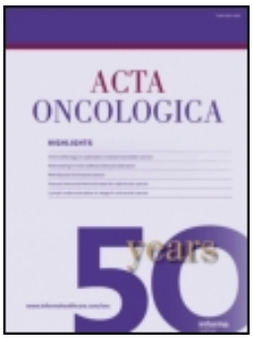

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Thomas Björk-Eriksson, Göran Bjelkengren & Bengt Glimelius (2005) The potentials of proton beam radiation therapy in malignant lymphoma, thymoma and sarcoma, Acta Oncologica, 44:8, 913-917, DOI: 10.1080/02841860500355983

To link to this article: https://doi.org/10.1080/02841860500355983

Acta Oncologica, 2005; 44: 913–917

Taylor & Francis
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ORIGINAL ARTICLE

The potentials of proton beam radiation therapy in malignant lymphoma, thymoma and sarcoma

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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. Besides sarcomas of the base of skull, which are classical sites for proton beam therapy, it is estimated that about 40 patients yearly in Sweden with sarcomas at other sites are candidates for proton beam therapy. About 20 patients each with malignant lymphomas, chiefly in the mediastinum, and thymomas are also candidates to decrease doses to surrounding heart and lungs.

Malignant lymphomas constitute a heterogeneous group of diseases, all revealing great sensitivity to chemotherapy and radiation. Altogether about 2 000 new cases of malignant lymphomas are diagnosed in Sweden annually [1]. Radiation therapy is a well-established treatment in different lymphoma types both for limited and advanced stages [2,3]. In the latter situation, it is used against residual disease after chemotherapy.

Between 20 and 30 patients are annually diagnosed with thymoma in Sweden [1]. Thymoma is an epithelial tumour which usually grows slowly. At the time of diagnosis, about half the tumours are encapsulated and do not infiltrate the surrounding tissue. However, it must be emphasized that thymoma is to be regarded and managed as a potentially invasive tumour. It is often staged according to Masoka, who defined five stages (I–IVB) [4].

Three-quarters of thymomas are located in the anterior part of the mediastinum close to the great vessels, heart, lungs and the spinal cord. Treatment aims at removing all thymoma cells. There are several treatment options [5]. Surgery alone is usually recommended for stages I–II, radiotherapy for stages II–III, chemotherapy for stages III–IV and symptomatic treatment for stage IV. Radical surgery is the first choice in cases of minor, demarcated thymomas (stages I–II) [6]. About 30–60% of these patients are in such advanced stages at diagnosis that radiotherapy or chemotherapy are indicated [5,7,8].

The number of newly diagnosed patients in Sweden with soft tissue sarcoma in 2003 was 270, and the number of newly diagnosed primary bone tumours was 70 [1]. About 35 of the patients are children or adolescents. Radiotherapy is important both in addition to surgery and as the sole local treatment [9]. In soft tissue sarcoma most patients receive radiotherapy, generally as part of the primary treatment [10].

Radiation therapy for malignant lymphoma

The radiation doses needed to locally eradicate lymphomas are much lower than in solid tumours, about 30–40 Gy versus 60 Gy or more. Since the prognosis for patients with malignant lymphoma is generally favourable [11], many patients are at risk for long-term adverse effects. The greatest experi-

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(Received 23 August 2005; accepted 15 September 2005)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860500355983

ence about long-term effects of radiation is present in Hodgkin's lymphoma (HL), since radiation has been extensively given and survival is long. Increased risks of cardiac mortality and morbidity after irradiation against mediastinum and secondary malignancies have been described [3]. Increased risks of breast cancer in young patients in HL [12,13] has been of particular concern, see also [14]. Although the relative importance of radiation in the cure of patients with malignant lymphomas has decreased, it is probably being given to almost as many patients as in the past, although much less frequently as the only treatment, and in lower doses (rather 30–35 Gy instead of 36–40 Gy) and smaller volumes to decrease the risk of the serious late adverse effects. There is, then, an increasing demand for proper planning of the lymphoma treatments, which used not to be the case. FDG-PET scans have been introduced in the RT planning of thoracic lymphoma, decreasing the subjectivity of the target definition [15].

In a comparative dose planning study, intensity-modulated radiation therapy (IMRT) was compared to 3D-conformed radiation therapy (3D-CRT) [16]. It was found that IMRT improved planning target volume coverage and reduced pulmonary toxicity parameters, i.e. the risk of pneumonitis. Whether the risk of late secondary malignancies was influenced was not analysed.

Clinical experience of proton beam therapy, model studies

Lymphoma has not traditionally been looked upon as a target for proton therapy, partly because the lymphomas are usually not small, demarcated tumours and the radiation doses have been low. Thus, clinical experience of proton therapy in malignant lymphomas is lacking. No comparative model studies have been identified.

Assessment of the number of cases suitable for proton beam therapy

The purpose of proton therapy in malignant lymphomas is not to improve the possibilities of local tumour control but to decrease the dose to surrounding tissues. Given the lack of experience, it is extremely difficult to estimate the number of patients potentially gaining from protons. HL is presently diagnosed in about 130 patients yearly in Sweden, and irradiation is given to the mediastinum in about 70 patients. In the SBU survey [10], 20 treatments were given, extrapolated to about 85 treatments every year, likely equivalent to the same number of patients yearly. Using conventional radiation, a significant dose to the breast or the heart is given to at least every third case under the age of 30–40 years. Thus, potentially 20 patients could benefit from proton beam therapy in order to more or less eliminate the risk of heart, lung and breast parenchyma radiation.

Need for research

Comparative dose planning studies according to lymphoma site in the mediastinum in particular could give an indication of how limited the radiation doses could be to the risk organs lung, heart and breast parenchyma, on similar lines to what was recently done in comparing IMRT and 3D-CRT [16]. Otherwise, it is unlikely that further knowledge can be achieved before a facility is in clinical use.

Summary assessment

It is estimated that about 20 patients with lymphoma yearly can be treated to minimize the risk of late complications further. If a proton therapy facility is available, potentially many more patients could be of interest to treat, i.e. also patients with other lymphomas than HL if the incremental costs are considered reasonable. Knowledge from randomized studies are probably unobtainable, since the results cannot be estimated until after 10–20 years of follow-up.

Radiation therapy for thymoma

All histological sub-types of thymoma are radiation-sensitive. External radiation can be used for curative treatment, either alone (stage III) or combined with surgery (pre-or post-operative treatment for stages I–II) or chemotherapy [5,17]. The radiation dose levels used historically vary between 40 and 60 Gy. In a comprehensive review of thymoma treatment [5], large radiotherapy volumes are recommended, including the supraclavicular fossae and the entire mediastinum extending to the diaphragmatic crura [5,18–20]. Five- and ten-year survivals after radiotherapy of biopsy-verified or non-radically removed stage III thymoma are around 40–60% and 30–40%, respectively [21].

It is important to take into account the risks of both acute and late side effects of radiotherapy for thymoma, up to a dose level of 40–60 Gy [17]. There is a risk of serious side effects from organs-at-risk (OARs) even at 40 Gy, the lowest recommended radiotherapy dose. Reported acute side effects of irradiation of the mediastinum include pneumonitis [22], pericarditis [23], and oesophagitis. Pulmonary

fibrosis, valvular stenosis [24], cardiac conduction system block [25] and coronary vascular lesions [26] are among the late side effects.

Clinical experience of proton beam therapy for thymoma, model studies

No published reports of any clinical experience with proton beam therapy, or any model studies for thymoma, can be found in medical scientific publications.

Assessment of the number of patients for proton beam therapy

Proton beam therapy is estimated to be potentially beneficial to about 20 thymoma patients per year in Sweden. The primary advantage would be a possible dose reduction to OARs, while maintaining the above-mentioned therapeutic dose levels.

Need for research

Clinical research and model studies may reveal whether protons will be sufficiently advantageous compared to three-dimensional conformal radiotherapy (3D CRT), primarily to reduce acute and late side effects.

Summary assessment

Just over half of the thymoma cases diagnosed in Sweden, or about 20 patients, are assessed as eligible for proton beam therapy within the framework of clinical studies. Potential advantages would primarily consist of a reduction in acute and late side effects, which are prominent with the large treatment volumes and radiation doses in current use in 3D CRT for thymoma.

Radiation therapy for sarcoma

Radiotherapy is of special importance in sarcomas close to important organs at risk, for example in tumours of the base of skull, in the orbital region and close to the spinal cord. Surgical resection in these areas is often incomplete and radiotherapy is therefore of importance [27–32]. Radical surgical resection may, however, sometimes also be difficult at other sites, such as in the retroperitoneum. Retrospective studies have shown that the radiation dose is of importance for tumour control [33]. Close to organs at risk it is frequently not possible to reach adequate dose levels.

Clinical experience of proton therapy in sarcoma

Proton therapy has been used, either alone or as a boost in combination with photon therapy, in tumours of the base of skull, and has given apparently better results than photon therapy (these studies have been described in the chapter about intracranial tumours). All studies are phase II studies. Proton therapy has also been used in tumours of the spine in combination with photon therapy with likewise good results [34]. Orbital rhabdomyosarcomas have been successfully treated with protons and at lower radiation doses to organs at risk than would be possible with photon therapy [35]. Combined photon/proton treatment of 47 patients with tumours of the axial skeleton resulted in favourable local control and overall survival in another study [34].

Model studies

Dose planning studies have shown advantages for proton therapy in tumours close to the orbit and for paraspinal tumours [36–38]. In one of these studies, intensity-modulated protons (IMPT) was compared to intensity-modulated photon therapy (IMXT) [37]. Better sparing of surrounding tissues using IMPT compared to IMXT was also observed in a patient with a pelvic Ewing sarcoma [39].

Number of cases suitable for proton therapy

Proton therapy is of importance in cases where the tumour is located close to important organs at risk. If proton therapy is available, the patients should then be offered it. The number of cases is low and can be estimated to about 10% of the number of sarcoma patients. In addition to the 20–25 patients with tumours of the base of skull, this would mean about 40 patients per year.

Need for research

Possible benefits of proton therapy in other types of sarcoma than in the base of the skull should be made the subject of studies. The lower dose levels in surrounding tissues can be advantageous even if no major organ at risk is in the vicinity, because the volumes treated are often large. This can be studied in dose planning studies and, if benefits are found later on, in clinical studies.

Summary assessment

Proton beam therapy in sarcoma is primarily of importance in tumours close to major organs at risk, as in tumours of the base of skull, orbit and spine. It

is possible, however, that proton therapy can also be of importance in extensive, non-resectable retroperitoneal sarcomas or large sarcomas also at other sites. Thus, the potential number of patients could be higher than the estimated 40 or so cases each year at the "classical" sites.

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