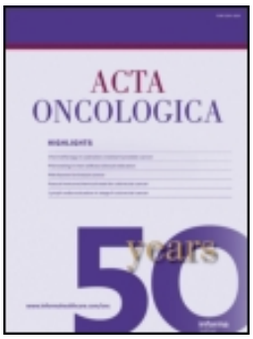

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ORIGINAL ARTICLE

The potential of proton beam radiation therapy in lung cancer (including mesothelioma)

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Abstract
A Swedish group of 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. It is estimated that about 350 patients with lung cancer and about 20 patients with mesothelioma annually may benefit from proton beam therapy.

In 2003 almost 3000 patients in Sweden were diagnosed with lung cancer [1]. Small cell lung cancer (SCLC) was diagnosed in 550 cases, 19%. The remaining 81% were non-small cell lung cancers (NSCLC). Long term results are poor [2]. Whereas combination chemotherapy is the treatment of choice for SCLC, surgical resection with lobectomy or pneumonectomy is the standard approach for limited disease NSCLC. Adjuvant chemotherapy has recently been shown to prevent recurrences and improve survival in good performance patients after radical surgery for some groups of patients with early stage NSCLC [3–5]. In contrast, adjuvant radiotherapy is detrimental after surgery for stage I+II NSCLC, likely due to the increased toxicity of the radiation [6].

The number of newly diagnosed patients with pleural mesothelioma in Sweden was 100 in the year 2002 [1]. Mesothelioma has a poor long term prognosis even if some patients can survive for a long time. The disease is often advanced when diagnosed, and radical treatment is not possible [7]. Surgery is limited to some cases with limited extension and chemotherapy is of limited value. Radiotherapy is sometimes given as a palliative treatment.

Radiation therapy in lung cancer

Concerning radiation therapy used preferentially in locally advanced cases, addition of chemotherapy or trials with continuous, hyperfractionated accelerated radiotherapy have shown some improvement in results [8].

Radiation therapy has also been used extensively also in limited disease stage patients, since many patients are not suitable for surgical resection because of comorbid conditions. There are multiple reports on the use of conventional radiotherapy, reviewed in Rowell and Williams [9] and Zimmermann et al. [10], revealing that local failures are generally seen in 40–60% of the patients. To reach a satisfactory level of tumour control in NSCLC, a radiation dose of about 90 Gy is needed. This is difficult to achieve, particularly as treatment volumes often have to include regional lymph nodes, and the patients often have a reduced lung function due to smoking habits. Small, peripheral lung cancers, on the other hand, have been successfully treated with high radiation doses given with stereotactic technique [11,12].

Limited disease SCLC is usually treated with chemotherapy in combination with radiotherapy. The radiation doses needed are lower, but the treated volumes are often large, which means that

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the risk of side effects from primarily lung tissue has to be taken into account.

Clinical experience of proton therapy in lung cancer

Clinical studies have shown that it is possible to give higher radiation doses with a combination of photon therapy 45 Gy and proton boost 28.8 Gy, in total 73.8 Gy, without causing any higher degree of toxicity [13–15]. Most of the experience is derived from the Loma Linda University Medical Center (LLUMC), CA, USA. A study of lung tissue reactions measured via CT has also shown that conformal proton therapy gives less damage to lung tissue compared to a combination of photon and proton therapy [13,14]. More recently, the LLUMC reported there experience using hypofractionated proton beam therapy to 68 patients with early stage NSCLC [16]. After doses of 51–60 CGE (Cobalt Gray Equivalent) in 10 fractions, local control rates were 87% for T1 tumours and 49% for T2 tumours at 3 years. Toxicity was minimal. Carbon ions have also been successfully applied in stage I NSCLC [17,18].

Model studies in lung cancer

Dose planning studies have shown that proton therapy gives a lower dose to lung tissue and also to other organs at risk, than what is possible with photon therapy. Since aerated lung tissue is less dense than other soft tissues of the body, the stopping region of protons is less precise in the lungs than in other tissues. This had been specially studied by Moyers et al. [15]. A dose escalation to 90 Gy is more often possible with proton therapy than with photon therapy [19].

Assessment of the number of cases where proton therapy is suitable

According to the SBU survey, 68% of the lung cancer patients are given radiation therapy and of these 25% are given radical treatment, or about 485 cases each year [20]. Probably most of the patients referred for radical radiotherapy will be offered proton therapy, if easily available. A reasonable appreciation is 350 patients each year. Light ions, or photons using a stereotactic technique, may be an alternative to protons in small tumours, where only the primary tumour is treated.

For palliation, photon or electron therapy should be adequate, and proton therapy will only be used in a few cases.

Need for research

Lung cancer should be an important area for comparative studies between photon and proton therapy [21]. With regard to small, peripheral tumours studies should compare stereotactic photon therapy to proton therapy. Treatment with light ions is also of interest in this situation. If the results appear favourable, studies can compare radiotherapy to surgery also in patients who are operable.

For NSCLC with larger and centrally located tumours and for tumours with lymph node metastases, dose planning studies should compare photon therapy to proton therapy, with the intention to increase the dose to, if possible, 90 Gy. If proton therapy alone or as a boost appears advantageous clinical studies should be initiated.

In SCLC proton therapy should be studied as a boost to primarily affected volumes and, if possible, also when treating large volumes in patients with reduced lung function.

The appropriate target volumes in the different stages of NSCLC have been a matter of debate for years [8,22,23]. It is possible that the argument "Why worry about disease you cannot see when you cannot control the disease that you can see" [22] must be replaced once the possibilities to deliver higher doses, e.g. using protons, to visible disease are improved. Better imaging possibilities, particularly using position emission tomography [24,25], will then aid in the target delineation, and facilitate the delivery of higher radiation doses to volumes in need of this for higher tumour control [26,27]. These aspects must be the focus of future clinical research to verify the potential advantages.

Summary assessment

About 350 lung cancer patients each year will potentially benefit from proton therapy. Most of them should be included in clinical studies. Proton therapy will in most cases give advantages in the form of reduced radiation doses to organs at risk and also a possibility of dose escalation, which could give increased long term survival. When treating small, peripheral tumours, light ions could potentially also be advantageous.

Radiotherapy in mesothelioma

The mesothelioma is generally located close to the lung which limits the possibilities for radiotherapy in higher doses, and for the tumours involving the abdominal cavity, the intestine also limits the radiation dose. As the tumour is often advanced, a radiation dose to large volumes is needed. This is virtually never possible using conventional techniques [28].

Clinical experience and model studies of proton therapy in mesothelioma

None known

Number of cases suitable for proton therapy in mesothelioma

Proton therapy can at the moment only be recommended for a few patients with limited disease, where protons can give a better limitation of the dose in lung tissue. In these cases proton therapy can thus facilitate a higher tumour doses than is possible with photons. The number of cases per year will probably not exceed 20. If better chemotherapy is developed in the future, the situation may change and more patients will be suited for radiotherapy after initial chemotherapy.

Need for research

At the moment there is no need for research of proton therapy in mesothelioma.

Summary assessment

Dismal disease with poor prognosis and few possibilities for radical treatment at present. About 20 patients per year can be considered suitable for proton therapy.

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