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ORIGINAL ARTICLE

The potential of proton beam radiation therapy in head and neck 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 head and neck cancer, including thyroid cancer, it is assessed that at least 300 patients annually will gain sufficiently from proton beam therapy, both to improve tumour control and to decrease toxicity to compensate for the increased treatment costs using protons.

Head and neck (H&N) cancers are usually treated with radiotherapy, surgery alone or a combination of surgery and pre- or postoperative radiation therapy [1]. Therapeutic decisions are based on results of previous trials, local treatment traditions and known prognostic factors, both patient characteristics and clinico-pathological features. As distant metastasis are rare H&N cancers represent malignancies where loco-regional control is the most important factor likely to determine survival. Local recurrence rates increase with increasing stage from around 0% for stage I, AJCC [2], up to 50% for stage IV tumours [3]. With the possible exception of small focal recurrences, local failure is associated with poor prognosis. Besides the risk of a loco-regional recurrence, there is also a risk of treatment related side-effects. Radiation therapy can e.g. lead to dry mucus membranes and radionecrosis while surgery can result in e.g. mutilation with cosmetic and functional loss.

There are several different tumour histology types within the head and neck region. The most common is squamous cell carcinomas either poorly, moderately or well differentiated. There are also many tumour sites of origin within the head and neck (e.g. oral cavity, pharynx, larynx, paranasal sinuses, and salivary glands) with each site having numerous subsites. In Sweden annually approximately 1100 patients are diagnosed with H&N cancers with a median age of 70 years and the majority are men [4]. Thyroid cancers are usually not counted to the true H&N cancers but rather classified as malignant tumours of the endocrine system. The number of patients annually diagnosed with malignant thyroid in Sweden is approximately 320, the majority being females [4].

Due to the poor treatment outcome for stage III and IV H&N cancers chemotherapy, mainly cisplatinum based, has been used since the middle of the 1980s [5]. Over the years chemotherapy in combination with loco-regional treatment has been delivered neo-adjuvant, adjuvant or concomitant. Despite numerous randomized clinical trials it must still be admitted that the effects of chemotherapy on survival of patients with H&N cancers is uncertain whereas a positive effect is observed on local control and prevention of development of distant metastasis [6–9].

Other studies of advanced stages of H&N cancer have focused more on the possibility of organ

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preservation as the primary end-point and it seems as if induction chemotherapy followed by radiation therapy is an acceptable alternative to surgical resection in the head and neck region [10–12]. Today studies on targeted drugs like e. g. the epidermal growth factor receptor (EGFR)-binding antibody cetuximab in combination with loco-regional treatment attain great interest [13].

Thyroid cancers are mainly treated with surgery, but radiotherapy, both external beam- and radioisotope therapy, using radioiodine, contributes to tumour control [14,15].

Radiotherapy in head and neck cancer

External beam radiotherapy (EBRT) of H&N (and thyroid) cancers is technically advanced and demanding of resources. A reliable immobilisation of the patients is a prerequisite for a successful outcome of the irradiation. EBRT is administered either as 3D-CRT (3-dimensional conformal radiotherapy) or as IMRT (intensity modulated radiotherapy). At some centres brachytherapy (BT) is offered either with high dose rate (HDR), pulse dose rate (PDR) or low dose rate (LDR) after-loading techniques, either in combination with external radiotherapy or as a single treatment modality. Apart from delivering a high and homogenous absorbed dose in the planning target volume (PTV), efforts must be made to avoid excessive doses in to the organs at risk (OAR) of the head and neck region, such as the spinal cord, brainstem, brain, optic chiasm, eyes, salivary glands, inner ear and the pituitary gland. Using IMRT and a treatment planning system (TPS) for inverse dose planning, different dose constraints for the different OAR:s can be set in the TPS, which then optimises the dose distribution automatically [16]. H&N radiotherapy with curative intent is based on the principle of irradiating all known tumour tissue with a margin up to a radical dose, which usually means a biological equivalent dose of at least 66 to 70 Gy in 33–40 fractions. Additionally, adjuvant radiotherapy is often administered to clinically uninvolved lymph nodes of the neck, commonly to a dose of 46–50 Gy in 23–25 fractions. Using conventional fractionation, i. e. weekly doses of 10 Gy, usually delivered as 2 Gy per fraction, these doses imply a total treatment time of six and a half to seven weeks. There is a large interest in evaluating the effect on tumour control probability (TCP) and survival through altered fractionated radiotherapy, usually hyperfractionated and accelerated, in the management of H&N cancers. A recently published overview of randomized studies of altered fractionated H&N radiotherapy by Bourhis et al. states that both hyperfractionated and accelerated radiotherapy may improve TCP as compared to conventional radiotherapy along with increased but manageable toxicity and a modest improvement in survival [17]. The main acute side effect in all the analysed studies was mucosal reactions with a strong correlation to the degree of acceleration of the schedule.

BT offers the advantage of concentrating the dose to the tumour and spare the surrounding mucosa avoiding the marked toxicity of EBRT to the mucosa and can be used either alone, e.g. in the case of small tumours and/or for re-irradiation, or in combination with EBRT [18–21].

As already pointed out the most common chronic side-effect of H&N radiotherapy is xerostomia with concomitant nutritional- and dental problems with impaired quality of life [22,23]. The radiation effect on parotid gland function is the subject of studies, both regarding volume and dose [24]. Radiotherapy-induced soft tissue necrosis and/or osteonecrosis following external beam radiotherapy occur in between 0.4% to 56% in patients receiving doses of 70 Gy to the H&N region [25]. Other late side effects that may impair the quality of life of the patients are trismus [26] and stenosis of the oesophagus [27]. The effects on irradiation of the optic chiasm and eyes are well known and radiation induced neuropathy is one of the most disabling late effects that may occur in patients treated with EBRT for H&N cancers [28–31]. Hearing impairment with or without otorrhea, fibrosis of the neck and temporal lobe necrosis is reported following ERBT alone of nasopharyngeal carcinoma [32]. Thyroid dysfunction is reported to be as common as 40% in patients 5 years after radiotherapy for H&N cancer and thyroid function testing is therefore suggested to be part of routine post-treatment follow-up of this patient category [33]. Radiation induced secondary cancers appear both after radioisotope therapy for thyroid cancers and after EBRT of H&N cancers [34], and there are also reports describing an increased risk due to the implementation of the new techniques 3D-CRT and especially IMRT [35,36].

Clinical experience of proton beam therapy

Altogether almost 40 000 patients the world over have received proton beam radiotherapy since the first patient was treated in 1954 at Berkeley. It has not been possible to ascertain how many of these are H&N cancer patients. A MEDLINE search has not revealed any randomized controlled studies concerning treatment of these cancers. Individual case descriptions exist [37–40]. Increased loco-regional control without increased toxicity is observed in patients with locally advanced oropharyngeal cancer treated with protons as a concomitant boost with photons [41].

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Model studies

Several model studies have been published, above all from the Lomax Group (at Paul Scherrer Institute) in Switzerland, all arguing in favour of protons compared with photons [24,42–49]. In a model study of tonsil cancers, it is shown that a higher tumour dose can be administered with protons than with photons, with presumed superior local control and survival, at the same time as a lower dose is delivered to the spinal cord, mandible and contralateral parotide glands, resulting in improved quality of life and less risk of complications. The physical properties of proton beams make this irradiation particularly favourable for orbital, peri-orbital and paranasal tumours. High doses to such critical organs as the eyes, optic nerves and chiasma, carrying the risk of late tissue reaction can then be more easily avoided [44,50]. Low radiation dose to the salivary glands, implying fewer xerostomia problems, is referred to as another advantage of proton beam therapy [42,47,51]. Several of the model studies have compared intensity-modulated photons and protons, always revealing at least some advantage using protons. No advantage can be expected, however, where irradiation of laryngeal cancer is concerned, and probably not for targets in or close to the skin.

Assessment of the number of cases eligible for proton beam therapy

In the SBU survey of 12 weeks in the autumn of 2001, 156 patients received radiotherapy for primary head and neck cancer [52]. On an annual basis this means about 650 patients irradiated. The SBU report indicates than an estimated 30% of the cases are in need of a higher radiation dose for better tumour control [53]. In order to improve tumour control by dose escalation in some patients and reduce toxicity in others, it is assessed that overall up to every other patient will have a sufficient benefit from proton beams compared with IMRT. This proportion varies according to tumour site. In nasopharyngeal and paranasal sinus tumours, about 60 of the 80 irradiated patients are potential candidates, whereas very few, if any, patients with laryngeal cancer will benefit. It should be noted that BT with an interstitial approach may carry advantages for the delivery of high localized doses in e.g. the tongue [19]. A secure fixation of these movable parts is a requisite for precision radiotherapy with protons.

The late side effects after radiotherapy of the H&N region are strongly dependent not only on the total dose and dose per fraction but also on the volume that is irradiated. It is therefore reasonable to assume that patients that are irradiated on large volumes will have more benefit from proton therapy than those with small volumes. The irradiated volume will be mainly determined by the stage of disease. However, bilateral neck node irradiation almost invariably leads to large irradiated volumes with a significant risk of e.g. chronic xerostomia [54]. All of these patients are likely to benefit from proton beam therapy.

It has not been possible to accurately give a separate estimate of the number of patients with thyroid cancer, being candidates for proton therapy. Target coverage and reduced spinal irradiation is achieved using IMRT and can be an important alternative to proton therapy [55].

In salivary gland tumours (about 90 new cases every year in Sweden), the role of high-LET radiotherapy has been emphasized and both non-randomized and randomized trials have shown improved local tumour control using neutrons [56,57]. The feasibility and toxicity of treatment with carbon ions were recently described [58].

Cost-benefit estimate

The cost-effectiveness of proton beam therapy for H&N cancer has been estimated in a special study [59]. A 65-year-old man with hypopharyngeal cancer has been treated with state-of-the-art protons or with photons/electrons. Due to the great uncertainty surrounding increased anti-tumour effects and reduced side effects, as well as costs, a number of assumptions have been made in a sensitivity analysis. In the basic instance, where the risk of tumour death has been reduced by 23% and the number of dental treatments reduced as a result of reduced xerostomia, the cost per QALY gained is approximately SEK 35 000. Even subject to a number of other assumptions, e.g. concerning reduction of tumour death by 2% only, this treatment is cost-effective according to the general guidelines employed in studies of this kind [60].

Research needed

The extreme paucity of comparative studies illuminating the value of proton beam therapy compared with photon therapy means that there is scope for controlled randomized studies. When the current ARTSCAN study ongoing in Sweden is concluded in a few years' time, probably all the H&N cancer patients (except those with laryngeal cancer) can go on being randomized for photon or proton beam therapy. With the present rate of inclusion this would mean about 100 randomized patients per annum. Methods to early assess late adverse effects, e.g. from the salivary glands should be explored [24,61].

Summary assessment

It is estimated that upwards of 300 H&N cancer patients can be eligible for proton beam therapy annually. This should increase the chances of local tumour control and, accordingly, cure. At the same time, side effects, above all xerostomia, should diminish. As many of the treatments as possible should take place within the framework of randomized studies.

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