European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-020-06175-5

HEAD AND NECK

Proton pencil-beam scanning radiotherapy in the treatment of nasopharyngeal cancer: dosimetric parameters and 2-year results

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Received: 1 April 2020 / Accepted: 26 June 2020

Abstract

Objectives Patients with nasopharyngeal cancer are candidates for proton radiotherapy due to large and comprehensive target volumes, and the necessity for sparing of healthy tissues. The aim of this work is to evaluate treatment outcome and toxicity profile of patients treated with proton pencil-beam scanning radiotherapy.

Materials and methods Between Jan 2013 and June 2018, 40 patients were treated for nasopharyngeal cancer (NPC) with IMPT (proton radiotherapy with modulated intensity). Median age was 47 years and the majority of patients had locally advanced tumors (stage 2–8 patients. (20%); stage 3–18 patients (45%); stage 4A–10 patients. (25%); stage 4B–4 patients. (10%). Median of total dose was 74 GyE (70–76 GyE) in 37 fractions (35–38). Bilateral neck irradiation was used in all cases. Concomitant chemotherapy was applied in 34 cases. (85%). Median follow-up time was 24 (1.5–62) months.

Results Two-year overall survival (OS), disease-free survival (DFS), and local control (LC) were 80%, 75%, and 84%, respectively. Acute toxicity was generally mild despite large target volumes and concurrent application of chemotherapy with skin toxicity and dysphagia reported as the most frequent acute side effects. The insertion of a percutaneous endoscopic gastrectomy (PEG) was necessary in four cases (10%). Serious late toxicity (G > 3. RTOG) was observed in two patients (5%) (dysphagia and brain necrosis).

Conclusion IMPT for nasopharyngeal cancer patients is feasible with mild acute toxicity. Treatment outcomes are promising despite the high percentage of advanced disease in this group.

Keywords Nasopharyngeal carcinoma · Proton therapy · Pencil-beam scanning · Dosimetry · Toxicity

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Published online: 04 July 2020

Introduction

Radiotherapy plays a crucial role in the treatment of nasopharyngeal cancer (NPC). intensity-modulated radiotherapy (IMRT) treatment results for early stage NPC are excellent and reach up to 98%. However, even with N2-3 disease, the 5-year survival rate is 78% [1]. The 5-year overall survival rate is high even for T4 disease [1]. With the high proportion of surviving patients avoidance of radiotherapy-induced side effects—both acute and especially late and very late—are becoming increasingly important. Mucositis, dysphagia, skin reactions, weight loss, and pain are the most common acute side effects. Modern IMRT techniques help to reduce these side effects; however, hospital admission is still deemed necessary during radiotherapy or chemoradiation in 42% of patients [2]. Dysphagia, xerostomia, hearing loss, necrosis of temporal lobes, cranial nerve injury, and optical tract impairment are the main late side effects [3]. Reduction of adverse effects is critical in patients with high curability and long-life expectancy. Most late side effects are dose-dependent and proton radiotherapy with pencil-beam scanning (PBS) technique may be able to reduce these side effects due to dose reduction in organs at risk (OAR).

The purpose of this study is to present the feasibility of PBS proton radiotherapy in the treatment of NPC, dosimetric parameters, early treatment outcomes, as well as acute and late side-effect profiles.

Materials and methods

Between January 2013 and June 2018, we treated 40 patients with nasopharyngeal cancer using PBS proton radiotherapy to the primary tumor and bilateral neck lymph-node areas. The majority of patients were treated with concomitant chemotherapy. All patients treated during this time period with the curative intent are included in analysis. The majority of patients (65%) were referred for proton therapy from other centers due to advanced disease and unsatisfactory dose parameters for critical organs from intensity-modulated photon radiotherapy or young age. Others were self-referrals. Demographic and treatment characteristics are shown in Table 1. Staging was based on the TNM classification 7th edition. All patients signed informed consent to the treatment. All procedures were performed in accordance with appropriate ethical standards.

Immobilization, set-up, and planning procedures

Patients were treated using standard five-point immobilization devices (thermoplastic masks) in the supine position.

Table 1 Demographics and treatment parameters of patients

Age (years)	Median 47.2	22.8–73.2
Sex		
Male	30	70%
Female	13	30%
Race		
Caucasian	41	95.5%
African/America	0	0%
Asian	2	4.5%
Histology		
Squamous cell	38	89.5%
Lymphoepithelial	2	4.5%
Undifferentiated	3	7.0%
T stage		
T1	7	16.5%
T2	12	28.0%
T3	9	21.5%
T4	15	35.0%
N stage		
N0	3	7.0%
N1	11	25.5%
N2	25	58.0%
N3	4	9.5%
Grade		
G1	1	2.3%
G2	6	14.0%
G3	23	53.5%
G4	11	25.5%
NA	2	4.7%
Clinical stage		
I	0	0%
II	8	18.5%
III	19	44.2%
IVa	10	23.3%
IVb	6	14.0%
GTV volume of primary tumor		
Mean 82.02 cc	Min 9.3 cc	Max 238.2 cc
Total dose		
Mean 72.9 GyE	Min 60 GyE	Max 76 GyE
Concomitant chemotherapy		
Yes	33	22.5%
No	7	17.5%
Number of cycles (DDP weekly)		
Mean 3.7		
Overall treatment time		
Mean 52 days	Min 44 days	Max 65 days
Average number of treatment plans per patient		
Mean 4.2		

Dental treatment was performed to remove metal bridges and replace amalgam dental fillings with composite fillings prior to planning CT to reduce artifacts on CT scans. Computer tomography was utilized for the treatment planning (scans 2.5 mm) and image registrations with planning magnetic resonance (MRI) and positron emission tomography with fluorodeoxyglucose (PET FDG) scans were performed prior to contouring.

Target volume delineation

The contouring of targets and organs at risk (OAR) was performed using Focal software (Elekta AB). The contouring of target volumes was performed using the same recommendations as for photon radiotherapy. Gross tumor volume (GTV) encompassed the primary tumor. Expansion from GTV to clinical target volume (CTV) was 1 cm (excluding bones and air cavities) with the extension of CTV to the posterior third of maxillary sinuses, nasal cavity, sphenoidal sinus, and pterygopalatine fossa. Lymph-node CTV encompassed bilateral level Ib-V and VII lymph-node areas for elective irradiation, and involved lymph-node areas in dose-escalation phase of treatment, in accordance with standard recommendations [4, 5]. Level VII was included as area with high risk of lymph-node involvement in accordance with published recommendation [6].

CTV-to-PTV (planning target volume) expansion was 5 mm for lymph-node areas and 3 mm for primary tumor CTV. The following OAR were contoured: brain, brainstem, temporal lobes, eyes, retinas, lenses, optic nerves, optic chiasm, cochleas, parotid glands, pharyngeal constrictors, oesophagus, larynx, thyroid gland, spinal cord, and the temporomandibular joints.

Dose prescription and chemotherapy

The treatment was performed in three sequential phases—50–56 GyE in 25–28 fractions for bilateral neck lymph-node areas Ib to V and VII, 20 GyE in ten fractions for primary tumor CTV and involved lymph-node neck areas, and finally—in selected cases—a boost of 4–6 GyE over 2–3 fractions for residual nasopharyngeal tumor mass. An example of dose distribution is shown in Fig. 1**.** Weekly cisplatin (40 mg/m^2) was administered based on the decision of the attending physician. Neoadjuvant and adjuvant chemotherapy were indicated based on the decision of the attending physician in referring center and due to number of referring centers there is wide heterogeneity in the prescription of neoadjuvant and adjuvant chemotherapy.

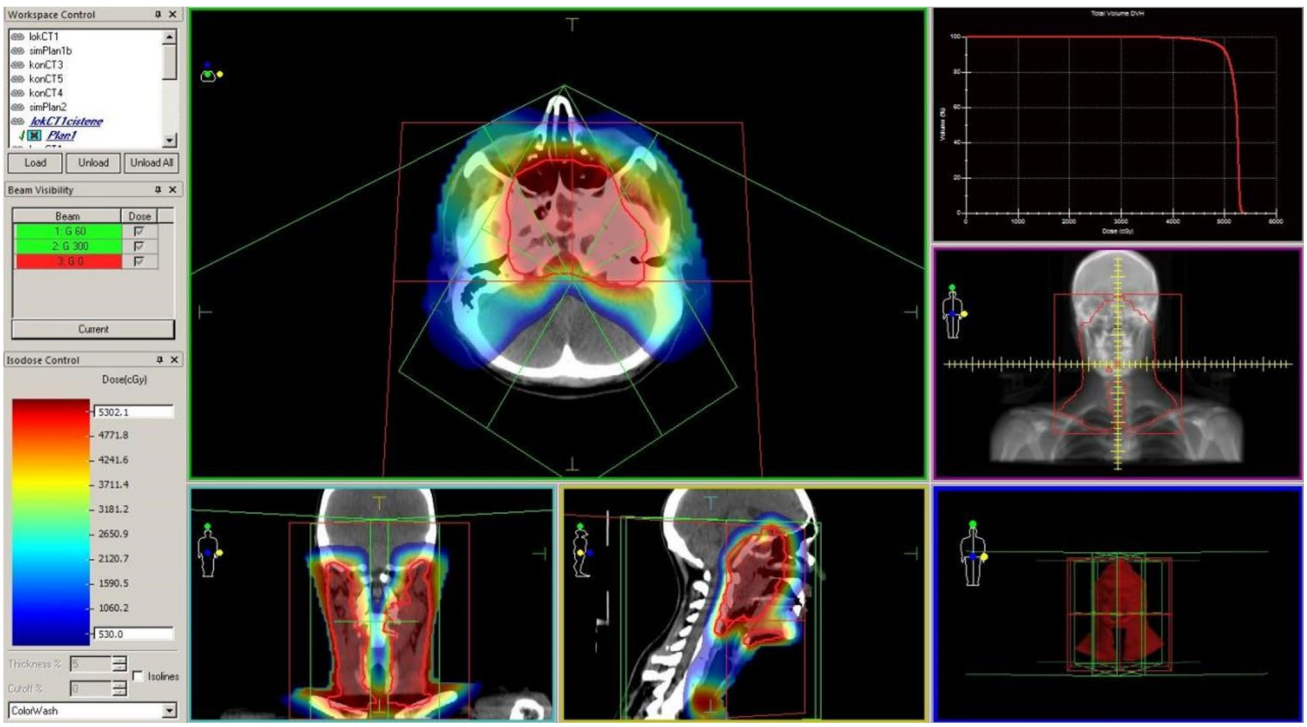

Fig. 1 Example of typical dose distribution for irradiation of primary nasopharyngeal tumor and bilateral neck region. (color wash with 10% isodose line as lower limit

Planning, optimisation, and robustness

The dose was calculated in Grays (Gy) and conversion to a radiobiologically equivalent dose (GyE) was performed using factor 1.1. For treatment planning, XiO 4.80 (Elekta AB) treatment planning software was used. All treatment plans were carried out using the IMPT technique with a full optimisation approach. All patients were treated with a three-field arrangement—two anterior oblique for upper part of the treatment volume and one anterior for lower part of the treatment volume—for whole neck irradiation. This technique of three overlapping fields was chosen as optimal for the IMPT due to the most significant reduction of the radiation exposure of healthy tissues of patients—it should be emphasized that the approach to IMPT planning in terms of field arrangement is significantly different from IMRT planning. Two anterior oblique fields were used for the second and third phases of the treatment. Average treatment time for one fraction of IMPT with three fields was 24 min., including all set-up procedures. The number of layers was appropriate to the size of the PTV to avoid ripples in the depth profile. Spot spacing was chosen to be 4 mm. No class solution was introduced into the planning process. The dose distribution was measured with a 2D detector in several depths in the water phantom and evaluated using gamma analysis (ΔD 3%. DTA 3 mm) with the acceptance criteria set at 95% of the points with $\gamma < 1$.

Treatment plans were also inspected in the mean of robustness evaluation (ie evaluation of stability of treatment plans against set-up uncertainties and range uncertainties). For the plan, the isocenter was artificially moved by 2 mm in each spatial direction to mimic set-up errors and their influence on dose distribution. This approach has shown minimal changes in dose to critical organs if the movement is limited to 2 mm. Such precision is usually well achieved during the set-up of each fraction. Additionally, to mimic range uncertainty and also to take into account possibility of planning CT calibration imperfections, another two sets of plans were developed with 2 mm shifts. One with a CT calibration curve shifted by + 3.5% and a second with − 3.5%. For each treatment plan, we created 12 plans to evaluate plan robustness. If more than one of those plans failed to fulfill constraints, the plan was re-examined and changes to the optimisation process were performed. The cause of an excessive dose to a critical structure was determined and specific measures were applied to modify dose distribution in a proper way. Afterwards another round of robustness evaluations were performed. Treatment was delivered with Proteus 235 (IBA, Belgium).

Adaptive re-planning

All patients were treated using daily image guidance with kV–kV with correction of positions done via a robotic treatment couch. Check-ups using computed tomography were performed once a week. These checks-ups were based on image fusion with planning CT, comparing all structures and preparation of quality assurance plans to evaluate changes in dose distribution. New plans were prepared when dose distribution changed due to tumor regression changes in cavity contents or changes in patient contours. Limits for dose changes were individual and dependent on the location of the change; however, more than a 5% change in dose inside the critical organ or target volume was considered as an indicator for re-planning. Due to the complexity of geometry, re-planning was performed for almost each patient with cases involving more than three adaptations to the treatment plan.

Results

Median time of follow-up was 24 months. All patients were treated without interruptions. Two-year overall survival, disease-free survival, and locoregional control were 80%, 75%, and 84%, respectively (Fig. 2). Ten (25%) of the patients died, eight (20%) due to disease progression, and 2 (5%) due to other reasons. Disease progression was seen in 11 (27.5%) patients. Six (15%) of them had only local progression; six (7.5%) had only distant progression, and two (5%) had a combination of local and distant progression.

Dosimetry

Dosimetric parameters of treatment plans are shown in Table 2. Numbers are for the whole treatment course, with conversion to GyE with coefficient 1.1.

Table 2 Dosimetric parameters of treatment plans

	Dose [CGE]			
Structure	min	max	mean	median
PTV Dmean	47.17	84.46	74.45	75.19
PTV D_{max}	58.21	87.48	77.78	77.89
Spinal cord D_{max} (2% of volume)	5.45	48.80	24.12	21.59
Brain stem D_{max} (2% of volume)	26.07	67.51	48.86	49.99
Brain Dmean	0.00	20.53	4.94	3.70
Parotis right Dmean	17.49	71.75	40.25	31.75
Parotis left Dmean	20.63	75.63	47.68	50.34
Larynx Dmean	0.00	50.59	32.55	34.50
Esophagus Dmean	0.02	47.33	20.28	21.24
Cochlea dx. Dmean	0.00	76.22	34.89	27.58
Cochlea sin Dmean	0.00	75.15	41.97	43.18

Table 3 Acute toxicity (RTOG scale)

Symptoms	Grade 0	Grade 1	Grade 2	Grade 3
Skin toxicity	0 (0%)	8 (18.6%)	29 (67.4%)	6 (14%)
Mucositis	1 (2.3%)	11(25.6%)	28 (65.1%)	3 (7%)
Xerostomy	4 (9.3%)	33 (76.7%)	6 (14%)	0 (0%)
Dysphagia	9 (20.9%)	12 (27.9%)	18 (41.9%)	4 (9.3%)

Table 4 Late toxicity (RTOG scale)

Morbidity	Grade 2	Grade 3 +
Eye	0 (0%)	0 (0%)
Skin	4 (9%)	0 (0%)
Subcutaneous tissue	4 (9%)	0 (0%)
Joint	1 (2%)	0 (0%)
Brain	0 (0%)	1 (2%)
Bones	0 (0%)	0 (0%)
Pharynx/esophagus	2 (5%)	0 (0%)
Salivary gland	3 (7%)	0 (0%)
Ear	3 (7%)	0 (0%)

Acute toxicity was evaluated using the RTOG scale and is shown in Table 3. Acute toxicity was generally mild despite extensive target volumes and application of concurrent chemotherapy, with skin toxicity (five patients grade 3–12.5%) and dysphagia as most frequently reported acute side effects. The insertion of a PEG was necessary in four patients (9.3%). Usage of analgesics was as follows: nine patients (20.9%) required no analgesics. 19 patients (44.2%) required non-steroid anti-inflammatories (NSAID). Nine patients (20.9%) required mild opioid analgesics and only six patients (14%) required strong opioids during treatment. Weight loss deviation from the pre-treatment baseline was > 15% in 13 patients (30.2%), < 15% and > 5% in 26 patients (60.5%), and < 5% in four patients (9.3%).

Late toxicity was evaluated at the last follow-up visit and is shown in Table 4. One case of symptomatic temporal lobe necrosis occurred 23 months after radiotherapy and one case of clinically significant subcutaneous fibrosis was observed in a patient with systemic connective tissue disease.

Discussion

Proton beam therapy with passive scattering was used in the past due to technical reasons only for limited target volumes and in the treatment of nasopharyngeal cancer mainly as re-irradiation [7] or as a boost after IMRT [8]. Pencil-beam scanning technology and IMPT allow the use of proton therapy for the entire course of treatment for NPC.

The dosimetric advantages of IMPT in the treatment of head and neck cancer have been previously confirmed. Widesott et al. [9] demonstrated that in comparison of IMPT and tomotherapy, IMPT offered a better sparing of OAR at medium-to-low doses. They also demonstrated a better normal tissue complication probability (NTCP) for the parotid glands. Better dosimetry parameters for the majority of OAR were also identified by Lewis et al. [10] Jakobi et al. [11] compared the dosimetry parameters of IMRT and IMPT, and identified patients with tumors in the upper region of the head and neck as patients who could derive the greatest benefit from IMPT, especially due to the reduction of the swallowing-related side effects [12]. Therefore, due to the good prognosis and younger age, patients with NPC appear to be suitable candidates for proton radiotherapy, mainly due to the reduction of acute and late side effects.

One of the major pitfalls of using IMPT for the treatment of head and neck cancer patients is the robustness of treatment plans. Plans with low robustness are sensitive to set-up and calibration errors, and may lead to underdosing or overdosing of target volume or critical organs. Van Dijk et al. [13]. Have shown that for head and neck tumors, prepared plans can be robust enough to significantly reduce NTCP. Similar conclusions were published by Malyapa et al. [14] who demonstrated that IMPT is robust enough for the treatment of head and neck cancer. The treatment field arrangement as used at our institution is, in comparison with other approaches, certainly robust enough [15].

The adaptive approach is an essential part of IMPT to the head and neck area. This is because IMPT is more sensitive to anatomical changes [16]. Interfraction changes were also studied by Müller BS et al. [17]. They found that IMPT has—compared to IMRT—larger absolute differences between planned and reconstructed doses, but doses to OARs are higher in IMRT plans. IMPT was less stable in target coverage with a higher risk of local underdosage throughout the treatment course. We consider regular anatomical controls using CT scanning minimally once a week, with preparation of quality assurance treatment plans absolutely necessary for the treatment of NPC with IMPT. We evaluated quality assurance (QA) plans individually with respect to target coverage and OAR doses. Using this individual approach, the average number of treatment plans for a patient was 4.2, including adaptive re-planning.

The 2-year overall survival in our group is 80%. This is comparable with published data for non-endemic NPC. For example, Fountzilas et al. reported for NPC patients (with 25% of patients with stage IVB) treated with concomitant photon chemoradiotherapy 3-year overall survival 71.8% [18]. Another group evaluated the results of concomitant chemoradiotherapy in T4 nasopharyngeal tumours. Three-year local control was 89% and overall survival was 78.9% [19]. The doses used in the present patient group are similar

to those used for photon radiotherapy and, therefore, overall survival is expected to be similar. It should be emphasized that 26 (65%) of the patients were indicated for proton therapy for the highly advanced tumors that did not allow the use of IMRT radiotherapy. Our patient population is thus burdened with a sample selection bias of advanced cases, and in this context, the results are considered promising. A comparison with proton radiotherapy is possible through the work of Lewis et al. who reported the use of PBS in ten patients. The 2-year local control was 100% and the overall survival was 88.9%. However, Lewis et al. treated patients with less advanced disease progression. 6 of 10 (60%) patients were stage T1 and T2 [10].

The acute toxicity of chemoradiotherapy for nasopharyngeal carcinoma is high even with the use of IMRT. Cao et al. [19] reported in advanced nasopharyngeal carcinomas grade 3 mucositis including pharyngitis in 21% of patients and dermatitis grade 3 in 10% of patients. RTOG 0225 describes the incidence of acute gastrointestinal toxicity grade 3 and higher in 67.5% of patients and oral mucositis inhibiting food intake in 29.4% of patients [20]. Songthong AP et al. reported incidence of acute toxicity grade 3 and higher in concomitant CHRT for NPC, 9% for dysphagia (CTCAE v4. tube feeding) and weight loss > 20% in 6% of patients. Oral mucositis grade 3 or higher was present in 15% of patients and dermatitis in 7–9% of patients [21]. Incidence of PEG placement is 9.3% in our patient group reflecting a better dosimetry on relevant OAR. On the contrary, dermatitis grade 3 was observed in our group in 14% patients, which is in line with the published data on a slightly higher incidence of skin toxicity for proton radiotherapy [22].

Published late toxicity data for concomitant photon chemoradiotherapy describes a cumulative incidence of xerostomia in 44%, hearing impairment in 25%, and temporal lobe necrosis in 6% of patients [23] RTOG 0225 had the following incidence of grade 2 + late toxicities: auditory 13%; salivary gland 31%; skin 4%; mucositis 22%; esophagus 17.6% [20]. The late toxicity in our patients group is so far mild. Only symptomatic temporal lobe necrosis is present as a grade 3 late toxicity and the late toxicity profile is promising, but needs longer follow-up for the reliable evaluation.

There are several limitations to this study—the low number of patients, the retrospective nature of the study, and short follow-up time. Despite these limitations, it is, to the best of our knowledge, the largest patient population treated with pencil-beam scanning proton radiotherapy to date.

Conclusion

IMPT for the nasopharyngeal cancer patients is feasible with mild acute toxicity. Dosimetry of treatment plans is quite positive and the treatment outcome is promising despite the high percentage of the patients with very advanced disease. Proton therapy should be considered in young patients or patients with advanced disease close to critical organs with significant serious toxicity risk.

Funding The work was supported by the European Regional Development Fund-Project: "Engineering Applications of Microworld Physics" (No. CZ.02.1.01/0.0/0.0/16_019/0000766).

Compliance with ethical standards

Conflict of interest We declare that there is no conflict of interest, we follow the Ethical Standard Statement, and we grant the informed consent with publication of this paper.

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