

Proton radiotherapy for treating the most common carcinomas

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A literature review is presented on proton radiotherapy when used for treating the most common carcinoma types such as cancer of the lung, breast and prostate. This is based on analytic parameters of dosimetry and clinical outcomes (efficacy and toxicity), along with studies on cost-effectiveness as compared to those achieved by conventional photon radiotherapy.

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Introduction

Technological advances made in radiotherapy have enabled treatment outcomes to improve. After raising beam energy, (from kilo- to mega-volts), advanced technologies in radiation therapy have now become adapted in terms of equipment, methods of beam formation and advanced therapies such as Intensity-Modulated Radiation Therapy (IMRT), Stereotactic Body Radiation Therapy (SBRT), Dynamic Conformal Arc Therapy, Image-Guided Radiation Therapy (IGRT), Adaptive Radiation Therapy (ART) and the introduction of particle-based therapies (e.g. with protons, carbon ions) [1]. Although such progress has allowed a more precise dose to be delivered to the clinical target volume, the physical characteristics of the beam limit the sparing of healthy tissue in the instance of photon radiation therapy.

One solution is to use a proton beam whose physical properties, especially the manner in which energy is deposited (so-called Bragg curve), permit the proposed therapeutic dose to be precisely given to the clinical target volume whilst limiting the dose delivered to healthy tissue and/or critical organs that either surround the tumour or are in the path of the irradiating proton beam [2–4]. Proton radiotherapy thereby enables dose escalation without increasing any risk of developing side effects and complications (i.e. a so-called safe dose escalation).

The proton beam's physical properties enable clinical indications to be determined, especially in defining low radiosensitive tumours localised within the vicinity of critical organs [3, 4].

Proton radiation therapy has been employed for the last 50 years of the twentieth century, where technology has steadily advanced from using a spread out Braag peak (SOBP) to an actively scanning beam (possible techniques of intensity-modulated proton therapy — IMPT) now used for improving dose distribution [1, 5–9]. As there are no randomised clinical trials for proton radiotherapy, it is only considered a standard procedure for intraocular choroidal melanoma (for preserving the eyeball and vision) as well as other rare tumours like those of the skull base and paediatric cancers, where the main priority is to limit the risk of developing complications. Within the last 90 years of the twentieth century, the development of proton radiotherapy has occurred within clinical centres (previously this had been in centres for physics) for treating cancer, and not just for those aforementioned cancers at the so-called "classical locations".

In recent years, the number of cancer centres providing radiotherapy worldwide has been constantly increasing. According to the Particle Therapy Co-Operative Group (PTCOG), there were 63 such centres globally operating in the first quarter of 2016 with another 33 under construction; this

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compares to just 28 operational centres from 2010. These increases, together with an increased use of proton radiotherapy in not just for the non-classical clinical cases, have led to a steady increase in the number of treated patients, which in 2010 was 73,804 and rose to 118,195 in 2014 [10, 11].

The question now arises about using proton radiotherapy for the most common cancers such as those of the lung, breast and prostate, which in 2012 were globally diagnosed as being respectively 1.8 million people (1.2 million males and 0.6 females), 1.7 million women and 1.1 million men [12]. In the same year in Poland, corresponding numbers for these cancers were respectively: 22 thousand (15 thousand males and 7 thousand females), 17 thousand and 11 thousand [13, 14].

Non-small cell lung cancer (NSCLC)

Radiation therapy is a standard treatment procedure for cases of NSCLC that are either inoperable for medical reasons (I–II stage) or are at the advanced stage III [15]. However, this entails giving a sufficiently high radiation dose which has been confirmed by studies concerning the effects of escalating dose on local control (LC); for every 1 Gy dose increment, the LC increases by 1% [16–19]. In cases of locally advanced stage III NSCLC, radiotherapy is used in combination with chemotherapy, usually as a concurrent therapy [15, 20–24].

A limiting factor in radiation therapy for NSCLC patients is that complications develop in the lungs and/or oesophagus which, for those at stage I–II, prevent the dose from being escalated whereas at stage III, this requires sub-optimal combination treatment during simultaneous radio-chemotherapy. The question thus arises whether proton radiotherapy can permit dose escalation because of the physical properties of the beam associated with the sparing of critical organs, when compared with photon radiation therapy and thereby improve treatment outcomes?

Studies that compare dosimetry (dose and tissue volumes receiving defined dose levels) received by critical organs in NSCLC patients, both at first and third stage, show that using a proton beam significantly reduces the dose and volume of irradiated critical organs as well as the integral dose [23, 25–27]. This particularly applies to the tissue volume receiving low doses (e.g. a lung volume receiving a dose of 5 or 10 Gy i.e. the V5 or V10 value), as compared to photon radiation, where respectively a 2–3-fold and 1.5–2-fold reduction of these values is observed for proton radiotherapy for stages I and III, even in cases of escalating the dose; 87.5 Gy_{RBE} vs 66 Gy [23]. Register et al. showed that compared to SBRT, proton radiotherapy when used on centrally located NSCLC I tumours significantly reduced the values: mean lung dose and lung volume receiving 5, 10, and 20 Gy and the maximum doses to the aorta, heart, pulmonary vascular and spinal cord. The differences are

particularly apparent for proton irradiation techniques used with intensity-modulated proton therapy (IMPT) employing the so-called pencil scanning beam [28]. The gains resulting from the “sparing effect” of proton radiotherapy to critical organs is also observed in NSCLC III patients. A dosimetric study by Nichols et al. compared proton radiotherapy with 3D CRT and IMRT, where the former showed a significant reduction in: lung volume receiving 20 Gy (V20), the mean lung dose (MLD), the bone marrow volume receiving 10 Gy (V10), the mean heart dose and the mean oesophageal dose. When compared to 3D CRT, the reductions were respectively 29%, 33%, 30%, 66% and 22%, whilst compared to IMRT, the corresponding values were 26%, 31%, 27%, 42% and 12% [29].

Reducing the dose and the irradiated volume of critical organs results in the toxicity of radiation therapy being reduced. For proton radiotherapy, complications in the lungs or oesophagus at the G2 severity occur in several percent of patients, but G3 complications are rarely seen [30–44].

Such data indicate that thanks to the sparing of critical organs, proton radiotherapy reduces the rates and severities of complications, thereby it possesses the potential to improve the therapeutic index in patients with inoperable lung cancer and likewise for both I and III stages of NSCLC.

High efficacy and tolerance was found by applying hypofractionation to proton radiotherapy when escalating the dose (50–70 Gy_{RBE} in 10 fractions or 15 fractions of 45–60 Gy_{RBE}) in patients with early lung cancer [31, 33, 34, 36, 38, 45]. Two- and 3-year overall survival (OS) rates ranged respectively 81–98% and 72–88% whilst for local control (LC) these were 80–97% and 74–96% respectively [33–36, 38, 39, 46]. Failure rates ranged from 2–6% (loco-regional recurrence) to 17–22% (distant metastases) [34, 35, 38].

The possibility of safely escalating the doses in proton radiotherapy can also be used in NSCLC III, where LC can be improved, and hence the survival without increasing the risk of treatment-related mortality [23, 47]. Standard management of NSCLC III patients consists of radio-chemotherapy, but is of limited efficacy since 50% of patients develop loco-regional recurrence, which reduces overall survival [48–51]. Dose escalation in photon radiotherapy for treating NSCLC III patients is controversial, because the irradiated volume size is accompanied by severe complications and an increased risk mortality associated with this treatment.

Dosimetric parameters (e.g. V5, V30) regarding critical organs (e.g. lungs, oesophagus) are significant prognostic factors for overall survival rate [48, 52, 53]. Because proton beam enables possible “sparing” of critical organs it can thereby potentially reduce complication rates, (e.g. radiation pneumonitis observed in 8% versus 32% after photon radiation therapy) and thus promises improved treatment outcomes [47]. Studies from 2015 on NSCLC III patients, evaluating escalating dose tolerability of proton radiotherapy when it was used concurrently with chemotherapy,

indicate that this procedure is well tolerated and that the 2-year overall survival ranges 51–57% [43, 44].

A retrospective study by Sejpal et al., on the toxicity of various radiation therapy methods (proton beam vs 3D CRT vs IMRT) used in combination with chemotherapy, suggests that proton radiation therapy significantly reduces severe complication rates ($G \geq 3$) in the lungs and oesophagus; rates being respectively 2%, 30%, 9% (complications in the lungs), and 5%, 18%, 44% (complications in the oesophagus). It should be noted that proton radiotherapy was administered at a higher dose to the tumour volume than for photon radiotherapy; 74 Gy_{RBE} vs 63 Gy [40]. Such study outcomes then became the basis for undertaking prospective studies. One such randomized trial study, compared toxicity and LC when using simultaneous chemotherapy with proton radiotherapy versus photon radiotherapy (used at doses of 66 and 74 Gy_{RBE} vs 74 Gy). Another was the RTOG phase III study, that assessed overall survival after radiotherapy at doses of 70 Gy (photon vs proton) when used concurrently with chemotherapy.

Breast cancer (BC)

Within the multidisciplinary treatment of breast cancer the role of radiotherapy is established post-mastectomy and breast-conserving therapy, of which it then forms an integral part. The advantages of postoperative radiotherapy is that it reduces rates of loco-regional failure and breast cancer mortality, where such rates at 15-year follow-up are respectively 19% and 5%. Unfortunately, such conferred benefits are handicapped by an increased risk of developing late cardiac complications. The mortality risk from cardiac complications increases with the time elapsing after treatment, and is found to be 1.27 at 15 years post-radiotherapy [54–57].

One of the clinical symptoms of cardiotoxicity related with radiotherapy is coronary heart disease, which is accompanied by the so-called major coronary events (MCE). The estimated MCE rates are 7.5% for every 1 Gy of mean heart dose [57]. Apart from dose, the risk of cardiac complications is significantly affected by the dose fractionation schedule adopted and the irradiated heart volume [58, 59]. In turn, the dose and the irradiated heart volume depends on the tumour location (in left vs in right breast), the size of the clinical target volume (irradiation with or without regional lymph nodes) and the radiotherapy technique used. In left-side cases, the risk of developing diseases of the coronary artery and mitral valve together with death from cardiac causes are respectively 1.25, 1.54 and 1.58 when compared to the right-side of breast cancer [60, 61].

Studies that compare dosimetry parameters for radiotherapy in BC patients, indicate that the irradiated heart volume, which receive high or low dose (V20, V5), is reduced when using a proton beam compared with photon beams; where mean heart doses are respectively 19 Gy vs 23–25 Gy [62–68].

The probability of cardiac complications was estimated at 0.5% for the proton beam and 2.1% for the photon beam radiotherapy [69].

Proton radiotherapy, as compared with the photon counterpart, allows a more homogeneous irradiation with a high dose target volume with limited doses delivered to the heart, lung and the opposite breast which is a particular advantage of IMPT [70–73]. This is particularly relevant for clinical situations where irradiation of regional lymph nodes is required. When compared to photon radiotherapy, a study by Bradley et al. indicated that proton radiotherapy, either at post-mastectomy or breast-conserving treatment, not only provides a substantially superior irradiation coverage at a high dose (D95) of the nodal target volume but also reduces average dose values: V5 in the heart (0.6% vs 16.3%), V5 and V20 in the lung (respectively 35.3% and 21.6% vs 60.5% and 35.5%) [81]. A study by McDonald et al. compared V5 value in the heart using different radiation therapy techniques post-mastectomy, which found 36% for the photon-electron, 21% for photon and 4% for proton beam used in radiotherapy [74].

The sparing effects of proton radiotherapy on critical organs is particularly apparent in cases of left-sided BC where using IMPT, as compared with IMRT, allowed a 20-fold reduction of heart dose and for the left anterior descendens (LAD) artery region (a lower arm of the left coronary artery), which is a critical structure in the development of late cardiac complications [67, 75–80]. Such findings are indicative of a potential benefit in using proton radiotherapy for adjuvant radiotherapy of BC patients, especially when risk factors for cardiac complications are present [80].

Some clinical studies have evaluated cosmetic effects and skin tolerance in BC patients treated by proton radiotherapy. Doses ranging at 30–50 Gy_{RBE} in 10–24 fractions are well tolerated; skin reactions of G1–2 severity are observed in 60–79% cases, telangiectasia at G1 grade in 15–26% and a cosmetic effect, self-assessed by the patients, as being good or satisfactory in 80–90% [65, 81–84].

Studies have also taken advantage of accelerated partial breast irradiation (APBI) [85, 86]. The efficacy of proton radiotherapy is similar to other radiotherapy techniques used in such cases, with 5-year disease-free survival and overall survival rates being respectively 94% and 95% [81]. Dosimetric comparisons of various APBI techniques demonstrate that proton radiotherapy, when compared with IMRT and brachytherapy, significantly reduces the maximum dose delivered to health breast tissue, the mean heart dose, the mean chest wall dose and the mean lung dose [87]. Findings by Girodet-Galland et al. show that symptoms of skin reactions are more common in proton radiotherapy compared to photon radiotherapy [82]. Recommendations for BC patients undergoing proton radiotherapy is to use multiple beams at each fraction of radiotherapy, or using scanning beams which improves tolerance and cosmetic outcomes [82, 83].

Prostate cancer (PC)

The efficacy of radiotherapy for treating PC patients depends on the dose delivered to the target volume as confirmed by randomised studies which escalate the dose up to the 76–79 Gy level as used in external beam radiotherapy [88–91]. Development of complications cannot be completely ruled out when doses are deposited to critical organs by advanced techniques (e.g. IMRT, arc and helical radiotherapy techniques) that employ modern technologies (e.g. image guided radiation therapy or adaptive radiotherapy); this also applying to the risk of developing complications to the gastrointestinal tract and urogenital system along with the risk of secondary tumours [92, 93].

Due to its physical properties, proton radiotherapy offers the potential for further reducing the risk of developing complications. Dosimetry studies have shown a 30–50% dose reduction to critical organs when using proton beam compared with the photon beam, even when advanced radiotherapy techniques are applied [94–100]. Reducing the mean dose of the rectum or its wall, the bladder and small intestine, (and regrettably increasing the dose to femoral bone heads) is observed in cases where the proton beam is used as booster in IMRT [101].

Clinical findings indicate that in cases of early tolerance, developing complications at G2 and G3 grades is respectively 5–12% and 1–2% likely for the urinary tract but is respectively less than 3.5% and 0.5% for the rectum [95, 96, 99]. With the passing of time after treatment, complication rates rise after 5 years at the G2 level; 21–31% in the urinary tract and 10–18% in the rectum [88, 95, 96, 102–107]. It should be emphasised that late complications are more common for those patients where attempts at dose escalation were made using proton radiotherapy alone or in the booster form after conventional radiation therapy [103, 107, 109]. A randomised phase III study by Shipley et al. indeed confirmed this, where the efficacy of 75.6 Gy (photon radiotherapy with proton “boost”) vs 67.2 Gy (photon radiotherapy) was compared. Within 8-year post-treatment, complication rates for the rectum and the urinary tract were 32% and 19% respectively when proton radiotherapy was administered as a “boost” to photon radiotherapy as respectively compared to 12% and 8% rates when proton radiotherapy was used alone [109]. Retrospective studies on early toxicity showed that the complication rates were statistically significantly reduced in the urinary tract during 6 months after proton radiotherapy compared to IMRT, but such differences gradually diminished with time of observation [102].

Other clinical data has demonstrated clear differences in complication rates for the gastrointestinal tract, where the less toxic method proved to be photon radiotherapy using the IMRT technique [110]. An assessment of the quality of life (QOL), through comparing proton radiotherapy with IMRT, Hoppe et al. showed no differences in summation

scales for the intestine, urinary incontinence, urinary tract obstruction and libido. Rectal symptoms were the only ones different, which occurred more frequently after IMRT [111].

A randomized study by Zietman et al. which compared proton “boost” doses of 19.8 Gy_{RBE} vs 28.8 Gy_{RBE} given after photon beam dose of 50.4 Gy, showed that after administering the total doses of respectively 70.2 Gy vs 79.2 Gy, the former had significantly lower rates of biochemical failure than the latter; 32.4% vs 16.6% ($p < 0.0001$). No significant differences in the rates and severity of side effects were however found, nor in overall survival rates [88, 103].

Proton radiotherapy is also used as a stand-alone radiotherapy so that doses can be increased to 74–78 Gy_{RBE} by conventional fractionation or in hypofractionation dose regimens of 35–60 Gy_{RBE} in 5–20 fractions [99, 104, 106, 107]. Outcomes from these procedures demonstrate high efficacy but low toxicity. After five years, biochemically recurrence-free survival was 93–100% (low risk PC), 85–99% (intermediate risk PC) and 74–76% (high risk PC). A prospective randomised study by Vargas et al. compared two doses of proton radiotherapy (i.e. 38 Gy_{RBE} in 5 fractions vs 79.2 Gy_{RBE} in 44 fractions) and found similar efficacy and tolerability for both. Nor were any differences seen between these groups in their quality of life using the EPIC scale (Expanded Prostate Index Composite) [112].

Although proton radiotherapy enables dose escalation without increased early toxicity (both in “boost” and stand-alone modes), this effect is nevertheless lost over time after treatment in cases of symptoms found in the gastrointestinal and urinary tracts.

Conclusions

Despite the undoubted advantages of proton radiotherapy, it is still considered a study method. Reasons for this are the lack of modern and controlled clinical trials that compare this method with current photon radiotherapy techniques, as well as its high operating costs. Even though there have been clinical studies for the last 60 years on proton radiotherapy, these have been on relatively small numbers of patients which, particularly in the case of common cancers, not only precludes formulating definitive recommendations but makes it even difficult to come to any preliminary conclusions. A classic example is the problem of comparing toxicity and efficacy of proton radiotherapy with brachytherapy in patients suffering early prostate cancer.

A cost-effectiveness analysis by Verma et al. [113] showed that proton radiotherapy is cost-effectiveness (based on QALY which is quality-adjusted life-years) for paediatric brain tumours, well-selected breast cancer, locoregionally advanced lung cancer and in head & neck cancers with a high risk of toxicity to the mucous membrane. In cases of prostate and early lung cancers, this technique has however not shown to be cost-effective as a medical procedure.

Thus for most common cancers, the “entrance door” to the widespread use of proton radiotherapy may only be opened through modern and controlled clinical trials. This assumes that its superiority over photon radiotherapy can be demonstrated in terms of toxicity, local control and overall survival, together with lowered operating costs.

Conflicts of interest: none declared

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