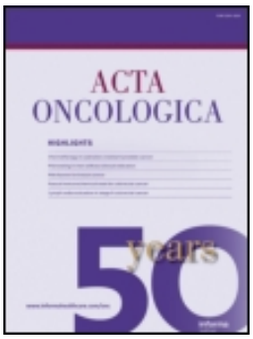

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ORIGINAL ARTICLE

The potential of proton beam radiation therapy in gastrointestinal cancer

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Abstract
A group of Swedish oncologists and hospital physicists have estimated the number of patients in Sweden suitable for proton beam therapy. The estimations have been based on current statistics of tumour incidence, number of patients potentially eligible for radiation treatment, scientific support from clinical trials and model dose planning studies and knowledge of the dose-response relations of different tumours and normal tissues. In gastrointestinal cancers, it is assessed that at least 345 patients, mainly non-resectable rectal cancers, oesophageal and liver cancers, are eligible. Great uncertainties do however exist both in the number of patients with gastrointestinal cancers suitable for radiation therapy, and in the proportion of those where proton beams may give sufficiently better results.

Cancers in the gastrointestinal tract and associated organs, chiefly the liver, biliary tracts and pancreas are common, and constitute with almost 9 000 new cases a year in Sweden almost one-fifth of the total number of cancers. Due to a generally less favourable prognosis than for other common tumour types, more than a quarter of all cancer deaths in Sweden are ascribed to a gastrointestinal cancer. Except for the most proximal, oesophagus, and distal, rectum and anus cancers, radiotherapy has traditionally played a minor role in treatment of these malignancies. Reasons for this are mainly the localization in or adjacent to radiosensitive organs and a tendency to metastasize early.

Oesophageal cancer

Every year slightly less than 400 patients in Sweden are diagnosed with oesophageal cancer [1]. The majority are men with a median age of 72 years. There is a shift in histologic type and tumour location, with an increasing proportion of adenocarcinomas in the lower part on behalf of squamous cell carcinomas in the upper parts [2]. The early cases are operated upon, while the more advanced cases are irradiated, more and more frequently in combination with chemotherapy [3,4]. The disease, however, is often so advanced that only palliative treatments are possible. The survival rate in the western world is less than 10% after five years. In Japan, where screening is performed with oesophagoscopy on symptomless persons, early detection of oesophageal cancer leads to surgery which can cure about 45% of the patients.

Radiotherapy is often performed as conformal radiotherapy (3D-CRT) against the primary tumour with a 5 cm margin cranially and caudally and the lymph nodes in mediastinum. For cancer located in the upper third, the supraclavicular fossae are included. For cancer in the lower third of oesophagus the coeliacus region is generally included. The optimal target is, however, poorly defined [5]. There is a potential role for FDG-PET in radiotherapy planning in oesophageal cancer [6]. The doses to the spinal cord, the lungs, heart, liver and kidneys must be limited. Thus, the challenges in irradiation of oesophageal cancer are many, making this site an ideal candidate for the application of sophisticated technologies [7–10]. Sometimes intraluminal brachytherapy is performed when the patient has low

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lung capacity or as a complement to laser treatment or stenting. In Japan, brachytherapy is used as a boost to the external radiation therapy in early cases, with increased survival [11].

Acute oesophagitis is mandatory to a greater or lesser extent. Long-term side-effects like pneumonitis or lung fibrosis can develop, but this has seldom been a clinical problem, since most of the patients die of their cancer before these side-effects appear. Improved long-term survival after multimodal therapies may change this.

Clinical experience of proton treatment

A few case-reports exist from Japan [12,13]. Doses around 80–88 Gy have then been given, which have resulted in a substantial number of oesophageal ulcerations. Heterogeneous cancer manifestations and heterogeneous treatments make it impossible to evaluate the benefits of protons compared to photons.

Model studies

Model studies have indicated quite a substantial benefit for proton treatment compared to photon treatment in avoiding high radiation doses in several risk organs surrounding the oesophagus [14,15].

Assessment of the number of patients eligible for proton beam therapy

In the second SBU radiotherapy report about 19 patients received curative radiation treatment against the primary tumour, extrapolating to about 80 patients yearly [16]. It was estimated that 20% of all patients with oesophageal cancer would have potential benefit of the higher doses that can be given with protons. The expected number of patients per year would then be about 80.

Research needed

There is an urgent need for randomized trials comparing photons and protons in order to substantiate the potential benefit that dose modelling studies indicate. With the most recent advances in radiation therapy delivery, there is also a need for further dose modelling studies to better define the patient groups that would potentially benefit the most.

Summary assessment

It is estimated that about 80 patients per year with oesophageal cancer might benefit from proton treatment. This figure, however, is highly uncertain. The chances of local control would then increase. At the same time, radiation toxicity, especially from the lungs would diminish. As many as possible of these treatments should be within properly controlled trials.

Gastric cancer

Incidence of gastric cancer in Sweden has declined, with some 1 000 patients diagnosed in recent years [1]. Surgery is the only established treatment, resulting in long-term cure for about 20% of the patients [17,18]. In cases where radical surgery is possible, the long-term survival rate is approximately 40%. Until recently, chemotherapy had only modest effects for palliation, with no proofs of significant gains as adjuvant therapy [19]. Pre- and postoperative therapy improved survival in one trial including 503 patients with operable gastric and lower oesophageal cancer [20].

A randomised study [21] has shown improved survival following the addition of chemoradiotherapy to radical surgery at stages IB-IV (MO). Apart from this study [21], very limited use has been made of radiotherapy for treating gastric cancer. In the American study, survival rose by 10% after five years' follow-up. The post-operative radiotherapy was given to the operation bed and to all lymph nodes at risk. The target volume is large and located close to several risk organs, lower parts of the heart and lungs, liver, kidneys and small intestine. The study showed substantial acute morbidity from the chemoradiotherapy. In a recent comparative model planning study, it was shown that 3D conformal photon therapy resulted in superior dose distributions compared with antero-posterior-posteroanterior (AP-PA) beams potential reducing toxicity [22]. The results of the study have been criticised above all on account of poor-quality surgery. It is impossible to tell whether the improved survival is due to compensation for poor surgery or whether the same or possibly a better effect would be seen with good surgery including a more adequate lymph node dissection [23].

Clinical experience of proton beam therapy, model studies for gastric cancer

None available.

Assessment of the number of cases eligible for proton beam therapy

Chemoradiotherapy after surgery for gastric cancer is not clinical routine in Sweden. This treatment has

come to be routine at many centres in the USA [24] and is being widely discussed in Europe. Even though comparative model studies using proton beams are lacking, it is reasonable to assume that protons give better dose distribution and, consequently, less impact on normal tissue than photons. This is probably the case even if varying quantities of air in the remaining ventricle/ventricle substitute have more effect on the proton than on the photon dose distribution.

If protons are to be given in primary gastric cancer, this must be done within a controlled clinical study. All patients who have undergone a radical resection for a gastric cancer below 75 years of age are potentially eligible for inclusion in a controlled study.

Research needed

Given the complete lack of model studies, these will have to be undertaken so as to provide a sounder basis for the potential advantage of proton irradiation against the tumour bed and remaining lymph nodes at risk. When a clinical proton facility is available, gastric cancer should be a suitable diagnosis for a controlled study.

Summary assessment

Radiotherapy is not being routinely used in Sweden for treating gastric cancer. Therefore, an adequate assessment of the number of potential patients is not easy. Potentially, though, many patients can be eligible for inclusion in a randomised study if treatment routines are altered, and it should also be possible for a very limited number of patients with local relapse without any other known spread to be treated with a view to better dose distribution.

Pancreatic cancer

The incidence of pancreatic cancer is declining, with upwards of 800 new cases diagnosed recently [1]. Between 10 and 15% of these cases are operable when discovered and about 30% have locally irresectable tumours and no known distant metastases. Even in case where this cancer is radically resectable, it recurs in the majority of patients and long-term cure can only be achieved in a minute percentage of the cases diagnosed [17].

Radiotherapy for pancreatic cancer has been used both pre-, intra- and post-operatively and as sole treatment, usually combined with chemotherapy for unresectable cancer. Pre- and/or intraoperative irradiation can increase respectability, but has in some reports only had minor impact on short-term survival and unfortunately no impact on long-term survival [25–28]. Post-operatively, chemoradiotherapy has been given in isolated randomised studies. The results, taken together, are inconclusive, a positive effect having been seen in some studies but not in others [29–31]. Chemoradiotherapy as sole treatment has achieved long-term relapse-free survival in a handful of patients with morphologically verified pancreatic cancer, and it is possible that the results achieved with chemoradiotherapy for locally advanced cancer are no worse than those achieved with surgery for operable cancer [30,32,33]. One small randomised trial, however, found that for patients judged to be resectable, radiochemotherapy was inferior to surgery [34].

Clinical experience of proton beam therapy, model studies for pancreatic cancer

None available.

Model studies

Since, on account of adjacent risk organs such as the medulla, liver, duodenum and small intestines and kidneys, adequate coverage of the primary tumour and the adjuvant lymph nodes is difficult and complicated to achieve, a modality is needed which can deliver a higher radiation dose to the tumour target. In a study by Zurlo and co-workers [35], proton beam therapy has yielded a better physical dose distribution.

Assessment of the number of cases eligible for proton beam therapy

Since the value of radiotherapy for treating pancreatic cancer has not been shown, it is impossible to make a really firm estimate of the number of cases eligible for proton beam therapy, but it is possible, with reasonable morbidity, to deliver an adequate radiation dose with photons to the pancreas and adjacent tissues where there is a high risk of tumour infiltration. Adequate assessment of the value of radiotherapy calls, for example, for proton beam therapy, in which case up to 240 patients, i.e. those aged under about 70 and with non-metastasing disease, are potentially eligible for inclusion in a clinical study. That study, in order to be conclusive, will probably have to be randomised. In the SBU survey, 12 treatments, corresponding to roughly 50 patients, were given in Sweden in the course of a year.

Summary assessment

Potentially up to 240 patients annually can be considered for a clinical study to evaluate proton beam therapy. Realistically speaking, however, this figure is probably far too high in relation to the present state of knowledge and therapy tradition. Pancreatic cancer, however, is a diagnosis for which a clinical proton facility in Sweden can facilitate randomised studies aimed at judging whether long-term survival can be increased for one of the diagnoses having the worst prognosis of any kind of cancer.

Cancer of the liver

Most liver cancer cases in Sweden are secondary, and so surgery, radiotherapy and other local treatment methods seldom come into question, except for colorectal cancer and perhaps a few other kinds of cancer. In future, therefore, the improvement undergone in recent years by the systematic treatment of colorectal cancer [36,37] may drastically influence the feasibility of local treatment as "consolidation", e.g. for relatively limited tumours following good effect with the systematic treatment.

Surgery is the only established curative treatment for primary cancer of the liver, mainly hepatocellular and cholangiocellular cancer. But it is seldom possible to remove the tumours (perhaps in 30–60 of the 370 new cases diagnosed in Sweden annually), either because inadequate function of the remaining liver, e.g. in cases of liver cirrhosis, or owing to proximity to great vessels. In cases of this kind, various local methods such as radiofrequency therapy, cryotherapy, interstitial laser therapy, ethanol therapy and radiotherapy have been tested [38,39]. Long-term survival has been reported, mostly in small series, but the value of these methods remains unproven, one possible reason being that the practitioners of a technique have lacked the capacity, knowledge or interest to carry out conclusive studies.

The liver is a relatively radiosensitive organ which cannot tolerate elevated doses to large volumes [40]. This has made it impossible to deliver an elevated dose to any tumour, with the result that radiotherapy has been mainly palliative [41]. A dose-response relationship appears to exist for primary hepatocellular cancer [42]. Using a stereotactic frame and many radiation fields, it has been possible to deliver relatively high doses in a small number of fractions to individual tumours measuring up to 6–7 cm. Experience of this stereotactic irradiation is limited. Most experience has been reported from Radiumhemmet, Stockholm Sweden [43]. As mentioned above, long-term survival has been reported with primary hepatocellular, cholangiocellular and secondary colorectal cancer.

Clinical experience using proton beam therapy

Protons have been used with alleged success, mainly in Japanese or Asian series, but no good reports exist [44–46]. At the Tsukuba Cancer Center, 236 medically and technically inoperable patients with hepatocellular cancer were treated with protons (5 CGEx16). Several of these patients had multiple tumours. Local control was achieved in 85% of the patients [47]. Most of the patients relapsed in other parts of the liver. Thus clinical treatment studies cannot constitute good evidence for proton beam treatment of many patients with liver cancer. Carbon ion therapy has also been used in patients with hepatocellular carcinoma with liver cirrhosis [48].

Model studies

Advanced radiation technology is needed in order to attain an elevated dose against cancer of the liver. Protons are capable of achieving, with fewer fields, better dose distributions than are possible, for example, with stereotactic techniques, though this has not been studied more closely. Physical dose advantages have been described in abstract terms, mainly from Asia. The demand for good fixation and control over the respiratory movements is probably greater with protons than when using photons.

Assessment of the number of cases eligible for proton beam therapy

Despite the lack of good evidence from clinical treatment studies or model studies, liver cancer is an interesting group of tumours which should be made a subject of clinical studies with protons. Protons can present an interesting alternative to surgery in cases where there is doubt concerning the remaining liver function or proximity to great vessels. They can also be an alternative to other local treatment methods such as radiofrequency therapy, interstitial laser therapy or stereotactic radiotherapy using photons. These techniques are developing relatively fast, but good evidence is still lacking. It is reasonable to suppose that protons can achieve an effect comparable to that of the above methods. At the same time larger tumours can probably be treated with protons than presently with these other techniques. Fifty cases annually in Sweden, equally divided between primary and secondary cases, is a very conservative estimate of the number of potential patients.

Research needed

Adequate comparative dose planning studies with many patients and optimal algorithms are desirable and should be feasible relatively soon. Clinical experience of proton beam radiotherapy for cancer of the liver should be systematically canvassed. Studies may possibly be reported between now and 2008, even though, to our knowledge, none of the studies in progress is randomised.

Clinical studies will have to be initiated when a facility is available. In the western world, randomised studies will probably be required in order to prove the value of protons. Depending on the type of cancer, the occurrence of simultaneous liver cirrhosis etc., the arms of comparison may be surgery, some other local method of tumour destruction or stereotactic irradiation with photons. The endpoint should then be local tumour control and survival. If 20% of liver cancer patients in Sweden are includable, this means a potential of 65 patients annually for studies.

Similar studies should be feasible for secondary colorectal cancer of the liver. These cases are considerably more numerous than those of primary cancer of the liver, and it is estimated that up to at least 200 patients annually may be includable in randomised studies. In these studies, survival must be the primary endpoint.

Summary assessment

It is estimated that in the first instance 65 Swedish patients annually may be eligible for proton beam therapy, given the possibility. The chances of local tumour control and, survival prospects with them should then increase. The treatments should take place within randomised studies. There is a future potential here of many more patients than indicated above. According to the SBU report, radiotherapy was given to about 75 patients in Sweden annually for primary cancer of the liver and bile ducts. It is not known how many patients were treated for colorectal cancer metastases in the liver.

Rectal cancer

Radiotherapy is widely used for rectal cancer, which is diagnosed in about 1 800 new Swedish patients annually [1]. In case of primarily operable rectal cancer, radiotherapy is used to reduce the risk of local relapse and to influence survival somewhat. In cases of primarily unresectable rectal cancer or in case of local relapse without previous irradiation, radiotherapy is given with or without cytostatics to achieve tumour reduction, to make surgery possible and, consequently, long-term cure.

In cases of operable rectal cancer, one week's irradiation together with good surgery produces outstandingly good results, with only isolated patients suffering a symptomatic local relapse [49]. Although long-term side-effects have been described following rectal cancer irradiation [50–52] and the risk of these effects can probably be reduced by using protons instead of photons, it is not reasonable to suppose that protons will replace conventional radiotherapy for primarily operable rectal cancer.

A combination of preoperative irradiation and cytostatics can facilitate surgery in 60–70% of patients, and long-term cure is achieved for one patient in every three [49,53,54]. Some patients who are apparently operated radically, however, suffer local relapses and greater tumour control is desirable. Present-day irradiation, which covers the primary tumour region and the regional lymph nodes, gives acute morbidity, especially when combined with cytostatics, and if the radiation load to adjacent organs, especially the small intestine and bladder, can be reduced, this will be an advantage. Chemotherapy is likely to be increasingly used in the light of recent studies showing a comparatively large number of patients with considerable down-staging and down-sizing, even if results from randomised trials are still limited [55–59]. In that case it should also be possible to raise the dose delivered to the primary tumour target.

Although the risk of local recurrence after primarily combined irradiation and good surgery of a primarily operable rectal cancer is very low, the local recurrences occurring are a major clinical problem. In these cases it is almost impossible, using conventional radiotherapy, to provide further adequate supplementary irradiation which, combined with surgery, can facilitate cure. IORT or brachytherapy has been tried without its value being amenable to proof [60,61]. Attempts are made with external radiotherapy, but in limited doses.

Clinical experience of proton beam therapy for rectal cancer

No proton irradiation has, to our knowledge, been given for primary rectal cancer, but a comparative IMXT-IMPT study is being planned in Boston.

Model studies

Irradiation for rectal cancer has for the most part been fairly standardised, for a long time without three-dimensional dose planning. Since both acute and long-term side-effects have been noted, increasing demands have been made for a better-defined target and more adequate radiotherapy. These de-

mands are likely to be increased, not least because the trend favours combination with increasingly intensive cytostatic therapy for the achievement of better anti-tumour effect. Comparative dose planning studies have been made of various conventional techniques [62]. The importance of IMRT has only recently been studied [63]. One study, comparing protons with conventional irradiation for locally unresectable rectal cancer, found clear physical advantages and less risk of complications from the intestines [64]. These differences were greatest for rectal cancers located high up, where the volume of small intestine is greater, but it is also essential for tumours located low down that an adequate radiation dose should be deliverable to the lateral lymph nodes up towards the internal iliac vessels.

Potential number of patients

About 15% of rectal cancers are primarily unresectable, and half of these have no metastases at diagnosis. These patients, then, numbering about 150 annually, are potential candidates for radiotherapy. In the SBU survey, prolonged irradiation to about 50 Gy was given to 21 patients, 91 on an annual basis. To these are added a number of cases of local recurrence which are also in need of more advanced radiotherapy in order to achieve a better outcome. About 50 such patients are judged eligible for radiotherapy. Since the median age for rectal cancer is relatively high, not all these 200 patients are expected to be eligible for protons; 150 patients annually is a more conservative estimate.

Further research needed

The tools available for planning at the time of the 1995 comparative model study [64] were limited, and further model studies are needed. Needless to say, IMRT must then also be included in the comparison even if not yet used clinically [65].

Apart from the above mentioned model studies, it is doubtful whether further knowledge can be obtained before there is a facility available. Patients can be irradiated at the centres which now have access to protons with a gantry system and acute toxicity recorded. When a clinical facility is available, a controlled study will be desirable, comparing conventional pre-operative radiotherapy with proton beam therapy, both being combined with cytostatics. The endpoint of the study should be local tumour control, acute toxicity and long-term survival.

Summary assessment

It is estimated that in the first instance 150 Swedish patients annually may be eligible for proton beam therapy. Treatment of this kind can then provide greater tumour control, at the same time as the acute and long-term side-effects can be limited.

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