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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 suboptimal combination treatment during simultaneous radiochemotherapy. 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 ≥ 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.

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References

1. Thariat J, Hannoun-Levi JM, Myint AS et al. Past, present, and future of radiotherapy for benefit of patients. *Nat Rev Clin Oncol* 2013; 10: 52–60.
2. Paganetti H, van Luijk P. Biological considerations when comparing proton therapy with photon therapy. *Semin Radiat Oncol* 2013; 23: 77–87.
3. Uhl M, Hrfarth K, Debus J. Comparing the use of protons and carbon ions for treatment. *Cancer J* 2014; 20: 433–439.
4. Jiang GL. Particle therapy for cancers: a new weapon in radiation therapy. *Front Med* 2012; 6: 165–172.
5. Tobias CA, Lawrence JH, Born JL et al. Pituitary irradiation with high-energy proton beams: a preliminary report. *Cancer Res* 1958; 18: 121–134.
6. Lawrence JH. Proton irradiation of the pituitary. *Cancer* 1957; 10: 795–798.
7. Wilson RR. Radiological use of fast protons. *Radiology* 1946; 47: 487–491.
8. Shirai T, Furukawa T, Inaniwa T et al. Recent progress of new cancer therapy facility at HIMAC. *Proc IPAC2011* 2011; 3604–3606.
9. Suit H, DeLaney T, Goldberg S et al. Proton vs carbon ion beams in the definitive radiation treatment of cancer patients. *Radiother Oncol* 2010; 95: 3–22.
10. www.ptcog.com.
11. Jerman M. Particle therapy statistics in 2014. *Int J Particle Ther* 2015; 2: 50–54.
12. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108.
13. Zatoński WA, Sulkowska U, Didkowska J. Kilka uwag o epidemiologii nowotworów w Polsce. *Nowotwory J Oncol* 2015; 65: 179–196.
14. Wojciechowska U, Didkowska J, Zatoński W. Nowotwory złośliwe w Polsce w 2012 roku. Warszawa: Krajowy Rejestr Nowotworów, 2014.
15. Jett JR, Schild SE, Keith RL et al. Treatment of non-small cell lung cancer, stage IIIB: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132 (3 Suppl): 266S–276S.
16. Bradley J, Graham MV, Winter K et al. Toxicity and outcome results of RTOG 9311: a phase I–II dose-escalation study using three-dimensional conformal radiotherapy in patients with inopeable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005; 61: 318–328.
17. Onishi H, Araki T, Shirato H et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004; 101: 1623–1631.
18. Partridge M, Ramos M, Sardaro A et al. Dose escalation for non-small cell lung cancer: analysis and modelling of published literature. *Radiother Oncol* 2011; 99: 6–11.
19. Hayman JA, Martel MK, Ten Haken RK et al. Dose escalation in non-small cell cancer\using three-dimensional conformal radiation therapy: update of a phase I trial. *J Clin Oncol* 2001; 19: 127–136.
20. Curran WJ, Paulus R, Langer CJ et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011; 103: 1452–1460.
21. Furuse K, Fukuoka M, Kawahara M et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresected stage III non-small cell lung cancer. *J Clin Oncol* 1999; 17: 2692–2699.
22. Schild SE, Stella PJ, Geyer SM et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the eldery. *J Clin Oncol* 2003; 21: 3201–3206.
23. Chang JY, Zhang X, Wang X et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in stage I or stage III non--small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 65: 1087–1096.
24. Curran WJ, Paulus R, Langer CJ et al. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: Randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011; 103: 1452–1460.
25. Hoppe BS, Huh S, Flampouri S et al. Double-scattered proton-based stereotactic body radiotherapy for stage I lung cancer: a dosimetric comparison with photon-based stereotactic body radiotherapy. *Radiother Oncol* 2010; 97: 425–430.
26. Macdonald OK, Kruse JJ, Miller JM et al. Proton beam radiotherapy vs three-dimensional conformal stereotactic body radiotherapy in primary peripheral, early-stage non-small-cell lung carcinoma: a comparative dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2009; 75: 950–958.
27. Wang C, Nakayama H, Sugahara S et al. Comparisons of dose-volume histograms for proton-beam vs 3-D conformal x-ray therapy in patients with stage I non-small cell lung cancer. *Strahlenther Onkol* 2009; 185: 231–234.
28. Register SP, Zhang X, Mohan R et al. Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 80: 1015–1022.
29. Nichols RC, Huh SN, Henderson RH et al. Proton radiation therapy offers reduced normal lung and bone marrow exposure for patients receiving dose-escalated radiation therapy for unresectable stage III non-small--cell lung cancer: a dosimetric study. *Clin Lung Cancer* 2011; 12: 252–257.
30. Nakayama H, Satoh H, Sugahara S et al. Proton beam therapy of stage II and III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 81: 979–984.
31. Bush DA, Cheek G, Zaheer S et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-year experience at Loma Linda University Medical Center. *Int J Radiat Oncol Biol Phys* 2013; 86: 964–968.
32. Iwata H, Murakami M, Demizu Y et al. High-dose proton therapy and carbon-ion therapy for stage I non-small cel lung cancer. *Cancer* 2010; 116: 2476–2485.
33. Bush DA, Slater JD, Shin BB et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest* 2004; 126: 1198–1203.
34. Hata M, Tokuuye K, Kagei K et al. Hypofractionated high-dose proton beam tharapy for stage I non-small-cell lung cancer: prliminary results of a phase I/II clinical study. *Int J Radiat Oncol Biol Phys* 2007; 68: 786–793.
35. Nihei K, Ogino T, Ishikura S et al. High-dose proton beam therapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 65: 107–111.
36. Nakayama H, Sugahara S, Tokita M et al. Proton beam therapy for patients with medically inoperable stage I non-small-cell lung cancer at the University of Tsukuba. *Int J Radiat Oncol Biol Phys* 2010; 78: 467–471.
37. Nakayama H, Satoh H, Sugahara S et al. Proton beam tharapy of stage II and III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 81: 979–984.
38. Hatayama Y, Nakamura T, Suzuki M et al. Clinical outcomes and prognostic factors of high-dose proton beam therapy for peripheral stage I non-small-cell lung cancer. *Clin Lung Cancer* 2016; 11: 5–10.
39. Makita C, Nakamura T, Takada A et al. High-dose proton beam therapy for stage I non-small cel lung cancer: clinical outcomes and prognostic factors. *Acta Oncol* 2015; 54: 307–314.
40. Sejpal S, Komaki R, Tsao A et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for non-small cell lung cancer. *Cancer* 2011; 117: 3004–3013.
41. Chang JY, Komaki R, Lu C et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III non-small cell lung cancer. *Cancer* 2011; 117: 4707–4713.
42. Oshiro Y, Mizumoto M, Okumura T et al. Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol* 2012; 7: e370–375.
43. Hatayama Y, Nakamura T, Suzuki M et al. Preliminary results of proton-beam therapy for stage III non-small-cell lung cancer. *Curr Oncol* 2015; 22: e370–e375.
44. Hoppe BS, Henderson R, Pham D et al. A phase 2 trial of concurrent chemotherapy and proton therapy for stage III non-small cell lung can-

cer: results and reflections following early closure of single-institution study. *Int J Radiat Oncol Biol Phys* 2016; 95; 517–522.
45. Gomez DR, Gillin M, Liao Z et al. Phase 1 study of dose escalation in hypofractionated proton beam therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013; 86: 665–670.
46. Bush DA, Slater JD, Shin BB et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest* 2004; 126: 1198–1203.
47. Bonnet RB, Bush D, Cheek GA et al. Effects of proton and combined proton/photon beam radiation on pulmonary function in patients with resectable but medically inoperable non-small cell lung cancer. *Chest* 2001; 120: 1803–1810.
48. Hoppe BS, Flampouri S, Henderson RH et al. Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: technique and early results. *Clin Lung Cancer* 2012; 13: 352–358.
49. Dillman RO, Hendon J, Seagren SL et al. Improved survival in stage II non-small-cell lung cancer: seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996; 88: 1210–1215.
50. Kong FM, Ten Haken RK, Schipper MJ et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005; 63: 324–333.
51. Auperin A, Le Pechoux C, Rolland E et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; 28: 2181–2190.
52. Cox JD. Are the results of RTOG 0617 mysterious? *Int J Radiat Oncol Biol Phys* 2012; 82: 1042–1044.
53. Bradley JD, Paulus R, Komaki R et al. Standard-dose vs high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; 16: 187–199.
54. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extend of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 366: 2087–2106.
55. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; 378: 1707–1716.
56. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; 383: 2127–2135.
57. Darby SC, Ewertz M, McGale P et al. Risk of ischemic heart disease in women after radiotherapy for braest cancer. *N Engl J Med* 2013; 368: 987–998.
58. Offersen B, Hojris I, Overgaard M. Radiation-induced heart morbidity after adjuvant radiotherapy of early breast cancer — is it still an issue? *Radiother Oncol* 2011; 100: 157–159.
59. Curigliano G, Cardinale D, Suter T. Cadiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012; Suppl 7: 155–166.
60. Gagliardi G, Constine LS, Moissenko V et al. Radiation dose-volume effect in the heart. *Int J Radiat Oncol Biol Phys* 2010; 76(3 Suppl): S77–S85.
61. Darby SC, MCGale P, Taylor CW et al. Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncology* 2005; 6: 557–565.
62. Shah C, Badiyan S, Berry S et al. Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy. *Radiother Oncol* 2014; 112: 9–16.
63. Xu N, Ho MW, Li Z et al. Can proton therapy improve the therapeutic ratio in breast cancer patiets at risk for nodal disease? *Am J Clin Oncol* 2014; 37: 568–574.
64. Ares C, Khan S, Macartain AM et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? *Int J Radiat Oncol Biol Phys* 2010; 76: 685––697.
65. MacDonald SM, Jimenez R, Paetzold P et al. Proton radiotherapy for chest wall and regional lymphatic radiation: dose comparisons and treatment delivery. *Radiat Oncol* 2013: 8: 71.
66. Fogliata A, Bolsi A, Cozzi L. Critical appraisal of treatment techniques based on conventional photon beams, intensity modulated photon beams and proton beams for therapy of intact breast. *Radiother Oncol* 2002; 62: 137–145.
67. Ares C, Khan S, Macartain AM et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? *Int J Radiat Oncol Biol Phys* 2010; 76: 685–697.
68. Moon SH, Shin KH, Kim TH et al. Dosimetric comparison of four different external beam partial breast irradiation techniques: three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, helical tomotherapy, and proton beam therapy. *Radiother Oncol* 2009; 90: 66–73.
69. Johansson J, Isacsson U, Lindman H et al. Node-positive left-sided breast cancer patients after breast-coserving surgery: potential outcomes of radiotherapy modalities and techniques. *Radiother Oncol* 2002; 65: 89–98.
70. Orecchia R, Fossati P, Zurrida S et al. New frontiers in proton therapy: applications in breast cancer. *Curr Opin Oncol* 2015; 27: 427–432.
71. Fagundes M, Hug EB, Pankuch M et al. Proton therapy for local-regionally advanced breast cancer maximizes cardiac sparing. *Int J Particle Ther* 2015; 1: 827–844.
72. Xu N, Ho MW, Li Z et al. Can proton therapy improve the therapeutic ratio in breast cancer patients at risk for nodal disease? *Am J Clin Oncol* 2014; 37: 568–574.
73. Cuaron JJ, Chon B, Tsai H et al. Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Int J Radiat Oncol Biol Phys* 2015; 92: 284–291.
74. Bradley JA, Dagan R, Ho MW et al. Initial report of a prospective dosimetric and clinical feasibility trial demonstrates the potential of protons to increase the therapeutic ratio in breast cancer compared with photons. *Int J Radiat Oncol Biol Phys* 2016; 95: 411–421.
75. Jimenez RB, Goma C, Nyamwanda J et al. Intensity modulated proton therapy for postmastectomy radiation of bilateral implant reconstructed breasts: a treatment planning study. *Radiother Oncol* 2013; 107: 213–217.
76. Mast ME, Vredelveld EJ, Credoe HM et al. Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients. *Breast Cancer Res Treat* 2014; 148: 33–39.
77. Lin LL, Vennarini S, Dimofte A et al. Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer. *Acta Oncol* 2015; 54: 1032–1039.
78. Correa CR, Litt HI, Hwang WT et al. Coronary artery findings left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol* 2007; 25: 3031–3037.
79. Marks LB, Yu X, Prosnitz RG et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys* 2005; 63: 214–223.
80. Flejmer A, Nystom PW, Dohlmar F et al. Potential benefit of scanned proton beam versus photons as adjuvant radiation therapy in breast cancer. *Int J Particle Ther* 2015; 1: 845–855.
81. Bush DA, Do S, Lum S et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys* 2014; 90: 501–505.
82. Galland-Girodet S, Pashtan I, MacDonald SM et al. Long-term cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated parial-breast irradiation: a phase 1 trial. *Int J Radiat Oncol Biol Phys* 2014; 90: 493–500.
83. Chang JH, Lee NK, Kim JY et al. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiother Oncol* 2013; 108: 209–214.
84. MacDonald SM, Patel SA, Hickey S et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys* 2013; 86: 484–490.
85. Taghian AG, Kozak KR, Katz A et al. Accelerated partial breast irradiation using proton beams: initial dosimetric experirnce. *Int J Radiat Oncol Biol Phys* 2006; 65: 1404–1410.
86. Bush DA, Slater JD, Garberoglio C et al. Partial breast irradiation delivered with proton beam: results of a phase II trial. *Clin Breast Cancer* 2011; 11: 241–245.
87. Hansen TM, Barlett GK, Mannina EM et al. Dosimetric comparison of treatment techniques: brachytherapy, intensity-modulated radiation therapy, and proton beam in partial breast irradiation. *Int J Particle Ther* 2015; 2: 376–384.
88. Zietman AL, Bea K, Slater JD et al. Randomized trial comparing conventionl-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/American College of Radiology 95-09. *J Clin Oncol* 2010; 28: 1106-1111.
89. Cahlon O, Hunt M, Zelefsky KJ et al. Intensity-modulated radiation therapy: supportive data for prostate cancer. *Semin Radiat Oncol* 2008; 18: 48–57.

90. Cahlon O, Zelefsky KJ, Shippy A et al. Ultra-high dose (86,4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. *Int J Radiat Oncol Biol Phys* 2008; 71: 330–337.
91. Zietman AL, Chung CS, Coen JJ et al. 10-year outcome for men with localized prostate cancer treated with external radiation therapy: results of a cohort study. *J Urol* 2004; 171: 210–214.
92. Kosaki K, Ecker S, Habermehl D et al. Comparison intensity modulated radiotherapy (IMRT) with intensity modulated particle therapy (IMPT) using fixed beams or an ion gantry for the treatment of patients with skull base meningiomas. *Radiat Oncol* 2012; 7: 44 doi: 10.1186/1748-717X-7-44.
93. Paganetti H. Assessement of the risk for developing a second malignancy from scattered and secondary radiation in radiation therapy. *Health Phys* 2012; 103: 652–661.
94. Vargas C, Fryer A, Mahajan C et al. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; 70: 744–751.
95. Nihei K, Ogino T, Onozawa M et al. Multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. *Int J Radiat Oncol Biol Phys* 2011; 81: 390–396.
96. Mendenhall NP, Li Z, Hoppe BS et al. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; 82: 213–221.
97. Schwarz M, Pierelli A, Fiorino C et al. Helical tomotherapy and intensity modulated proton therapy in the treatment of early stage prostate cancer: a treatment planning comparison. *Radiother Oncol* 2011; 98: 74–80.
98. Talcott JA, Rossi C, Hipley WU et al. Patient-reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. *JAMA* 2010; 303: 1046–1053.
99. Slater JD, Rossi CJ, Yonemoto LT et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys* 2004; 59: 348–352.
100. Schulte RW, Slater JD, Rossi CJ et al. Value and perspectives of proton radiation therapy for limited stage prostate cancer. *Strahlenther Onkol* 2000; 176: 3–8.
101. Slater JD, Rossi CJ, Yonemoto LT et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys* 2004; 59: 348–352.
102. Yu JB, Soulos PR, Herrin J et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst* 2013; 105: 25–32.
103. Zietman AL, DeSilvio ML, Slater JD et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005; 294: 1233–1239.
104. Johansson S, Astrom L, Sandin F et al. Hypofractionated proton boost combined with external beam radiotherapy for treatment of localized prostate cancer. *Prostate Cancer* 2012; 2012: 654861.
105. Henderson RH, Hoppe BS, Marcus RB et al. Urinary functional outcomes and toxicity five years after proton therapy for low-and intermediate-risk prostate cancer: results of two prospective trials. *Acta Oncol* 2013; 52: 463–469.
106. Kim YJ, Cho KH, Pyo HR et al. A phase II study of hypofractionated proton therapy for prostate cancer. *Acta Oncol* 2013; 52: 477–485.
107. Mendenhall NP, Hoppe BS, Nichols RC et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2014; 88: 596–602.
108. Coen JJ, Bae K, Zietman AL et al. Acute and late toxicity after dose escalation to 82 GyE using conformal proton radiation for localized prostate cancer: initial report of American College of Radiology Phase II study 03-12. *Int J Radiat Oncol Biol Phys* 2011; 81: 1005–1009.
109. Shipley WU, Verhey LJ, Munzenrider JE et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys* 1995; 32: 3–12.
110. Sheets NC, Goldin GH, Meyer AM et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA* 2012; 307: 1611–1620.
111. Hoppe BS, Michalski JM, Mendenhall NP et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer* 2014; 120: 1076–1082.
112. Vargas CE, Hartsell WF, Dunn M et al. Hypofractionated versus standard fractionated proton-beam therapy for low-risk prostate cancer: interim results of a randomized trial PCG GU 002. *Am J Clin Oncol* 2015; Oct 29 [Epub ahead of print].
113. Verma V. Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. *Cancer* 2016; 122: 1483–1501.