard therapy, but unfortunately only 20–30% of patients are eligible for this curative treatment. This disappointing percentage may be increased through several paths. When the quantity of functioning remnant liver volume excludes successful resection, selective embolisation of the portal vein branch feeding the liver lobe containing the tumour may induce hypertrophy of the other liver lobe, resulting in increased remaining liver volume[9-11]. When adequate resection is hindered by difficulties in obtaining sufficient surgical margins, other techniques may be applied, such as cryotherapy or photodynamic therapy of the resection plane or RFA pre-treatment of the tumour directly before resection of the tumour[12]. By combining resection with local ablative techniques, the number of patients that may be curatively treated is increased.

Local ablative techniques may also offer curation when applied as single treatment. At present, local ablative techniques are of a predominantly palliative nature, but further developments and increased experience may increase its efficacy. Currently, RFA is the most promising technique for future widespread use as it is the most often used local ablative therapy for liver metastases. Initial experience with RFA in the Netherlands shows that local tumour control can be achieved with low complication rates (Chapter 7). It is expected that increased experience with RFA will improve these results. As new electrodes are being developed that will allow treatment of larger lesions, the applicability of RFA will further increase. But more importantly, as experience with this technique grows, the placement of electrodes in the tumour will also be improved. Adequate placement of the electrodes is of the utmost importance when treating tumours with RFA, as the induction of a sufficient necrotic margin around the tumour is essential in preventing new tumour outgrowth[13-15]. This pivotal part of the RFA technique may improve not only through increased experience, but also with the development of three-dimensional stereotactic systems that enable better electrode placement[16-18]. Finally, in the future, imaging techniques may be improved to the extent that real-time imaging of the exact area of necrosis induction during RFA becomes possible, securing overlapping electrode applications.

For the development of PDT as a treatment of colorectal liver metastases, a more difficult and longer road is lying ahead. While it is widely used for endoluminal treatment of mucosal tumours, this technique is still in its early development phase when it comes to treatment of solid tumours[19-21]. Our clinical trial has

shown PDT for colorectal liver metastases to be safe and feasible, with promising short-term efficacy results (Chapter 6). Current developments generate new commercially available photosensitisers and light delivery systems, that will further increase the clinical efficacy of PDT for solid tumours[22,23]. Photosensitisers are still being improved with regards to their activation wavelength, tumour selectivity and pharmacokinetics. Ideally, a photosensitiser should accumulate maximally and specifically in the target tumour within 1 hour after administration, so photosensitiser administration and subsequent tumour illumination may be performed in one continuous session. Also, there should be minimized accumulation of photosensitiser in other tissues, especially the skin, to avoid phototoxicity side-effects. If photosensitisers are manufactured that are activated by higher wavelengths, treatment of a larger tumour portion with each single application can be achieved. Thus, the number of necessary fibre insertions decreases, minimizing risk of incomplete treatment. Analogue to the electrode placement in RFA, adequate insertion of optical fibres may also be improved by the aforementioned developments in imaging techniques.

The combination of new photosensitisers and optical fibres may eventually allow for PDT to be performed in open procedures, without the currently impeding risk of light induced damage to other structures. For example, one could then conceive the immediate post treatment of resection planes of both primary tumours and liver metastases, to assure destruction of remaining micro metastases. But before these ideas can be realized, it is evident that more and larger clinical trials with PDT for solid tumours need to be performed.

While PDT has the disadvantage of delayed development and a restricted familiarity when compared to RFA, cryotherapy is used more often in clinical settings but is associated with higher complication rates[24-26]. However, new cryotherapy probes of smaller diameters are being developed and other technical aspects such as size and mobility of the cryotherapy generator are still being improved as well, so cryotherapy devices may soon match RFA generators in their highly praised easy and handy use. It still remains to be seen whether there is the necessary clinical zest to further improve this latter technique, with more and more clinicians switching over to RFA as the local ablative therapy of choice in colorectal liver metastases.

Local ablative therapies and the immune system

T cell responses against tumour associated antigens are seen in patients with both resected primary colorectal carcinoma and with metastasised colorectal carcinoma[27,28]. If present, these T cells apparently are not very effective, as patients developed disease. Accordingly, although experimental studies indicate that tumour specific immune responses can be induced by immunotherapy[29-32], the effectiveness of immuno-

therapy in clinical trials for colorectal cancer has yet to be demonstrated[33-35]. Apparently, although quality of immune response is present, its quantity is insufficient[36]. This could be partly due to the specific solid structure of colorectal liver metastases, with an extracellular matrix "protecting" tumour cells from recognition by the immune system[37]. Lymphocytes may be unable to penetrate this barrier and remain enclosed in the tumour stromal compartment, where they are not as effective as lymphocytes in the tumour epithelium[38]. Studies indicated that presence of lymphocytes in the tumour epithelium correlated with improved (disease-free) survival, whereas there was no relation between disease parameters and lymphocytes located in stroma of tumours[38,39]. Our findings described in Chapter 2 concur with this theory, as we saw that while a systemic immune response was not effective against established solid tumours, it effectively prevented circulating tumour cells, without the protective extracellular tumour matrix, from developing into lung tumours.

Studies in this thesis and done by other groups indicate that local ablative techniques like PDT, RFA and laser-induced thermotherapy (LITT) may generate or enhance a systemic tumour specific immune response. The mechanism through which this occurs is not yet fully elucidated. As illustrated in Chapters 3 and 4, it may partly be due to the local tumour destruction following RFA and PDT, with the tumour tissue remaining in situ. The protective extracellular tumour matrix is destroyed, enabling contact between tumour cells and cells of the immune system. Contrary to the situation following resection, tumour antigens become available for recognition by cells of the immune system and may thus induce a boost of the tumour specific immune response. The necrosis that is induced by local tumour ablation leads to inflammation, and the associated influx of neutrophils and macrophages may further promote the development of an immune response. Macrophages will release more inflammatory mediators, which chemotactic capacities enable a massive recruitment of immune effector cells to the damaged site. This combination of mechanically facilitated antigen exposure and mediator induced increase of immune effector cells is a unique feature of local tumour ablation that may account for a stimulating effect on the development of a systemic immune response.

Although tumour specific immune responses in experimental studies are unequivocally present, no reports are available on the immune response in patients treated with local ablative therapies. One should be careful when translating in vivo research results to a clinical setting, as the immune system in cancer patients is influenced by many varying factors. These factors will interact via several complex pathways, and what is an immunostimulant in one patient, may be inhibiting in another. There is however circumstantial clinical evidence that can substantiate this hypothesis. In Chapter 5, we showed that serum antibodies directed against a panel of colon carcinoma antigens increased in patients with liver metastases that were treated with IHP or RFA, whereas antibody levels decreased following resection of liver metastases.
We concluded that local tumour ablation indeed has a stimulatory effect on the immune system.

More knowledge on the exact nature of the interaction between local ablative therapies and the immune system could provide interesting clues for further therapeutic developments. Combining local tumour ablation with immunotherapy may enhance beneficial effects in a clinical setting. The combination of increased experience, new technical possibilities and further research into immune response enhancing effects of local ablative therapies may eventually lead to the establishment of these treatments as full-fledged alternatives for resection of liver metastases.

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