ORIGINAL ARTICLE

Taylor&Francis
healthsciences

Can Photon IMRT be Improved by Combination with Mixed Electron and Photon Techniques?

Xiangkui Mu, Lennart Olofsson, Mikael Karlsson, Rickard Sjögren and Björn Zackrisson

From the Department of Radiation Sciences, Oncology (X. Mu, B. Zackrisson), Department of Radiation Sciences, Radiation Physics (L. Olofsson, M. Karlsson, R. Sjögren), Umeå University, SE-901 87 Umeå, Sweden

Correspondence to: B. Zackrisson, Onkologi, Umeå universitet, SE-901 87 Umeå, Sweden. E-mail: bjorn.zackrisson@onkologi.umu.se

Acta Oncologica Vol. 43, No. 8, pp. 727–735, 2004

Conformal radiotherapy or intensity modulated radiotherapy (IMRT) commonly leads to a large integral dose in the patient. Electrons would reduce the integral dose but are not suitable for treating deep-seated tumours, owing to their limited penetration. By combining electron and photon beams, the dose distributions may be improved. In this study, the possibility is explored of using a mixture of electron and photon beams for a deep-seated target volume in the head and neck region. Treatment plans were made for five simulated head and neck cancer cases. Mixed electron and photon beam plans (MB) were constructed using a manual iterative procedure. Photon IMRT plans were optimized automatically. Both electron and photon beams were collimated by a computer controlled multi-leaf collimator (MLC). Both methods were able to produce clinically acceptable plans. Criteria for the target dose were met similarly by both as were the criteria for critical organs. The integral dose outside the planning target volume (PTV) showed a tendency to be lower with MB plans compared with photon IMRT plans. A mixed electron and photon technique has the potential to treat deep-seated tumours. It is reasonable to expect that if computerized optimization tools were coupled with the mixed electron and photon beam technique, treatment goals would be more readily achieved than if using solely pure photon IMRT.

Received 3 May 2004
Accepted 8 September 2004

Deep-seated tumours are generally treated with 3-dimensional conformal radiotherapy (3D-CRT), which usually produces a dose distribution that ensures a high dose to the tumour and minimizes the dose to the surrounding normal tissues. This should lead to higher loco-regional tumour control, whilst keeping the risk of normal tissue complications at an acceptable level (1). The technique has been further improved by photon intensity modulated radiotherapy (IMRT) (2, 3). The volume of normal tissues that are irradiated to a high dose is commonly reduced with 3D-CRT and especially with IMRT compared with other conventional techniques. For tumours arising in the head and neck area this has been shown in several comparative treatment planning studies (4, 5) and in clinical studies (6). However, the volume that receives low radiation doses is usually larger with IMRT and, thus, the integral dose to the surrounding normal tissues may increase. This may introduce risks particularly for the long-term survivors who may be at risk of secondary, radiation-induced cancers (7). Other unwanted side-effects might be caused by low-dose hypersensitivity (8) though the clinical implications of this phenomenon are still not fully understood.

The limited in-depth range of electrons reduces the integral dose to the surrounding normal tissues, and this should enable sparing of normal structures downstream from the tumour. This property has been used in the treatment of breast cancer with segmented electron beams (9, 10), a 3-D bolus technique (11), and intensity modulated electron beams (12, 13). However, the depth dependent penumbra, the small effective field size, and the high skin dose limit the use of pure electron therapy in many other clinical situations.

Several research groups have investigated the possibility of improving the properties of electron beams (14, 15). For example, dose distribution of electron beams has been improved by combining them with photon beams. The addition of a low-weight, wedged, photon beam perpendicular to the distal part of an electron beam increases the treatment depth of the electron beam (14). Adding a narrow photon beam to the electron beam edges reduces the electron beam penumbra and enlarges the effective field size (15). Additionally, technical improvements that deliver iso-centric multi-leaf-collimated (MLC), electron beams have been proposed (16–18). Such collimators could be fitted to standard linear accelerators and would improve the

 ISSN 0284-186X
DOI: 10.1080/02841860410002761

efficiency of dose delivery. By combining these techniques, we have explored the possibility of treating a deep-seated tumour with the MLC-collimated mixed electron and photon beams.

Cancer of the head and neck is a common indication for IMRT, because of the many critical organs that exist in the region. Irradiation of these structures may lead to serious late complications, such as xerostomia. The quality of life is correlated with the severity of xerostomia, and parotid gland sparing by using IMRT may improve this side effect, hence IMRT may improve quality of life (19).

Therefore, in this treatment planning study, we explored the possibility of using a mixture of electron and photon beams to treat a complex target volume. Dose planning simulation was carried out in five head and neck cancer patients. Photon IMRT plans were produced for each patient for comparison. The plans do not reflect the actual treatment the patients received.

MATERIAL AND METHODS

The treatment planning computed tomography (CT) of five consecutive head and neck cancer patients was obtained. The patients were immobilized in a supine position. Slices 5 mm thick at 5 mm intervals were obtained. Similar targets were drawn for all five patients, irrespective of the actual target. The target configuration was chosen to give a clinically relevant example of the complexity of target delineation in the oropharyngeal mucosa and loco-regional lymph nodes. The parotids, spinal cord, and brainstem were outlined as critical structures. All patients received a primary radical treatment. The prescription dose was set to 70 Gy as a mean dose to the planning target volume (PTV).

The ICRU 50 (20) suggests a maximum degree of heterogeneity within the target of $+7\%$ and -5%. However, a larger dose inhomogeneity within the target is commonly reported in the literature (21). ICRU report No. 62, a supplementary report of ICRU 50, concluded that the dose variation within the target could be as much as 20% (22). Therefore, dose homogeneity in the PTV of $\pm 10\%$ was considered more realistic and used as a constraint in this study. Constraints for critical organs were set to a mean dose of less than 26 Gy to both parotids (6), a maximum dose of 50 Gy to the spinal cord, and of 60 Gy to the brainstem. The lymph nodes of the lower neck were treated with conventional opposed anterior and posterior cervical fields. A technique with a common isocentre for the upper and lower parts of the PTV could be used to solve the beam-matching problem. Other possibilities for treating the neck are offered by, e.g., photon IMRT or photons combined with a conventional, posterior electron 'strip'. We have therefore concentrated this study to the dose optimization of the upper part of the PTV, since the same technique for the neck treatment could be used in both situations under study.

All mixed photon and electron treatment planning was carried out using a TMS 6.0 treatment planning system (Nucletron B.V., the Netherlands). The electron algorithm of TMS is based on Monte Carlo pre-calculated pencil beams (23, 24). Good agreement between these calculations and measurements has been shown in cases relevant to this work (25). For photons, the pencil-beam dose calculation algorithm was used. Collapsed Cone Convolution (26) calculation was carried out for verification. Compared with the conventional pencil beam, it is a more precise algorithm that takes into account the transport of both electrons and scattered photons.

Photon IMRT was planned using the Oncentra treatment planning system (OTP, Version 1.2, Nucletron B.V., the Netherlands.) It allows the use of dose-volume constraints for each target/organ at risk, and for different weighting to be given to the constraints for different targets and organs at risk.

The electron beams in this study were generated with a racetrack microtron, (MM50, IBA, Belgium) which has electron energies in the range 7.5–50 MeV in 2.5 MeV steps. In conventional accelerators the maximum electron energy seldom exceeds 25 MeV. Consequently, the highest electron energy used was 25 MeV. Similar MLC-collimated electron beams can be obtained with a modified conventional linear accelerator (27). The 6 MV photon beam of a linear accelerator (Primus, Siemens AG, Erlangen, Germany) was used for photon IMRT plans.

Mixed electron and photon plan (MB)

Opposed bilateral electron beams of sufficient energy would give a useful dose distribution in some instances. However, the depth of the patients often precludes the use of such techniques with electrons of conventional energies (<25 MeV). Figure 1 shows the dose distributions of two opposed electron beams at a typical distance of 16 cm (in this patient material) between two beam entrances. The absorbed dose in the parotid region is low relative to the midline dose, but it exceeds the dose-volume constraint for the parotids. The width of the volume that is encompassed by, for example the 90% iso-dose is smaller than that needed to encompass the PTV. That is why this simple technique could not be used as a general solution for these cases. Instead the main electron-beam directions are from the anterior and oblique posterior, which avoid direct irradiation of the parotid glands, spinal cord and brainstem (Fig. 2a). Three photon beams were added in the same beam direction as the three main electron beams (Fig. 2a). Additionally, two anterior oblique photon beams were added, in order to improve the dose in the central region of the target (Fig. 2b), and to reduce the skin dose.

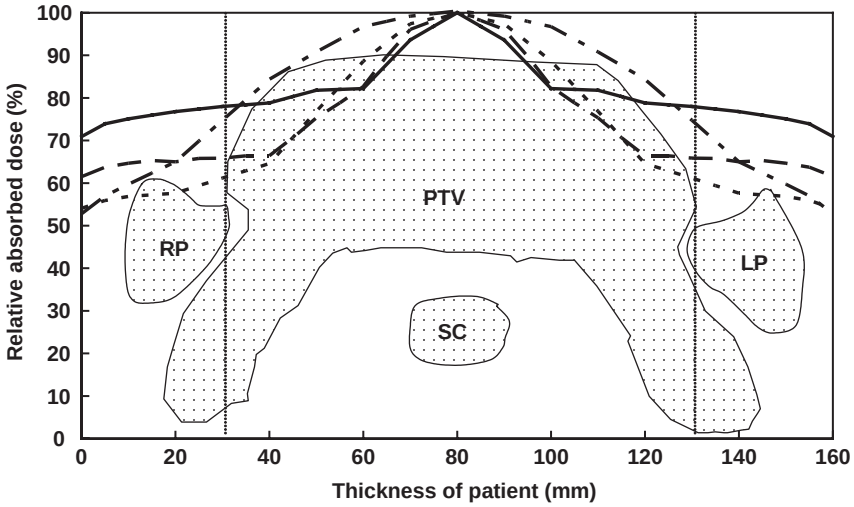

Fig. 1. Dose distribution of two opposed electron beams with energy of 20 (solid line), 22 (dashed lines), 25 (dotted lines), and 30 MeV (dot–dashed line). The thickness between beam entrances is 16 cm. The structures are PTV, RP (right parotid), LP (left parotid), and SC (spinal cord).

The effects of mixing electron and photon beams in a phantom are shown in Fig. 3. For the mixed electron and photon beam, the surface dose is reduced and the penetration depth is increased compared with a single electron beam.

Two laterally opposed, low-weight, narrow photon beams covered the anterior part of the target. This method has been described previously (14). Six to nine small photon beams and electron beams from the directions described above were added to improve the dose homogeneity within the target (Fig. 2c). The distance between the caudal border of the electron beams and the cranial border of the photon beams for the lower neck was at least 2 cm. The reason for this was to simplify the iso-centric matching of the upper (mixed beam) and lower parts (opposed photon beams) of the target.

The shape and direction of the beams were determined and modified by using the beams-eye-view (BEV) display function. Beam weights were adjusted manually (by iteration) until the dose constraints for the protocol were reached. For adjusting the dose in a volume, the weighting was done by changing the weight of the beam with the highest dose-contribution to that volume. If that was unsuccessful the beam with the second highest contribution was chosen etc. In total, seven beam directions divided into 15–20 beam segments were used in each mixed electron and photon plan. Energies used were 10 MV photons and 10–25 MeV electrons.

Photon IMRT plan

A static multi-segments intensity modulation technique was used for optimization. Seven beams were used with IMRT for comparison. The beam angles were at 215, 255, 306, 0, 54, 105, and 150 degrees. Dose constraints both for the target and critical organs were the same as for MB plans. Due to practical limitations of dose delivery, the total number of segments was limited to 70.

Dose planning comparison

Both the MB plan and the photon IMRT plan were performed for each patient. Isodose curves, dose volume histograms (DVHs) and data extracted from DVHs were used for comparison. The Wilcoxon signed ranks test was used for statistical inferences. The two-tailed test was used, except for the integral dose outside of PTV where the hypothesis was that electrons result in a lower integral dose outside of the PTV than photon IMRT.

RESULTS

Figures 4 and 5 show a comparison between the two techniques for patient no. 4. The isodose lines are displayed in transversal and coronal sections through the parotid glands and the PTV. It shows that the target was covered by a conformal dose distribution with both methods. The differences between them are small (Fig. 4, Table 1).

Table 1 shows a summary of data extracted from the DVHs for both photon IMRT plans and MB plans. The dose-volume constraints for the PTVs were not completely satisfied in most of the cases. The minimum doses in the PTV were 44–55 Gy for the mixed electron and photon technique and 46–55 Gy for the IMRT technique. The difference was not statistically significant. The typical location of the minimum dose volumes was the part of the PTV close to the parotid glands. This under-dosage is a consequence of a compromise between coverage of the PTV and avoidance of critical structures. Giving a different weighting to the optimization criteria may change the relation between these conflicting priorities. The proportion

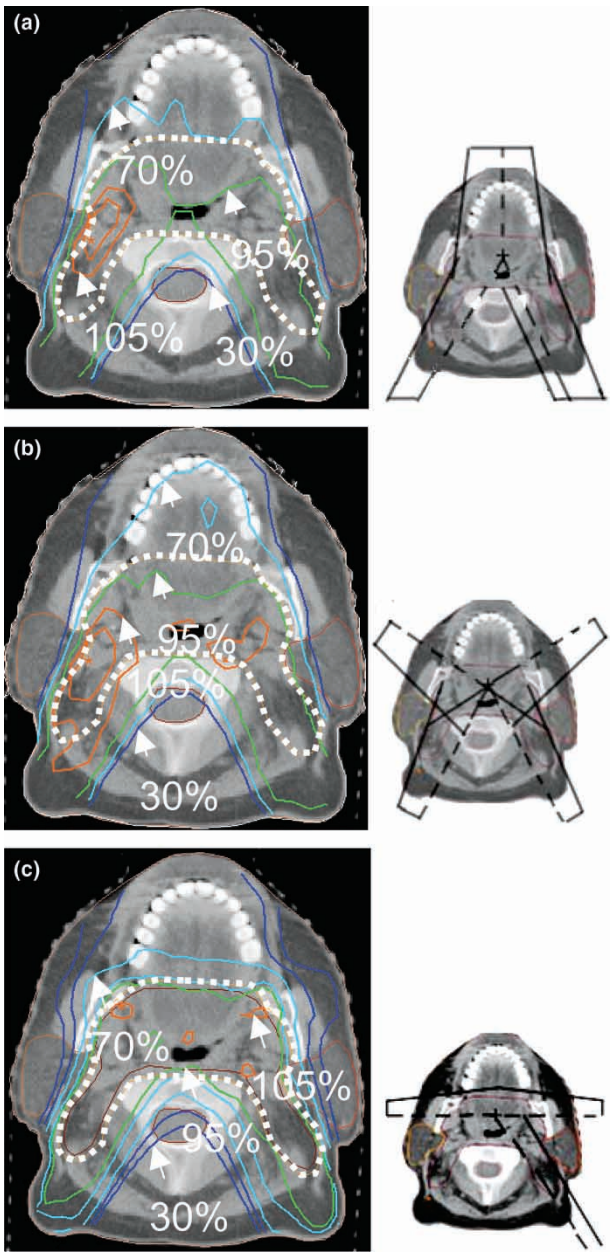

Fig. 2. The procedures of mixed beam forward planning: (a) the three main electron beams for shaping the dose distribution close to the shape of the PTV. Three photon beams were added in the same beam port to reduce skin dose and to increase dose to PTV; (b) two additional oblique anterior photon beams were added to compensate for a cold volume in front of the vertebral bone and simultaneously to decrease the skin dose; (c) two bilateral photon beams were added to increase penetration depth of electron beams; 6 to 9 electron and photon compensation beams were added for improvement of dose homogeneity in the target.

of the PTVs that received $\leq$90% of the prescribed dose were 2–6% with the MB plans and 1–4% with IMRT plans. The dose constraints for critical organs were fulfilled by both techniques, except for the parotid glands in patients 3 and 4 who had a mean dose higher than 26 Gy with the photon-IMRT technique. The dose outside the PTV was higher with photon-IMRT plans than with the MB plans, but a greater volume received in excess of 110% of the prescribed dose with the latter. The mean dose outside the PTV was higher with the IMRT technique than with that of the mixed electron and photon technique. This difference was statistically significant ($p < 0.05$). No statistically significant difference was detected for the size of the volumes receiving more than 110% of the prescribed dose. In summary, the constraints were met to the same extent by both the 'manual' mixture of electrons and photons and the automatically optimized IMRT technique.

DVH of the left parotid, spinal cord and brainstem are shown in Fig. 5. For the parotid glands the results are similar with both techniques. However, the DVHs of the spinal cord and brain stem indicate that there is a margin for further optimization in the MB plans.

Seven beams were used in both the mixed electron and photon and the IMRT plans. In MB plans, 15–20 segments (subfields) were needed, while the photon IMRT plans demanded 54–62 segments.

DISCUSSION

Radiotherapy of the head and neck region may cause patients irreversible and distressing side effects (28). More conformal dose distributions than in 3-D CRT can reduce the risk of xerostomia (6). It has also been shown that the dose distributions in target volumes in the head and neck region can be improved by photon IMRT compared with conventional treatment (4–6). Compared with photon IMRT, protons have an even greater capacity to deliver highly conformal dose distributions but with minimal integral doses (29, 30). Treatment planning studies have also shown that protons offer an advantage compared with IMRT in some head and neck tumours (31). Technical equipment such as proton facilities is likely to improve the radiotherapy of a large number of diseases in the future (32). However, proton therapy is presently not widely available and therefore alternative solutions should be sought. Electrons do not have the same rapid dose fall off at depth as protons but it is certainly more rapid than that of photons. The fact that electrons can be delivered from conventional accelerators makes it logical to explore their ability to improve the dose distribution of IMRT as a complement.

The integral dose to normal tissues is usually high when irradiating patients with IMRT. The main purpose of this study was to explore the potential of conventional-energy electrons to reduce this drawback. The normal tissues surrounding the tumour can be protected to some degree by using an energy-optimized electron beam. It is thus reasonable to assume that electron beams as a complement to photons should increase the conformity of the dose distribution. However, in the treatment of deep-seated

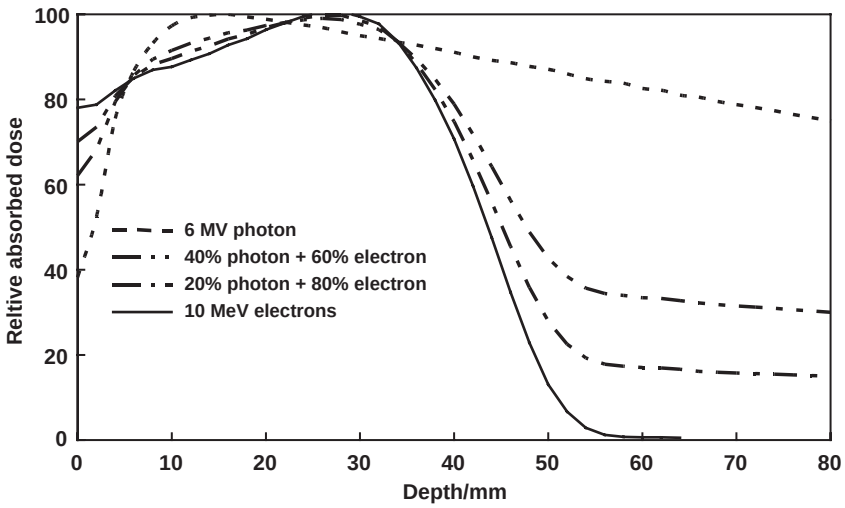

Fig. 3. Depth dose curves of mixed 10 MeV electrons and 6 MV photons. The surface dose is reduced and penetration depth is increased by adding different amounts of 6 MV photons to 10 MeV electron beams.

tumours with electrons alone, the required energies of electrons (>25 MeV) are not available with conventional linear accelerators. In addition, with electron energies <25 MeV, the high-dose region resulting from opposed electron beams is too narrow to cover most targets and the dose variation in the target is large (see Fig. 1).

It has been reported from dose escalation studies with photon IMRT techniques that the dose variation within the target increases with increasing target dose (33). More normal tissue sparing can be obtained if the homogeneity within the target is allowed to decrease (34). In Fig. 5 and Table 1 there is an indication that the maximum and

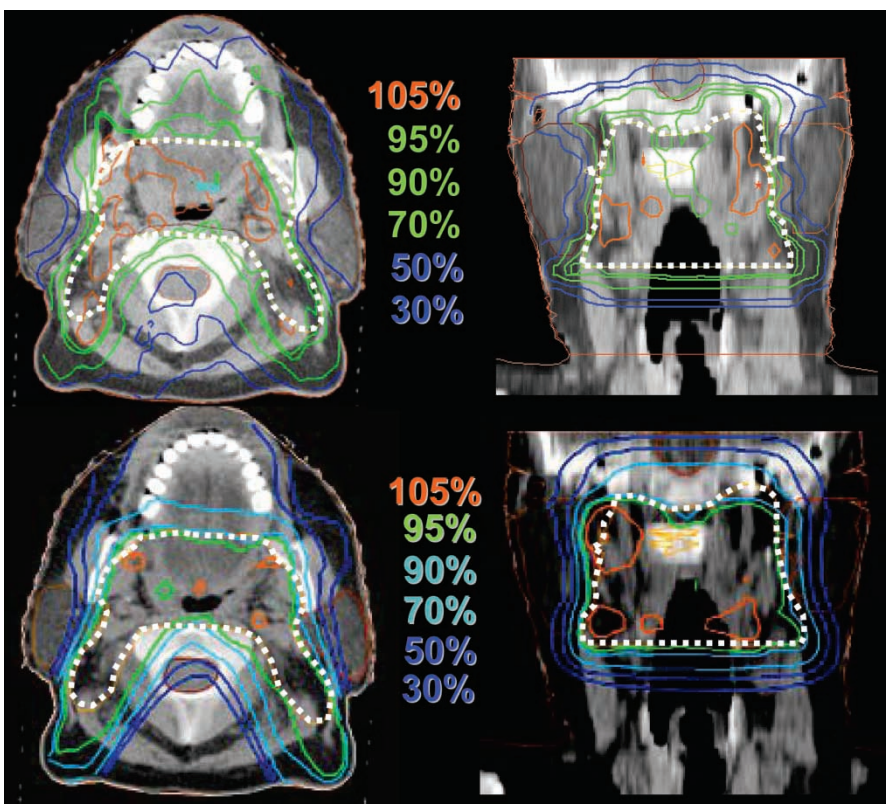

Fig. 4. Dose distribution of patient no. 4 for both the photon IMRT plan (upper part) and the mixed electron and photon beam plan (lower part) with isodose lines 30%, 50%, 70%, 90%, 95%, and 105%.

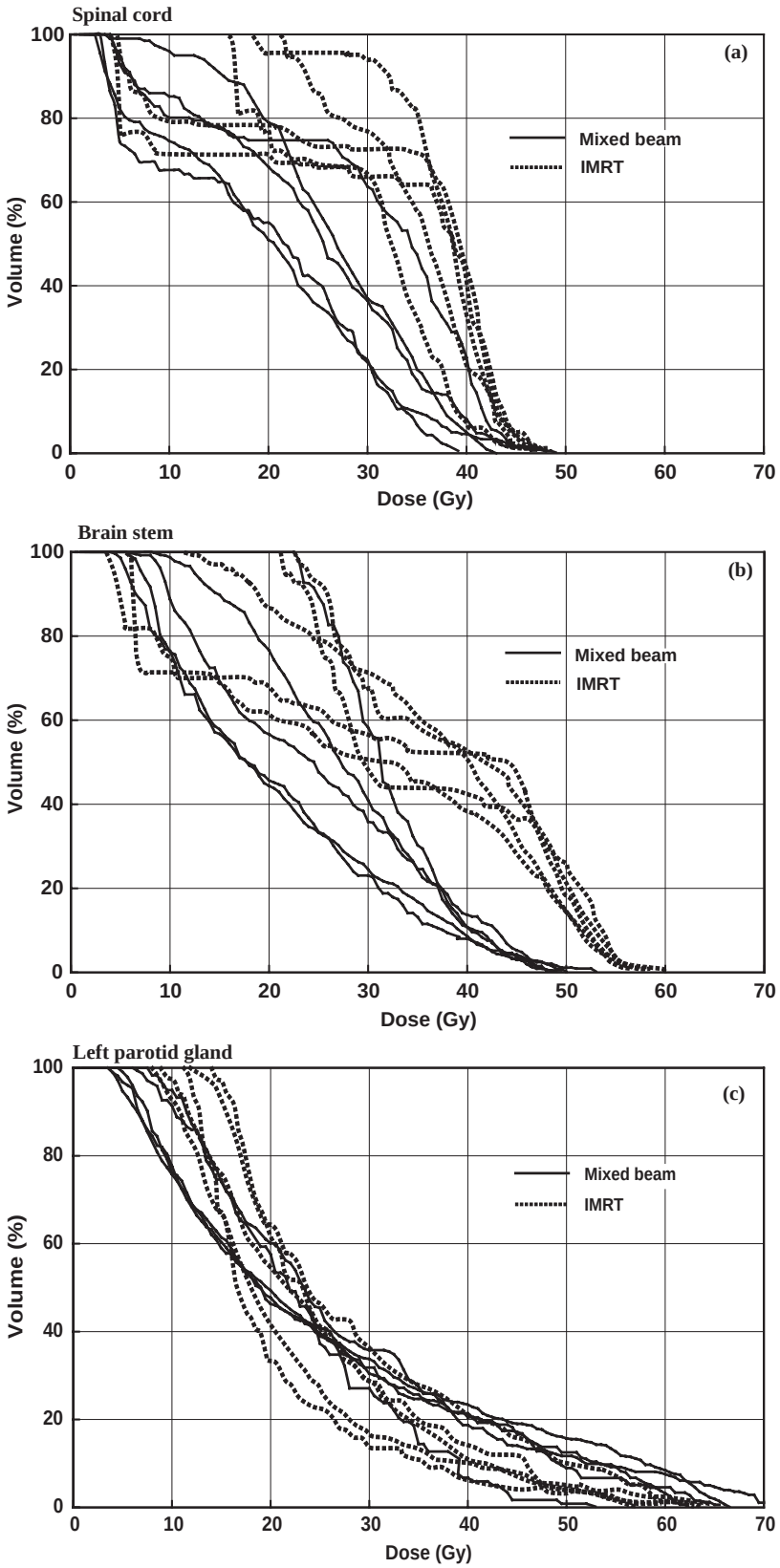

Fig. 5. DVHs for spinal cord, brain stem, and left parotid for both mixed electron and photon plans (solid line) and photon IMRT plans (dotted lines).

Table 1

Data from dose volume histograms for IMRT and mixed electron and photon plans

	Criteria	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
		MB	IMRT	MB	IMRT	MB	IMRT	MB	IMRT	MB	IMRT
PTV											
Volume (cm^3)		273	273	210	210	262	262	292	292	203	203
Max dose (Gy)	77	84	81	79	81	79	81	83	84	84	82
Mean dose (Gy)	70	70 (6)	70 (4)	70 (4)	70 (3)	70 (6)	70 (5)	70 (5)	70 (5)	70 (7)	70 (5)
Min dose (Gy)	63	55	55	53	54	46	47	52	46	44	47
V95 (%)		14	10	13	6	16	12	9	12	19	11
V90 (%)	0	2	2	3	1	3	3	2	3	6	4
V110 (%)		7	2	3	1	4	2	3	4	8	4
Spinal cord											
Max dose (Gy)	50	42	49	38	49	47	50	49	49	48	49
Brainstem											
Max dose (Gy)	60	49	57	47	58	50	59	53	60	49	60
Left parotid											
Mean dose (Gy)	26	24 (25)	25 (18)	23 (10)	21 (15)	24 (17)	29 (20)	25 (27)	22 (18)	27 (21)	29 (18)
Right parotid											
Mean dose (Gy)	26	23 (22)	26 (18)	26 (12)	23 (12)	16 (13)	29 (16)	24 (29)	22 (15)	26 (20)	29 (15)
Tissue outside the PTV											
Max dose (Gy)		84	81	75	80	79	80	83	84	84	82
Mean dose (Gy)		35 (24)	36 (22)	17 (20)	19 (21)	21 (20)	23 (19)	22 (23)	32 (18)	29 (24)	36 (20)
V110 (%)		24	43.8	0.0	0.0	0.0	2	10	13	18	8

Figures in parentheses represent one standard deviation.
V90, V95 and V110 are percentage volumes receiving $\leq$95%, $\leq$90% and $\geq$110% of prescription dose respectively.
MB = mixed electron and photon beam plan; IMRT = photon IMRT.

integral doses in the spinal cord and brainstem are lower with MB plans than with IMRT. This implies that a more homogeneous target dose could be obtained if the dose in two critical organs was allowed to increase.

The energies of electrons used in this study were kept below 25 MeV. The electron beam quality of the racetrack microtron is better than that of conventional linear accelerators (17). However, similar quality can be obtained with a modified treatment head of a conventional linear accelerator. The major modification needed is the addition of an helium atmosphere in the treatment head (18, 27). MLC-collimated electron beams can also be designed with other methods (35, 36).

With a comparable dose distribution in the target, this simulation study shows that the mixed electron and photon technique delivers a smaller integral dose to normal tissues than photon IMRT. However, at this point it is not clear whether this improvement will be clinically significant. The effects of low-dose hypersensitivity (8) have not been fully explored in the clinic. For young patients with a long expected survival the lower integral dose might be of importance in decreasing the risk of secondary malignancies caused by late radiation effects. It is noteworthy that the treatment plans of this investigation were produced in two completely different ways. The mixed electron and photon technique was planned by an iterative procedure that physically restricted the number of iterations and thus the optimization. The IMRT plans were made with fully automatic optimization. It is therefore reasonable to believe that if similar tools were available in both cases, i.e. automatic optimization, the results might well be more advantageous for the mixed electron and photon technique. This might particularly be the case if electron beams could be optimized together with photon IMRT. For that reason we believe that this method should be further investigated using optimizing algorithms for electrons. This will also allow comparative studies based on more cases than with this laborious forward planning technique.

In some photon IMRT techniques the time for each fraction may be substantially prolonged owing to the delivery of a large number of segments. This is partly due to the time for movements, adjustment and verification of the leaf positions. Prolongation of the time to deliver each fraction may cause tumour sparing as a result of the low mean dose rate (37). The mixed beam technique has the potential of being faster than the pure photon IMRT owing to the smaller number of segments. Thus, the risk of tumour cell recovery during fraction delivery will be smaller.

CONCLUSION

The aim of this study was to explore the feasibility of using mixed electron and photon beams to treat deep-seated tumours. With planning simulation of the head and neck, we obtained clinically acceptable results. The mixed electron and photon technique used in conjunction with computerized optimization tools should improve the therapeutic benefit of pure photon IMRT. To further investigate the possible benefits more advanced optimization tools need to be developed.

ACKNOWLEDGEMENTS

This work was funded by the Cancer Research Foundation in Northern Sweden and the Swedish Cancer Foundation.

REFERENCES

1. Scalliet P, Cosset JM, Wambersie A. Application of the LQ model to the interpretation of absorbed dose distribution in the daily practice of radiotherapy. Radiother Oncol 1991; 22: 180–9.
2. Tubiana M, Eschwege F. Conformal radiotherapy and intensity-modulated radiotherapy – clinical data. Acta Oncol 2000; 39: 555–67.
3. Verhey LJ. Physical considerations in the use of intensity modulated radiotherapy to produce three-dimensional conformal dose distributions. J Jpn Soc Ther Radiol Oncol 2000; 12: 191–203.
4. Cozzi L, Fogliata A, Bolsi A, Nicolini G, Bernier J. Three-dimensional conformal vs. intensity-modulated radiotherapy in head-and-neck cancer patients: comparative analysis of dosimetric and technical parameters. Int J Radiat Oncol Biol Phys 2004; 58: 617–24.
5. Wu Q, Manning M, Schmidt-Ullrich R, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. Int J Radiat Oncol Biol Phys 2000; 46: 195–205.
6. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999; 45: 577–87.
7. Glatstein E. Intensity-modulated radiation therapy: the inverse, the converse, and the perverse. Semin Radiat Oncol 2002; 12: 272–81.
8. Joiner MC, Marples B, Lambin P, Short SC, Turesson I. Low-dose hypersensitivity: current status and possible mechanisms. Int J Radiat Oncol Biol Phys 2001; 49: 379–89.
9. Zackrisson B, Karlsson M. Matching of electron beams for conformal therapy of target volumes at moderate depths. Radiother Oncol 1996; 39: 261–70.
10. Karlsson M, Zackrisson B. Matching of electron and photon beams with a multi-leaf collimator. Radiother Oncol 1993; 29: 317–26.
11. Perkins GH, McNeese MD, Antolak JA, Buchholz TA, Strom EA, Hogstrom KR. A custom three-dimensional electron bolus technique for optimization of postmastectomy irradiation. Int J Radiat Oncol Biol Phys 2001; 51: 1142–51.
12. Ma CM, Ding M, Li JS, Lee MC, Pawlicki T, Deng J. A comparative dosimetric study on tangential photon beams, intensity-modulated radiation therapy (IMRT) and modulated electron radiotherapy (MERT) for breast cancer treatment. Phys Med Biol 2003; 48: 909–24.
13. Asell M, Hyodynmaa S, Gustafsson A, Brahme A. Optimization of 3D conformal electron beam therapy in inhomogeneous media by concomitant fluence and energy modulation. Phys Med Biol 1997; 42: 2083–100.
14. Karlsson M, Zackrisson B. Exploration of new treatment modalities offered by high energy (up to 50 MeV) electrons and photons. Radiother Oncol 1997; 43: 303–9.
15. Korevaar EW, van Vliet RJ, Woudstra E, Heijmen BJ, Huizenga H. Sharpening the penumbra of high energy electron beams with low weight narrow photon beams. Radiother Oncol 1998; 48: 213–20.
16. Ma CM, Pawlicki T, Lee MC, et al. Energy- and intensity-modulated electron beams for radiotherapy. Phys Med Biol 2000; 45: 2293–311.
17. Karlsson M, Nystrom H, Svensson H. Electron beam characteristics of the 50-MeV racetrack microtron. Med Phys 1992; 19: 307–15.
18. Blomquist M, Karlsson MG, Zackrisson B, Karlsson M. Multileaf collimation of electrons – clinical effects on electron energy modulation and mixed beam therapy depending on treatment head design. Phys Med Biol 2002; 47: 1013–24.
19. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. Int J Radiat Oncol Biol Phys 2003; 57: 61–70.
20. ICRU. International Commission on Radiation Units and Measurements (ICRU). Prescribing, recording, and reporting photon beam therapy. ICRU Report 50, 1993.
21. Boyer AL, Geis P, Grant W, Carol M. Modulated beam conformal therapy for head and neck tumors. Int J Radiat Oncol Biol Phys 1997; 39: 227–36.
22. ICRU. International Commission on Radiation Units and Measurements (ICRU). Prescribing, recording, and reporting photon beam therapy (Supplement to ICRU Report 50). ICRU Report 62, 1999.
23. Lax I, Brahme A, Andreo P. Electron beam dose planning using Gaussian beams. Improved radial dose profiles. Acta Radiol 1983; Suppl: 49–59.
24. Lax I, Brahme A. Electron beam dose planning using Gaussian beams. Energy and spatial scaling with inhomogeneities. Acta Radiol 1985; Suppl: 75–85.
25. Blomquist M, Karlsson M. Test procedures for verification of an electron pencil beam algorithm implemented for treatment planning. Radiother Oncol 1996; 39: 271–86.
26. Ahnesjo A. Collapsed cone convolution of radiant energy for photon dose calculation in heterogeneous media. Med Phys 1989; 16: 577–92.
27. Karlsson MG, Karlsson M, Ma CM. Treatment head design for multileaf collimated high-energy electrons. Med Phys 1999; 26: 2161–7.
28. Zackrisson B, Mercke C, Strander H, Wennerberg J, Cavallin-Stahl E. A systematic overview of radiation therapy effects in head and neck cancer. Acta Oncol 2003; 42: 443–61.
29. Suit H, Goldberg S, Niemierko A, et al. Proton beams to replace photon beams in radical dose treatments. Acta Oncol 2003; 42: 800–8.
30. Turesson I, Johansson KA, Mattsson S. The potential of proton and light ion beams in radiotherapy. Acta Oncol 2003; 42: 107–14.

31. Mock U, Georg D, Bogner J, Auberger T, Potter R. Treatment planning comparison of conventional, 3D conformal, and intensity-modulated photon (IMRT) and proton therapy for paranasal sinus carcinoma. Int J Radiat Oncol Biol Phys 2004; 58: 147–54.
32. Svensson H, Moller TR. Developments in radiotherapy. Acta Oncol 2003; 42: 430–42.
33. Zhou J, Fei D, Wu Q. Potential of intensity-modulated radiotherapy to escalate doses to head-and-neck cancers: what is the maximal dose? Int J Radiat Oncol Biol Phys 2003; 57: 673–82.
34. Vineberg KA, Eisbruch A, Coselmon MM, McShan DL, Kessler ML, Fraass BA. Is uniform target dose possible in IMRT plans in the head and neck? Int J Radiat Oncol Biol Phys 2002; 52: 1159–72.
35. Klein EE, Li Z, Low DA. Feasibility study of multileaf collimated electrons with a scattering foil based accelerator. Radiother Oncol 1996; 41: 189–96.
36. Moran JM, Martel MK, Bruinvis IA, Fraass BA. Characteristics of scattered electron beams shaped with a multileaf collimator. Med Phys 1997; 24: 1491–8.
37. Mu X, Lofroth PO, Karlsson M, Zackrisson B. The effect of fraction time in intensity modulated radiotherapy: theoretical and experimental evaluation of an optimisation problem. Radiother Oncol 2003; 68: 181–7.