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Systematic review

Proton therapy in lung cancer: Clinical outcomes and technical issues. A systematic review

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Abstract

Background and purpose. To determine whether, according to the currently available literature, proton therapy (PT) has a role in the treatment of non-small-cell lung cancer (NSCLC), to assess its safety and efficacy and to evaluate the main technical issues specifically related to this treatment technique. **Materials and methods.** During March 2007, two independent researchers conducted a systematic review of the current data on the treatment of NSCLC with PT. **Results.** In total, 113 reports were retrieved, 17 of which were included in the analysis. There were no prospective trials (randomized or non-randomized). Nine uncontrolled single-arm studies were available from three PT centers, providing clinical outcomes for 214 patients in total. These reports were mainly related to stage I–II tumors, with results comparable to those obtained with surgery, without significant toxicity. In addition, two papers were found that compared photon and proton dose distributions, which showed a potential for dose escalation and/or a sparing of the organ at risk with PT. Finally, six studies analyzed dosimetric and technical issues related with PT, mainly underlining the difficulties in designing dose distributions that are representative of the dose actually delivered during treatment. **Conclusions.** Although from a physical point of view PT is a good option for the treatment of NSCLC, limited data are available on its application in the clinical practice. Furthermore, the application of PT to lung cancer does present technical challenges. Because of the small number of institutions involved in the treatment of this disease, number of patients, and methodological weaknesses of the trials it is therefore not possible to draw definitive conclusions about the superiority of PT with respect to the photon techniques currently available for the treatment of NSCLC.

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Lung cancer is estimated to be the primary cause of cancer-related death worldwide and the second most commonly diagnosed cancer in both men and women in 2006 [1]. The number of new cases (of which 75–85% are represented by non-small-cell lung cancers (NSCLC)) is increasing at an annual rate of about 3%. Despite the advances in detection and treatment, the overall 5-year survival still remains very poor, particularly in advanced stages [2,3].

Radiation therapy delivered with X-rays (XRT) plays a fundamental role in the treatment of NSCLC, either as a definitive treatment of medically inoperable or surgically unresectable disease or as part of a multimodality regimen (with chemotherapy and/or surgery) for locally advanced lesions [4–6]. A major problem for NSCLC patients treated with XRT continues to be local-regional failure, with the majority of patients still dying of the disease [5,7,8]. During the last 10 years there have been several technical advances in thoracic XRT that could allow radiation dose escalation [9–11]. Three-dimensional radiotherapy (3D-CRT), with or without chemotherapy, currently represents the most common therapeutic practice, while more sophisticated treatment techniques, such as intensity-modulated radiation

therapy (IMRT) and hypofractionated stereotactic irradiation (with and without respiratory gating), are now under evaluation for selected patient subcategories [12–17].

Proton therapy (PT), i.e. radiotherapy delivered with high-energy proton beams, is now rapidly becoming a treatment option for more and more patients, after years of pioneering work carried out in a few centers around the world.

In principle, with PT it should be possible to design and deliver better dose distributions than with photons, thus allowing a possible improvement of the clinical results. The theoretical advantages offered by the physical properties of protons might make PT particularly useful for patients with limited residual pulmonary function, with large and irregular tumor shape, or for those who are treated with concurrent chemotherapy. However, it is worth to note that PT has some particular physical/technological factors that may compromise this theoretical gain at least in part [18–23]. For instance, the dose distributions achievable with protons are very sensitive to the changes in radiological depths along the beam path; in lung, due to respiration and the presence of different tissues density this issue must be carefully considered.

The clinical benefit of PT in the treatment of NSCLC has not been assessed in depth so far: only very recently, after the data collection for our study, three systematic reviews on PT in clinical oncology considered this topic without reaching a clear conclusion about its efficacy in comparison to other irradiation modalities [24–26].

The aim of our study was to perform a systematic review of the scientific literature concerning the application of PT to NSCLC, giving a summary of the clinical experience gathered so far, and reporting treatment planning studies comparing protons with photons with technical considerations.

For a complete evaluation of their possible significance, it will be important to underline the quality, the external validity and the utility of the analyzed studies.

The systematic review of the results of other types of particle therapy (carbon ions) or recently available XRT modalities (e.g. tomotherapy, cyberknife, stereotactic irradiation) is beyond the scope of this paper.

Materials and methods

Two independent researchers, plus one to settle the disputes as suggested by NHS report on systematic review [27], searched the PubMed database through March 2007 to identify studies about lung cancer and PT published in the last 10 years. Search terms used included, *proton, therapy, and lung*; the search was limited to articles in English. Reference lists of key articles were screened for additional articles. Studies were included if they reported clinical outcomes of patients treated with PT for NSCLC. Studies were also included if they reported results of treatment planning (dose-volume histograms, tumor control probabilities, etc.) or if they addressed technical issues related to PT treatment planning in lung. Review articles were excluded.

Results

In total 113 reports were retrieved from the initial PubMed and reference lists search. As a result of the abstracts reading, 92 studies were excluded because they did not fit with the inclusion criteria and four because they were review papers. There was no discrepancy between the two reviewers. Out of the remaining 17 studies complying with inclusion/exclusion criteria, four clinical trials were related to initial reports updated in the next publications; we are going to consider only the latest publication in our review.

As schematically reported in Fig. 1, in the end 13 articles were available: five were related to clinical results, two to treatment planning data, and six to technical/dosimetric considerations.

Clinical results

Clinical results about PT in NSCLC have been reported by three Institutions: the Loma Linda University Medical Center (LLUMC, Loma Linda, CA, USA) [28,29], the Proton Medical Research Center (PMRC, Tsukuba, Japan) [30,31], and the National Cancer Center Hospital East (NCCHE, Chiba, Japan) [32] updated in a series of further reports. Two reports, the

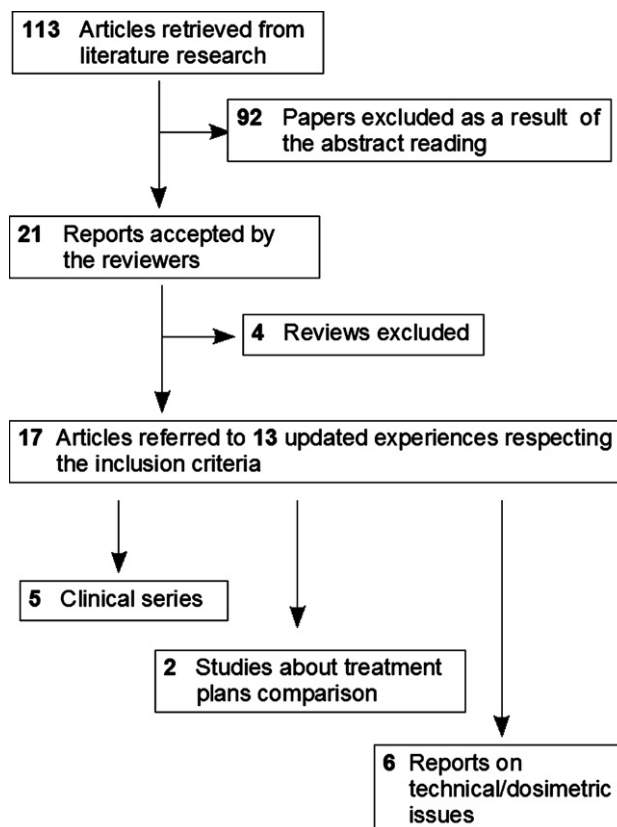


Fig. 1. Articles considered in the systematic review.

first series of Tsukuba [30] and the first report of LLUMC [28], refer to a heterogeneous patient population (stage I–IV and recurrences), the others are restricted only to limited stage disease (stage IA–IB).

In total, 214 patients were treated: 181 with early-stage diseases and 33 with more advanced lesions with a median follow-up of 14–30 months.

Early stages

The patients with limited disease were not candidate for surgical resection, either because they were medically inoperable, or because they refused surgery. Three studies are completely devoted to patients in early stage [29,31,32]. In the study of Bush et al. [29] 68 patients with clinical stage I (T1 29, T2 39) were treated with two hypofractionated schemes of 51 CGE in 10 fractions or 60 CGE in 10 fractions, in 2 weeks (where CGE = proton Gy \times 1.1). A 3-year local control of 74% with disease-specific survival of 72% was obtained, with a better control rate for T1 (87%) in comparison with T2 (49%). Acute toxicities were limited to mild fatigue and radiation dermatitis (mild-to-moderate erythema, not requiring treatment). No cases of radiation pneumonitis were observed. The study of Hata et al. [31] refers to 21 patients with stage IA (11 cases) or IB (10 cases) treated with a total dose of 50–60 Gy at a dose per fraction of 5–6 Gy (10-fractions) in a median of 15 days. A 2-year local control and cause-specific survival of 95% and 86%, respectively, was observed; no toxicities of grade 3–5 occurred (according to RTOG/EORTC morbidity scoring criteria). Nihei et al. [32]

treated 37 patients with stage IA (17 cases) and IB (20 cases) in a dose escalation study at total dose levels of 70–94 CGE with dose per fraction of 4–4.9 CGE obtaining a local control rate of 80%. Three cases of grade 3 late pulmonary toxicity (according to RTOG/EORTC radiation morbidity scoring scheme) were observed.

Advanced cases

The experience in patients with more advanced disease is more limited. In the study of Shioyama et al. [30] 14 patients with advanced stages (III, IV, recurrent disease) were treated. The short-term results (overall survival and cause-specific survival at 2 years) of the patients with stage III–IV (9 patients) were 62% and 70%, and of the recurrences (5 patients) were 80% and 100%, respectively. Long-term results (overall survival and cause-specific survival at 5 years) were both 0% for stage III/IV and 40% and 50%, respectively, for recurrences. In the initial experience of Bush et al. [28], 8 cases with stage IIIA were treated: 2-year overall survival and disease-free survival rates were 13% and 19%, respectively.

The details of the studies are reported in Tables 1 and 2.

Plan comparison studies

Two papers were analyzed comparing photon and proton dose distributions:

(1) Lee et al. [33] compared maximum prescription doses achievable with 3D-CRT vs. PT delivered with passive scattering, for a given set of constraints for the normal tissues. Neither dose-volume histograms (DVH) nor 2D dose distributions were shown in the article. For 5 out of 13 patients the proton technique was the only allowing dose escalation up to 90 Gy. However, 4 out of 13 patients could not be treated either with protons or with photons, even at a prescription dose of only 60 Gy.

(2) Chang et al. [34] compared the dose distributions obtained with photons (3D-CRT and IMRT) with those delivered with passive scattering PT at different dose levels in the PTV for 25 cases (10 stage I and 15 stage III).

For stage I lesions and a prescription dose of 66 Gy (66 CGE), PT did allow a 19%, 13% and 6% reduction in the mean values of lung V5, V10, and V20, respectively, compared to 3D-CRT. When, for the same patients, the prescribed dose was increased to 87.5 Gy (87.5 CGE) PT improved the same volume parameters by 21%, 16%, and 8% with respect to 3D-CRT.

For stage III tumors and a prescription dose of 63 Gy, the mean values of V5, V10, and V20 decreased by 15%, 11% and 5%, respectively, using PT. At a prescription dose of 74 Gy, the same values were reduced with PT by 18%, 14% and 8%, respectively (Table 3).

Finally, IMRT was used for a subgroup of 5 selected stage III patients with minimal tumor motion. For a prescribed dose of 60–63 Gy (60–63 CGE), the mean values of V5, V10, and V20 in the lung were reduced by 15%, 8% and 4%, respectively, with PT compared to IMRT. When the prescribed dose was set to 74 Gy (74 CGE), the same values decreased by 17%, 10% and 4% (Table 3).

Details were provided about the sparing for the other organs at risk (OARs) with PT, but no particulars were pro-

Table 1
Studies and patient characteristics

Reference	Country and period	Type of study	Selection criteria	No. of patients	Gender, median age (range)	P.S.	Stage	Histology	Median follow-up (range)
Shioyama et al. [30]	Japan 1983–2000	Single Institution	Medically inoperable or refusing surgery	51	M 43, F 8 74 years (25–87)	Swiss 0: 13, 1: 30, 2–3: 8	I: 28, II: 9, III: 8, IV: 1, recurrent disease: 5 IA: 11, IB: 10	SCC: 33, adenoca.: 17, large cell: 1	30 (18–153) months
Hata et al. [31]	Japan 2002–2005	Single Institution phase II study	Medically inoperable or refusing surgery	21	M 16, F 5 74 years (51–85)	ECOG 0–2	IA: 11, IB: 10	SCC: 6, adenoca.: 14, large cell: 1 NSCLC	25 (10–54) months
Bush et al. [28]	USA 1994–1998	Single Institution phase II study	Not candidate for surgical resection or patient refusal	37	M 15, F 22 72 years (54–87)	Karnofsky: 50–70: 17 80–100: 20	I: 27, II: 2, IIIa: 8	NSCLC	14 (3–45) months
Bush et al. [29]	USA nr	Single Institution phase II study	Medically inoperable or refusing surgery	68	M 30, F 38 72 years (52–87)	Karnofsky: mean 65 (50–90)	T1 29, T2 39	NSCLC	30 months
Nihei et al. [32]	Japan 1999–2003	Single Institution phase I dose escalation study + phase II	Medically inoperable or refusing surgery. Tumor size ≤ 5 cm; pO ₂ ≥ 60 torr	37	M 30, F 7 75 years (63–87)	Zubrod: 0–2	IA 17, IB 20	SCC: 15, adenoca: 15, others: 7	24 (3–62) months

Abbreviations: SCC, squamous cell carcinoma; adenoca, adenocarcinoma; NSCLC, non small cell lung cancer; M, male; F, female; P.S., performance status; OS, overall survival; LC, local control; nr, not reported.

Reference	Treatment regimens	Proton beam delivery	Technical notes	Treatment effects/ outcome	Toxicity	Remarks
Shioyama et al. [30]	TD: 49–93 Gy (median 76) dpf: 2.0–6.0 Gy (median 3.0) Overall treatment time 10–76 days (median 43) 33 pts. PT only, 18 pts. XRT + PT	Passive scattering Energy: 250 MeV	CT slices every 5 mm CTV: GTV + 5–10 mm PTV: CTV + 5 mm + some mm caudally; resp. gating after 1992	5-year OS: 29%, 70% (st. IA), 16% (st. IB); 5-year CSS: 47% 5-year LC: 89% (st. IA), 39% (st. IB); in-field recurrence: 1/9 (st. IA), 6/19 (st. IB) CR: 66% (14/21 pts.)	Acute lung tox. 92% Gr. 1, 6% Gr. 2, 2% Gr. 3	Very few acute and late tox. Results in st. IA comparable to surgery
Hata et al. [31]	TD: 50 Gy (3 pts.) dpf: 5 Gy TD: 60 Gy (18 pts.) dpf: 6 Gy Overall treatment time 13–19 days (median 15)	Passive scattering Energy: 155–200 MeV	Body cast, resp. synchronized CT slices every 5 mm, CTV: GTV + 5 mm, PTV: CTV + 5 mm + 5 mm caudally for resp. movement, resp. gating	2-year OS: 74%, 2-year CSS: 86%, 2-year LC: 95%, 2-year DFS: 79%, In-field recurrence: 1 (st. IB)	Acute tox. skin Gr. 1: 4, lung Gr. 2: 1, hematologic Gr. 1–2: 3 Late tox. Soft tissue Gr. 2: 2	100% OS in st. IA. All tumors located in peripheral regions
Bush et al. [28]	First arm: TD: 51 CGE in 10 fr. over 2 weeks : (19 pts.); second arm: 73.8 CGE with 45 Gy in 25 fr. (XRT) + 23.8 CGE in 16 fr. (PT) over 3 weeks — concomitant boost: (22 pts.)	Passive scattering 250 MeV	Target: XRT: mediastinum, PT: GTV + margin for tumor motion evaluated during normal respiration with fluoroscopy, typically 3 beams with PT	35 pts evaluable, 3-year LC: 74%, 2-year DFS: 63% 86% (st. I), 19% (st. III) 2-year LC 87% 2-year OS: 44% 39% (st. I), 13% (st. III)	2 pneumonitis (photons + protons) Several mild esophagitis (photons + protons)	3 local (in field) recurrence. Low OS rate but without evidence of recurrent cancer
Bush et al. [29]	TD: 51 CGE in 10 fr. over 2 weeks : (22 pts.); 60 CGE, in 10 fr. over 2 weeks: (46 pts.) No nodal irradiation	Passive scattering 250 MeV	Full body immobilization device, Fluoroscopy to evaluate target motion, Target: CTV (CT) + margin, 3–4 beams	68 pts evaluable, 3-year LC: 74%, T1:87%, T2: 49% DSS: 72%, 3-year OS: 44%	Mild fatigue, mild to moderate erythema. No pneumonitis, esophageal or cardiac tox.	Part of pts. enclosed in previous study [28]. LC improved compared to historical results; significant improvement in OS with higher TD (60 CGE): 55% vs. 27%
Nihei et al. [32]	TD 70–94 CGE, phase I dose levels: 70/80/88/94, dpf: 4–4.9 CGE	Passive scattering Energy: 150–190 MeV	CT images exhalation free, CTV: GTV + 8 mm, PTV: CTV + 10 mm, resp. gating, 2–4 portals	2-year LC: 80% 2-year OS: 84% 2-year LRRFS 79% (st. IA), 60% (st. IB)	Late Gr. 2 and 3 pulmonary tox. in 3 pts each.	Substantial late pulmonary tox. in larger target volumes (st. IB)

Abbreviations: TD, total dose; dpf, dose per fraction; fr., fraction; PT, proton therapy; XRT, X-ray radiation therapy; Gy, Gray; tox., toxicity; CGE, cobalt Gray equivalent; MeV, mega electron volt; CT, computerized tomography; CTV, clinical tumor volume; GTV, gross tumor volume; PTV, planning tumor volume; resp., respiratory; DSS, disease-specific survival; st., stage; LRRFS, locoregional relapse-free survival; DFS, disease-free survival; gr., grade; OS, overall survival; CSS, cause specific survival; pts., patients; LC, local control; CR, complete response.

Table 3
PT vs 3D-CRT and IMRT

	Prescription	V5 ± SE	V10 ± SE	V20 ± SE
<i>Stage I (10 pts.)</i>				
3D-CRT	66 Gy	31.8% ± 4.0	24.6% ± 3.5	15.8% ± 2.1
PT	66 CGE	13.0% ± 1.5	11.7% ± 1.4	9.8% ± 1.3
3D-CRT	87.5 Gy	34.5% ± 4.3	27.8% ± 3.7	19.3% ± 2.5
PT	87.5 CGE	13.4% ± 1.5	12.3% ± 1.4	10.9% ± 1.4
<i>Stage III (10 pts.)</i>				
3D-CRT	63 Gy	54.1% ± 3.3	46.9% ± 2.6	34.8% ± 1.5
PT	63 CGE	39.1% ± 1.4	35.6% ± 1.2	30.0% ± 1.3
3D-CRT	74 Gy	58.1% ± 5.0	50.9% ± 4.3	39.9% ± 1.9
PT	74 CGE	39.7% ± 1.4	36.6% ± 1.2	31.6% ± 1.2
<i>Stage III (5 pts.)</i>				
IMRT	60-63 Gy	58.5% ± 2.9	45.3% ± 2.1	34.5% ± 2.2
PT	60-63 CGE	43.1% ± 4.0	37.0% ± 1.8	30.8% ± 1.5
IMRT	74 Gy	61.5% ± 3.4	49.0% ± 2.3	37.1% ± 2.3
PT	74 CGE	44.0% ± 4.1	39.3% ± 2.5	33.3% ± 1.5

Abbreviations: 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiotherapy; PT, proton therapy; CGE, cobalt Gray equivalent; SE, standard error; pts., patients [34].

vided about the PTV coverage (e.g. minimum dose). Only in Chang's paper, a 4D-CT study was performed for all patients to allow consideration of tumor motion in planning.

Technical issues

Six articles were found dealing with physical and/or technical issues related to the use of PT for NSCLC [18–23].

Moyers et al. [18] evaluated three planning strategies with different aperture and distal margin definitions to determine which method could best provide adequate tumor coverage. They proposed that inclusion of target motion, range and set-up uncertainties into a plan should be performed separately for each beam direction. Instead of creating one single PTV, a 'beam-direction-based' protocol should be considered, in order to take correctly into account the effect of proton range uncertainty. In other words, for every beam direction specific 'safety volume' must be created, that takes into account the possible dosimetric effect of geometric uncertainties for that specific beam direction. As a consequence, they argued that the PTV concept (as specified in ICRU 62 [35]) can be used only to determine the lateral margins of beams and in general is of limited usefulness in proton therapy.

Similarly, Engelsman et al. [21,22] showed the inappropriateness of a purely geometric PTV definition, also underlining the need of a time-resolved density information, because of the pronounced density differences between tumor and surrounding lung tissue. They studied the effect of the so-called 'smearing' and aperture sizes on several combinations of systematic errors and breathing motions. Smearing (i.e. the procedure by which the range compensator is modified in such a way that target coverage is ensured also in presence of small range uncertainties) has the potential to compensate for respiration-induced density variation, but after smearing, the dose distribution is not as conformal as expected, leading to increased dose in healthy lung.

Paganetti et al. [19] applied 4D Monte Carlo simulation (based on 4D CT data sets) to analyze the impact of a 2-cm

amplitude breathing motion on the GTV and CTV dose distributions, when PT was delivered with passive scattering. Unexpectedly, for the case analyzed, breathing motion actually reduced the heterogeneity in target dose, resulting in a dose distribution within the GTV and CTV more homogeneous than in the planned ('static') dose distribution. The 4D Monte Carlo was then used by the same authors [20] to evaluate the benefit of 're-painting' (i.e. delivering a fraction dose by rescanning the target several times) a beam in intensity-modulated PT (IMPT). In scanning, because of the delivery technique, interplay effects may occur with respiration that are non-existent in treatments with scattered beams. They simulated different respiratory amplitude and reported that a four times re-painting can compensate at least in part the effects of a 1.5 cm GTV motion.

Like Engelsman et al. [22], also Kang et al. [23] studied four alternative proton planning strategies using a single CT dataset derived from a set of 4D-CT images of ten patients, to evaluate the 'actual' (cumulative) dose distributions compared to the 'apparent' dose distribution designed on a single CT dataset. Free breathing (FB), average (AVE) CT, maximum intensity projection (MIP) and average replacement of the internal gross tumor volume (AVE_RIGTV) strategies were considered. For each strategy, the resulting cumulative dose distribution in a respiratory cycle (10 phases) was evaluated using a deformable image registration method.

The MIP approach was rejected because it showed unacceptably poor 4D target coverage and less sparing of normal tissues than the other planning strategies. The FB and AVE plans generally needed a larger smearing parameter (2.5 cm), which resulted in improved target coverage, but the dose to normal tissues increased as well. Only the AVE_RIGTV plans obtained better 4D dose coverage than apparent dose coverage for the PTV, and critical structures sparing, for all patients involved with a moderate smearing parameter (1 cm).

Discussion

Owing to very limited clinical data available and to the fast technical evolution in PT, we analyzed all the evidences that can be found in the literature concerning the use of PT in lung tumors. This includes studies dealing with planning comparisons and with technical issues that must be addressed to translate in clinical practice the theoretical gain available with PT.

On a general point, we embrace Lodge's et al. proposal [24] to introduce an International Hadron Therapy Register, which would also render more uniform and comparable the results obtained from the various participating centers. This also recalls Olsen et al.'s "concerted effort" idea [25].

Nevertheless, it is important to stress the different 'weight' of the studies reported and to clearly distinguish between reasonable hypothesis and clinical evidence. As showed in the clinical results, no randomized clinical trials involving PT in lung cancer are available. Direct clinical comparison between PT and other modern irradiation modalities (such as stereotactic body radiation therapy (SBRT), for early-stage tumors) or between PT and IMRT (for more advanced lesions) is missing. Moreover, plan comparisons and technical studies surely provide useful information, but by nature they cannot provide solid information about the actual clinical gain.

Clinical outcome

Clinical results with PT in NSCLC have been reported by three institutions only (LLUMC, PMRC, and NCCHE) [28–32,36] with patient characteristics, treatment modalities, and results updated in subsequent reports.

All the clinical reports are phase I or I–II studies using escalated/accelerated PT including a limited number of patients treated in a period of time of some years with different techniques and schedules. The articles of the Tsukuba group [30,31] were preceded by a short report regarding the first 14 patients treated as a feasibility test [36]. The reports of LLUMC [28,29] are also corroborated by some studies related to the effects of protons as assessed with radiologic imaging [37], pulmonary function tests [38] and biologic values [39].

Early stages

Surgery (lobectomy or pneumonectomy) continues to provide the best chance for cure in early-stage patients producing the best reported survival outcomes with a 5-year survival rate of about 60% for stage I [40–42].

Patients not suitable for surgical procedures because of comorbid conditions such as chronic obstructive pulmonary and heart disease, advanced age, poor general status or refusing surgical intervention are usually referred for consideration for radiotherapy. XRT alone with different dose levels and fractionations has been widely employed delivering usually doses up to 60–70 Gy to the primary tumor [40,43].

The clinical results of XRT are reported as poorer than those obtained with surgery with median survival rate of 30 months and overall 5-year survival rates up to 30% [3,44–46]. These data indicate that conventional XRT is largely inadequate for a large fraction of the patients. The lack of local control is the main cause of failure, occurring in

approximately 40% of patients (range 6.4–70%) using total doses of 55–80 Gy [3,44,45]. The most likely cause of excessive recurrence rate is poor targeting and/or administration of inadequate doses [44].

Only recently, stereotactic XRT with photon beams has been used to treat stage I NSCLC in many institutions, and is more and more common to deliver doses that are biologically higher than those used in 3D-CRT. Even though results from randomized clinical trials are not available also for this modality, and although a systematic review of SBRT results is beyond the scope of this report, it is to underline that several publications have documented the efficacy and safety of the treatment of early-stage primary NSCLC with SBRT. The series (obtained from Pubmed) with at least 20 cases treated and a minimum follow-up of 12 months published after the 2000 [47–59] are reported in Table 4. The rates of local control are high (67–95% at 2 years) and they compare favorably with those of conventional treatment. Despite the use of higher biological doses than typically given in XRT, SBRT has rarely been associated with an increased rate of complications and the reported incidence of grade 3 toxicities is generally less than 5%, being radiation pneumonitis the most frequently observed. It is to note that median follow-up durations are short (15–43 months).

For the same early-stage lesions, encouraging results have been recently reported with the use of carbon ions [60]. Given the limited amount of patients treated, the experimental characteristic of this technique and the experience coming from a single institution, we decided to not consider these data for a comparison with the other irradiation modalities.

PT in lung cancer has been used primarily in the treatment of early stages. Whereas at the Chiba Institution [32] only limited stage disease (stage IA–IB) was treated, the reports of the series of Tsukuba [30] and of LLUMC [28] referred to a heterogeneous patient population and only more recently their attention has been focused on early-stage patients [29,31].

The results in limited stages are reported to be very encouraging with local control rates at 2 years of 80–95% and overall survival of 74–84%, obtained with very few acute and late toxicity: only in one study [32] a pulmonary toxicity of grade 3 was observed. These results compare favorably with the data of surgery where surgical resections (lobectomy or pneumonectomy) have been found to produce a 60–70% 5-year survival rate [40,61]. As observed also in conventional radiotherapy studies or surgical series [4,40,62–65], better results are reported for stage IA, 100% local control at 2 years [30,31], in comparison to stage IB, suggesting the usefulness to further increase the dose [29], even though the risk of toxicity could be substantial [32]. It is to note that in the study of Nihei et al. [32] a large pulmonary volume was treated and that, according to the linear quadratic model, the biological equivalent doses used were high (95–138 Gy equivalent, with $\alpha/\beta = 10$).

The best would be to evaluate these results in a randomized clinical trial that directly compares protons vs. SBRT, with the same fractionation. We believe that if the encouraging results of SBRT in early stage will be confirmed through sound studies, PT might not be able to sig-

Table 4
Studies of SBRT in lung cancer with at least 20 cases treated and a minimum of 1 year of follow-up published after 2000

Author	year	pts.	T1	T2	mDose [Gy]	fr.	% Survival					MS [months]	% LC (years)	% CR	% PR	% F-up	LR [months]	Toxicity	mPTV [cm ³]	mTD [cm] or mTV [cm ³]
							1 year	2 year	3 year	4 year	5 year									
Beitler et al. [50]	2006	75	nr	nr	40	5	63	45	—	—	17	17.2	nr	8	33	24	nr	2 pneum., 1 pleural effusion, 1 pneumothorax	nr	26.8 cm ³
Nyman et al. [51]	2006	45	18	27	45	3	80	71	55	—	30	39	80 (3)	9	63	43	9	3 atelectasia, 2 rib fractures, 49% acute mild tox.	79	3.5 cm
Uematsu et al. [47]	2001	50	24	26	50–60	5–10 5–12 boost	—	—	66	—	—	nr	94 (3)	nr	nr	36	3	10% marked COPD and poor respiratory function	nr	3.2 cm
Onishi et al. [59]	2007	257	164	93	18–75	1–22	—	—	—	—	70.8 [*] 30.2 ^{**}	nr	80 (3)	23	61	38	36	5.4% >Grade 2 tox.	66	2.8 cm
Nagata et al. [49]	2005	45	32	13	48	4	IA 93 IB 82	90 72	83 72	—	83 72	nr	IA 95 (5) IB 100 (5)	16	84	30	—	2 Grade 2 –pneum. no Grade 3 tox.	nr	nr
Hoyer et al. [58]	2006	40	22	18	45	3	—	48	—	—	—	nr	85 (2)	20	38	28	3	48% Grade ≥ 2 tox.	nr	3.0 cm
Xia et al. [52]	2006	43	25	18	70	10	I 100 II 93	91 64	91 64	—	—	nr	IA 95 (5) IB 100 (5)	68 56	32 33	30 54	2	2 Grade 2 pneum. 18% Grade 1–2 and 2% Grade 3 pneum. 16% Grade 2 -esop.	nr	3–5 cm
Timmermann et al. [53]	2006	70	35	35	60–66	3	—	54.7	—	—	—	32.6	95 (2)	nr	nr	17	3	14% Grade 3–4 tox.	nr	16.7 cm ³
Hof et al. [57]	2007	42	17	21	19–30	1	74.5	65.4	37.4	—	—	nr	67.9 (3)	nr	nr	15	6	no Grade 3–5 tox.	nr	18.5 cm ³
Zimmermann et al. [56]	2006	68	22	18	24–40	3–5	—	—	53	—	—	nr	88 (3)	64.7	29.4	17	4	6.4% Grade 3 pneum., 5% rib fractures	79	nr
Fritz et al. [55]	2006	33	nr	nr	30	1	83	63	53	39	—	20.4	94 (1)	nr	nr	18	2	24% pneum. at CT without symptoms	99.8	5.5 cm
Yoon et al. [54]	2006	21	13	8	30–48	3–4	89	—	51	—	—	nr	81 (2)	nr	nr	13	3	no Grade 3–5 tox.	43.9	nr
Fukumoto et al. [48]	2002	22	13	9	48–60	8	94	73	—	—	—	nr	67 (2)	29	65	24	1	no Grade 3–5 tox.	nr	2.7 cm

Abbreviations: mDose, median dose; pts., patients; fr., number of fractions; yrs, years; MS, median survival; C, local control; CR, complete response; gr, grade; PR, partial response; F-up, follow-up; LC., local recurrence; tox., toxicity; pneum, pneumonitis; esop., esophagitis; mPTV, mean planning target volume; mTD, median tumor diameter; TV, median tumor volume; nr, not reported; COPD, chronic obstructive pulmonary disease.
^{*} BED > 100 Gy.
^{**} BED < 100 Gy.

nificantly improve the clinical outcome in this patients category.

Advanced stages

The treatment of patients with tumors in advanced stages is even more challenging, being local control a major problem. The role of surgery in advanced stage is more limited. In operable tumors the overall 5-year survival is declining from the 63% in stage IA to 19% in stage IIIA [40]. Patients with completely resected stage III disease have 5-year survival rates of 7–24% [6] and with unresectable disease of 3–13% [61]. Radiotherapy alone is able to control only a minority of these lesions [66]. The limitations of irradiation in these stages are mainly due to the size of the lesions, often irregularly shaped or located next to critical normal tissues which determine dosimetric solutions that cannot be proposed to the patients because of the high risk of complications.

In order to improve these results, more aggressive treatments have been suggested escalating the dose [8,67], combining radiotherapy and chemotherapy [68–71] and using altered fractionations [72,73]. Such approaches are associated with significant toxicity [74–76].

In cases of advanced stages, SBRT is not applied due the excessive toxicity. For these advanced cases, the current irradiation standard is still represented by 3D-CRT delivered with conventional fractionation, usually combined with chemotherapy. IMRT is in theory a promising technique for patients with nodal involvement [10,11], but no clinical series are currently available on the benefit of IMRT on advanced stage NSCLC.

Thanks to its peculiar ballistic properties, PT could be a possible solution for the technical difficulties in irradiating advanced cases enabling high-dose delivery to the tumor while minimizing the irradiated volume and dose given to normal tissues. Unfortunately, the clinical data on the use of PT in advanced disease are very limited with 33 patients only available in the literature (11 stage II, 16 stage III, 1 stage IV and 5 recurrences) [28,30].

In the study of Shioyama et al. [30] 14 patients with advanced stages (III, IV, recurrence) were treated. Even though the short-term results of these few patients were very promising, with 70% and 100% cause-specific survival at 2 years, respectively, the long-term causing specific survival was disappointing for stage III–IV patients (0%) and more favorable for patients suffering from a recurrence (50%).

In the initial experience of Bush et al. [28], 8 cases with stage IIIA were treated: 2-year overall survival was only 13%, but it is to note that only one patient had an in-field failure.

Being no other reports on the treatment of advanced NSCLC with PT available in the literature at this moment, it is impossible to draw any significant conclusion in this setting of patients due to the limited number of patients treated. For these patients, protons could allow a better therapeutic ratio than IMRT [34], thus allowing to escalate the dose and/or to reduce the treatment toxicity. It is therefore important to carry out phase I–II studies in patients with advanced stage disease, where conventional photon techniques are not capable of delivering sufficiently high doses and where proton therapy is not necessarily more

challenging than IMRT from a technical point of view. It would be also interesting to evaluate the impact of several fractionations and chemotherapy protocols on PT treatments, that nowadays are delivered with 2–6 CGE dose per fraction.

Plan comparison studies and technical issues

The main difference of protons with respect to photons, i.e. their finite range in tissue, on the one hand makes proton irradiation very appealing, because of the dose distributions that can be produced; on the other hand, it makes it also quite problematic, because extreme care should be devoted to make sure that the differences between treatment planning and treatment delivery do not translate in tumor under-dosage or OARs over-dosage.

This is particularly true for lung tumors, where the need for compensating for breathing motion and for the changes in lung density due to respiration must be balanced against unnecessary irradiation of the healthy lung.

The study by Lee et al. [33] provided information on the minimum dose to PTVs, but no data are presented about target/OARs DVH, TCP or NTCP; moreover, as with for the majority of the cases studied by Chang et al. [34], the comparisons were made between 3D-CRT and PT. When IMRT was taken into account in the study by Chang et al. [34], the differences with respect to PT with regard to normal tissue doses were smaller than for 3D-CRT. It is interesting to note that in Chang's article the 'smearing parameter' was selected on the basis of the formula suggested by Moyers [18], and therefore the results could have been different if they had followed the margin 'recipe' proposed by Engelsman [21].

Furthermore, in order to extract useful information from the treatment planning studies we analyzed, we had to accept some implicit assumption of these studies, such as that:

– Proton and photon dose distributions in the target volume can be compared by PTV dose parameters. This is not obvious, as with protons the dose distribution is in general not invariant even for small displacements, making the use of the PTV difficult. Using different PTV definitions for photons and protons (e.g. defining field-specific PTVs for PT) is a step forward, though it might make the comparison more complex. In general, we think that future studies comparing photon and proton therapy, in particular for lung cancer, should move to different approaches of planning and reporting the dose, either including geometrical uncertainties in the planning procedure [77–79] and/or reporting the dose in terms of probability level [80,81]. In this context, the availability of 4D information is going to be crucial.

– The dose parameters chosen by the authors were the most appropriate to compare the dose distributions in the target. In some studies, protons and photons plans were compared in term of prescribed dose in the target, i.e. an implicit assumption was made that the same prescription dose does translate in the same quality of the dose distribution in the target, e.g. in terms of tumor control probability. This is not obvious, either for the problem of how the geometrical uncertainties are handled (see previous points), or because the prescribed dose unequivocally translates in a

TCP estimate only if the dose is perfectly homogeneous throughout the target volume.

Furthermore, it is also very difficult to extrapolate general considerations from the study by Moyers et al. [18] because their results were obtained on a single patient, with very specific characteristics, field arrangements and PTV definition.

The results by Engelsman et al. [21] show that smearing has the potential to compensate for systematic errors and respiration-induced density variation, but high degree of smearing and large margins will obviously lead to an increase in lung dose.

Beam gating techniques might be a solution in the case of large breathing motion (e.g. >1 cm), provided that a reliable surrogate of the actual target position is used to trigger the beam. Moreover, for protons, it could be of major importance to reproduce not only the target position but also the internal density changes along the path of proton beams. In this respect, Engelsman et al. [22] concluded that CT data extracted from 4D datasets representing an average target position plus patient-specific planning margins should be used to plan and deliver the prescribed dose to the target.

Using a different approach, Paganetti et al. [19,20] developed a technique, based on Monte Carlo simulations, that could be very useful for a pre-treatment uncertainty analysis, where the effect of motion is simulated on 'static' dose distributions.

In the Kang et al. study [23] the AVE_RIGTV strategy achieved the best overall 4D tumor dose coverage and critical structure sparing. In addition, the study underlined that radiation oncologists should determine the combined volume of the GTVs at all respiratory phases from the 4D-CT dataset to explicitly include target motion and deformation. In agreement with Engelsman et al. [22] Kang et al. found that the smearing margin was not necessarily as large as the range of tumor motion. Differently from Engelsman et al., Kang et al. did not optimize multiple plans for 4D-CT volumes at end-inhalation, mid-exhalation, and end-exhalation, but they only designed one treatment plan and can predict target coverage.

When it comes to advanced techniques of handling the geometrical uncertainties due to respiration, to date, there are no prospective evaluations on the clinical impact of the implementation of gating techniques or volume definitions that take movement into account. It is thus very difficult, if not impossible, to provide a quantitative evaluation of the clinical benefits produced by such technologies. Nevertheless, as already mentioned, because the PT is very sensitive to displacements in the lung region, it can be expected that a careful study on the definition of the volumes to irradiate and the adoption of gating techniques could be crucial in treatment with protons, especially if mobile and advanced stage lesions are to be treated.

Therefore, one could start treating patients with small respiratory movements, who by the way represent the majority of lung cancer patient.

Finally, no data are available on the potential benefit of PT delivered with spot scanning, where the dosimetric advantages potentially achievable with this technique have

to be balanced against its sensitivity with respect to intra-fraction motion.

Conclusions

The use of PT in NSCLC is mainly based on the theoretical advantages in dose distribution. Little clinical data are available, in terms of number of institutions involved, number of treated patients and quality of studies conducted (i.e. lack of randomized controlled trials), making it impossible to draw definitive conclusions about its efficacy.

Current data suggest that PT is a promising modality of irradiation in the treatment of early-stage disease, producing favorable results and low toxicity (both acute and late).

Indications for PT in advanced stages are based mainly on planning studies, that should be followed up by further clinical investigations.

Well-designed clinical trials and prospective studies will allow to better evaluate the benefits of PT with respect to other high-precision radiotherapy treatments (e.g. tomotherapy, stereotactic RT, cyberknife and IMRT), provided that the technical peculiarities of PT in lung treatment will be adequately taken into account.

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