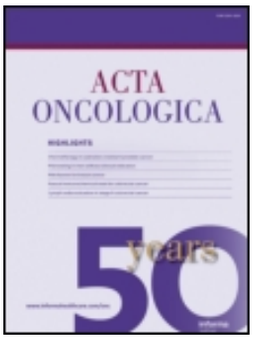

Acta Oncologica

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

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To cite this article: Bengt Johansson, Mona Ridderheim & Bengt Glimelius (2005) The potential of proton beam radiation therapy in prostate cancer, other urological cancers and gynaecological cancers, Acta Oncologica, 44:8, 890-895, DOI: 10.1080/02841860500355942

To link to this article: https://doi.org/10.1080/02841860500355942

Acta Oncologica, 2005; 44: 890–895

Taylor & Francis
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ORIGINAL ARTICLE

The potential of proton beam radiation therapy in prostate cancer, other urological cancers and gynaecological cancers

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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 prostate cancer it is estimated that annually about 300 patients and in gynaecological cancer about 50 patients, are candidates for proton beam therapy. Owing to major uncertainties, it has not been possible to give an estimate of the number of potential patients with urinary bladder cancer.

The incidence of prostate cancer has increased during recent years, due to increased use of PSA testing. Recent statistics reveal over 9000 new cases annually in Sweden [1]. If public PSA screening is implemented the number will temporarily increase even more.

Median age at diagnosis is presently somewhat lower, about 70 years, than in the past and there is a stage migration towards more early stages T1–T2, reflecting the increase in PSA testing. This change has gone much further in countries recommending PSA screening, such as USA [2].

Cancer of the bladder is diagnosed in about 2300 patients annually [1]. Seventy per cent of these cases are superficial and quite amenable to some form of intravesical treatment. Patients with muscularly infiltrative bladder cancer are treated with surgery, radiotherapy and cytostatics or combinations of these.

About 2700 cases of gynaecological cancer are diagnosed in Sweden every year [1]. Of these about 1300 are corpus cancer, about 825 ovarian cancer and about 450 cervical cancer. Vaginal cancer and vulva cancer are more unusual, totalling about 160 cases together.

Prostate cancer

Optimal treatment of prostate cancer is controversial especially for early stages (T12N0M0) where conclusive clinical studies still are awaited. Different alternatives are expectancy until tumour-related symptoms arise, radical prostatectomy or radical radiation therapy. One Swedish randomized study, SPCG 4 [3,4], showed that radical prostatectomy reduced the risk of overall cancer-related deaths and the rate of distant metastases. Another cohort study with a follow-up time >20 years, where primary expectancy was applied, showed an increased cancer-related death rate in patients who survived for more than 15 years [5]. Thus, there is fairly strong evidence that reasonably young patients with an early prostate cancer should be offered curative treatment. The strongest evidence is then for surgery [4,6,7]. The choice of therapeutic strategy in a patient with a newly diagnosed early prostate cancer is still difficult [8–10].

In more advanced stages, like T3N0M0 (and in stages T2N0M0 with unfavourable prognostic signs) radiation therapy is given to control local tumour growth and risk of tumour dissemination and death [7,11]. The intermediate and high risk group of

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(Received 23 August 2005; accepted 15 September 2005)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860500355942

prostate cancer benefits from a high target dose (>78 Gy) than previously used [12], whereas there is little evidence for this in the low risk group [13]. Patients with distant metastases are commonly treated by hormonal therapy. Hormonal therapy is also frequently used as (neo-) adjuvant therapy in localized disease [7,14].

Radiation therapy may be external beam therapy, brachytherapy or a combination of both [7]. A special feature of all radiation therapy of the prostate is the fact that the prostate gland will move between each fraction, so that a security margin of 15–20 mm has to be added to the prostate gland to safely cover the whole prostate volume. The urethra runs through the prostate and the anterior rectal wall is located dorsally in direct contact with the prostate gland. These are the most important organs at risk.

In the report from the Swedish Council on Technology Assessment in Health Care (SBU), the practice of curatively intended radiation therapy on prostate cancers was measured in the year 2001. At least 1625 patients were treated annually with curative intent [15].

Early and late reactions from the urethra, the rectal wall and neurovascular structures are the dominant sites giving rise to adverse effects, well described in many publications [16–32]. Increased total doses will result in more side effects. More sophisticated radiation techniques, particularly compared to those used in the past, may reduce the side effects, but randomised studies which compare the level of side effects using different techniques are almost entirely lacking [7,33].

Clinical experience on proton beam therapy in prostate cancer

Using protons, a great deal of experience on prostate cancer has been published from Boston and Loma Linda. A survey of 1255 patients with mainly T1–T2 tumours treated at Loma Linda between 1991 and 1997 with protons of 74 cGy (cobalt-gray equivalent) showed bNED = 73% at eight years [34]. Freedom from grade three to four toxicity from the rectum and the bladder were 99%. In a previous publication on 911 patients, the role of grade two toxicity from the rectum was 3.5% and from the bladder 5.4% [35]. It was concluded that protons at a dose of 75 Gy yielded disease-free survival rates comparable with other forms of local radiation therapy, and with minimal morbidity, based, however, upon a non-randomised comparison.

In a randomised study from Boston between 1982 and 1992, 202 patients were treated with 50.4 Gy photons using a four-field box technique. Half the patients were then given a photon boost of 17.2 Gy and the other half a proton boost of 25.2 Gy. After eight years, the local control was better in the proton group, 80% vs 60%, but the difference was not statistically significant ($p = 0.09$). The difference was, however, statistically significant in a subgroup analysis of high grade tumours [36]. The incidence of rectal bleeding was higher in the proton group. Some urinary and gastrointestinal tract toxicity persisted [21].

Preliminary experience using carbon ions was recently reported in 175 patients treated between 2000 and 2003 at Chiba, Japan [37].

Comparative dose-planning model studies

A comparative study of dose planning with photons and protons by Lee et al. [38] showed improved TCP and NTCP with protons compared to photons. More recent studies [39] have also confirmed the potential advantages of proton beams which result in a more homogeneous dose distribution. Only a limited number of patients have been planned with both proton and photon techniques and biological models have not been used to evaluate to what extent proton therapy is better than modern photon techniques like IMRT.

An estimation of suitable number of patients for proton beam therapy in Sweden

If protons were generally available it is likely that more patients would be selected for this therapy, given the physical advantages in the proton beam, permitting escalated doses with improved tumour control or reduced toxicity. However, it is far from clear whether the dose distribution advantages would be sufficient to be cost-effective.

T1–T2. Even if randomised comparative studies are lacking, it is reasonable to consider radical prostatectomy, monobrachytherapy, external beam radiotherapy (>72 Gy) or a combination of external beam + brachytherapy as isoeffective, yielding a local tumour control of 80–85% [7]. There is support in the literature for improved tumour control with dose escalation (>75 Gy) [6,40]. Dose escalation, unless the radiation technique is improved with better normal tissue sparing, also increases the risk of adverse effects [30,33] and there is still limited knowledge about the magnitude of these late toxicity effects using modern techniques.

In this report we do not consider that protons will have sufficient advantage in T1–T2, low risk cases. There is now also a strong trend in favour of the unique features of brachytherapy with relative dose

sparing of the urethra and the anterior rectal wall, although this is not universally agreed upon. Brachytherapy also offers a short treatment time.

About 1/3 of the patients who undergo a radical prostatectomy have positive surgical margins. About 900 prostatectomies were done during 2004 in Sweden. For a fraction of these non-radically operated patients, we expect proton beam therapy to be indicated, due to the better physical dose distributions. Brachytherapy is not suitable for these patients. Thus, we estimate about 100 patients per year to be suitable for proton beam therapy.

T3. Approximately 1/3 of the patients are in clinical stage T3NX at detection. After lymphadenectomy 60% of these are T3N0M0. Clinical data support a better outcome when dose escalation ($\geq$78 Gy) is applied. Prostatectomy is seldom possible and not recommended for this group. Approximately 40–50% of these patients have a life expectancy of less than 10 years and about 60% are treated by endocrine therapy only, so approximately 40% are considered for external beam radiotherapy.

T3 cases with a prostate volume exceeding about 50 cm^3 are not suitable for brachytherapy because of pubic arch interferences. We estimate that about 200 patients in stage T3N0M0 with particular features are suitable for proton beam therapy.

Cost-effectiveness calculations

In a separate study a calculation of cost-effectiveness was performed [41]. The calculations were based on a 65 years male treated by either photons or protons. It was assumed, however, based on uncertain data from clinical studies, that proton beam treatment would result in 20% fewer tumour-related deaths and 40% fewer treatment-related side effects.

The risk of death from prostate cancer is 2.5% per year. The cost per QALY will then be 239 000 SEK. In the discussion above we assumed proton beam treatment to be used mainly for high risk cases where it would be more appropriate to assume a 5% annual risk of cancer death. This assumption will result in a cost of 151 000 SEK per gained QALY. Thus, this calculation reveals that protons are cost effective, especially for patients with a somewhat worse prognosis than average.

Future research areas

Before protocols for clinical studies of proton therapy are initiated it would be appropriate to perform comparative dose planning studies between IMRT photon and proton beam techniques. It could also be possible to compare such studies with brachytherapy dose plans even if this is more complicated, due to dose inhomogeneities in the brachytherapy situation. These studies can predict the outcome in future clinical studies and thus aid in the dimension of the trials.

Recent radiobiological studies have estimated the α/β ratio for prostate cancer to be low (1.5–3) [42–44]. If this is true, hypo-fractionation with strictly conformal techniques like proton beam and brachytherapy could be very cost effective and also improve the therapeutic ratio. This issue must be evaluated in randomized protocols.

When a national proton facility is in clinical use all patients should be evaluated in prospective protocols with careful long-term follow-up. Some studies on more frequent occurring tumour groups could be evaluated in randomized protocols for more conclusive results. We consider patients after non-radical prostatectomy and high risk prostate cancers to be suitable in these aspects.

Summary assessment

We estimate that 300 patients every year will be suitable for proton beam therapy in Sweden, if treatment resources are available. Proton therapy dose escalation might give improved probability for tumour control without increased side effects. We consider large (T3), high risk tumours to be the most important group (about 200 patients per year). The cost for this treatment is estimated to 150 000 SEK per gained QALY.

Urinary bladder cancer

The role of radiotherapy in primary bladder cancer is unclear [45]. It has been used as pre-operative treatment to augment the likelihood of tumour control and as definitive treatment, either on its own or combined with cytostatics in cases where surgery is impossible or unsuitable. According to the review of literature undertaken recently by SBU [45], and an educational review [46], the literature on the subject is limited, with mostly small and inconclusive trials. Preoperative radiotherapy and surgery was standard treatment until about 1990, but this has since been removed in favour of cystectomy alone [45,47]. An SBU survey for 12 weeks in 2001 showed radiotherapy was given to about 50 bladder cancer patients against the primary tumour region. On an annual basis this means upwards of 200 patients irradiated. Just over 60% of these received "curative" radiation doses [48].

Clinical experience of proton beam therapy for urinary bladder cancer

There are no studies reported in which protons have been used for bladder cancer, but there have been four randomised studies comparing neutrons and photons. These studies [49–52] show that neutron irradiation does not increase tumour control or survival, and that it entails a heightened risk of serious side-effects [45].

Model studies

No studies have been reported. Since the small intestine and rectum are adjacent risk organs, it is possible that better dose distribution can be achieved with protons. It has not been studied whether this means greater tumour control through the feasibility of higher doses or through a reduction of long-term morbidity.

Assessment of the number of cases eligible for proton beam therapy

The number of cases eligible for proton beam therapy cannot be assessed, because the role of radiotherapy in the treatment of bladder cancer is poorly defined and no experience has been accumulated of model studies or of proton treatment of patients. If treatment is given, it would probably only be applied within clinical trials, apart from one or two exceptional patients where good dose distribution cannot be achieved with conventional irradiation.

Research needed

Model studies can give some idea of any potential for protons compared with 3D CRT and IMRT. There is a great need for clinical studies of radiotherapy for bladder cancer.

Summary assessment

It is estimated that between 100 and 150 bladder cancer patients annually in Sweden receive radiotherapy with a curative purpose. It is impossible to judge the fraction of these patients who could benefit from proton therapy.

Gynaecological cancer

Radiotherapy plays an important role in the treatment of cancer of the corpus and cervix uteri, vagina and vulva but is being used more and more rarely for ovarian cancer [53–55]. Radiotherapy still has a prominent role for cervical and vaginal cancer, both primary and recurrent. In the SBU survey [48] 359 radiation treatments were given, including 158 (44%) as external radiotherapy against the primary tumour. On an annual basis this implies about 1500 treatments, including 660 external with a principally curative purpose. The latest figures give a diagnostic breakdown of eight ovarian cancer cases, 133 vulva and vaginal cancer, 190 cervical cancer and 310 corpus cancer.

Clinical experience of proton beam therapy for gynaecological cancer

Protons have been used for irradiation for gynaecological cancer and the first cancer patient in the world to be treated, for example, was a woman with recurrent cervical cancer [56]. Since then a couple of minor studies have been reported from Japan [57–59]. The patients treated have not been judged possible to treat with intracavitary radiation, owing to very large tumours, anatomic deviations or other difficult medical conditions. The results are judged favourable, better than those which external photon therapy can achieve, and on a par with those yielded by intracavitary radiotherapy at the corresponding stage (if this had been possible to give) [59]. As an alternative to a conventional brachytherapy boost [60], 16 patients have been treated with stereotactic photon radiotherapy. The treatments were well tolerated.

Model studies

In a model study better dose distributions were seen in a patient with stage IB squamous cell carcinoma of the uterine cervix [61]. In the above-mentioned clinical trial [60] a comparative dose-planning study was performed between brachytherapy and stereotactic radiotherapy (dynamic-arc and IMRT) using photons. The external techniques improved dose homogeneity to the target and reduced the maximum dose to the rectum, when compared to brachytherapy.

Assessment of the number of cases eligible for proton beam therapy

This is very difficult to assess. One or two special situations may primarily come to be considered, e.g. primarily advanced cervical cancer where brachytherapy is not possible owing to anatomic conditions or does not provide adequate tumour coverage (e.g. stage III with bilateral parametrium extent (about 10–20 cases per annum), in isolated local/regional recurrences (about 20 cases per annum) or in isolated cases of cancer of the vulva and vagina, where tumour coverage cannot be achieved with

interstitial, intracavitary or conventional external therapy (about five cases per annum). A maximum of 50 cases annually may come to be considered. However, if stereotactic techniques gain more popularity in the future, see [60], many more patients can be potential candidates.

Summary assessment

As boost therapy towards volumes at risk to contain tumour cells, brachytherapy has an established role since very long. In cases where brachytherapy is for some reason difficult to perform, an external boost with protons may be a valid alternative. This may be of importance in up to about 50 patients annually in Sweden. However, there is a potential for treatment of many more patients, if clinical studies show that external boost irradiation has advantages over brachytherapy.

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