Chapter 9

Summarizing discussion

Volumetric modulated arc therapy

Despite the fact that volumetric modulated arc therapy (VMAT) is often referred to as a novel technique, Brahme et al. had already reported in the 1980s, the idea of using rotating beam therapy to create a non-uniform dose distribution [1]. A decade later, in 1994, saw the introduction of the Corvus® platform (Nomos, Pittsburgh, PA, USA), the first commercial tomotherapy system. The radiation dose was given by a small fan-beam megavolt (MV)-source with a binary multileaf collimator (MLC), rotating around the patient in a slice by slice way, analogous to CT imaging. Parallel to tomotherapy, arc therapy using a linear accelerator was explored. In 1995, Yu described a new method, called intensity-modulated arc therapy (IMAT), with changing field shapes during continuous gantry motion [2]. This has evolved so that currently different linear accelerator arc delivery systems exist, including RapidArc®, (Varian Medical Systems, Palo Alta, CA, USA), Elekta VMAT® (Elekta Inc, Stockholm, Sweden) and SmartArc® (Philips Inc, Andover, MA, USA). With a variable dose rate and gantry speed and continuously changing MLC apertures, VMAT delivery is faster and creates highly conformal dose distributions which in some cases results in improved target volume coverage and sparing of normal tissues, compared with conventional, static field intensity modulated radiotherapy (IMRT) techniques.

Because modern VMAT plans are a form of IMRT, they retain many of its advantages and disadvantages. Nevertheless, compared with static field IMRT, VMAT has the potential to offer additional advantages, such as a reduced treatment delivery time and a reduced monitor unit (MU) output. In static field IMRT, time is required to move into position for, and call up, each field, the maximum dose rate has often been lower, and small leaf openings are required for complex fluency distributions. A typical static IMRT plan for head and neck cancer (HNC) uses 5-9 beams, leading to a treatment time of around 10-15 minutes, compared to less than 3 minutes for a dual arc plan delivering 2 Gy [3-6]. The number of MU in a static IMRT plan is 2-3 times higher than a conventional radiotherapy plan, which has led to concerns of increased risk of secondary radiation-induced malignancies [7]. Stathakis et al. estimated a 40% increase in the risk of radiation induced malignancy using IMRT compared to conformal RT in HNC [8] A recent study however, using 3 theoretical risk models with different dose-risk relationships, reported otherwise: although the use of IMRT leads to a redistribution of the individual tissue risks, the total risk seemed to be comparable between the 2 techniques [9]. No direct comparisons between static IMRT and VMAT exist in HNC, but since several studies have reported reductions in monitor units of 50–60% using VMAT [3,4,10], it seems unlikely that VMAT would increase the risk of secondary cancers.

Increasing complexity

In 2008, Bortveld and Webb argued that single arc VMAT only had a potential use for relatively simple cases because of less conformal dose distributions compared to tomotherapy [11]. By using a collimator angle of 45%, Otto showed that equally good dose distributions could be achieved with single arc therapy

[12]. Verbakel et al. showed in a planning study for HNC that dual arc plans provided an at least similar OAR and better PTV dose homogeneity than single arc VMAT or static IMRT [3]. To confirm the findings of this planning study, RapidArc planning and delivery parameters in a group of HNC patients for whom IMRT plans were technically challenging were analyzed **(chapter 2)**. The high dose regions were shown to be very conformal with a conformity index (CI) of 1.13. The mean dose to ipsi- (IL) and contralateral (CL) parotid gland for this group of 35 HNC patients treated with RapidArc was 31.4 Gy and 26.1 Gy respectively, comparable to earlier results for patients with HNC treated with IMRT in our department [13]. Results are somewhat difficult to compare with other series, since other authors may have different dose prescriptions, approaches to delineation and optimization objectives. In our institute, objectives are set to achieve a V95% of 99% and 98% for the PTV_{boost} and $PTV_{elective}$ respectively, while keeping the boost and elective volumes receiving >107% of prescribed dose as small as possible. A report on early clinical experience with VMAT by Scorsetti et al. in a group of patients with locally-advanced HNC showed a V95% of 97.2% for the PTV_{boost} and CI of 1.21. Mean CL parotid dose was 21.5 Gy, but dose prescription to the $PTV_{elective}$ was 3.5 Gy lower when compared to our series [14].

From the beginning, parotid-sparing IMRT was considered standard in patients with HNC. However, parotid saliva lacks mucins that maintain a patient's subjective sense of hydration, and preserving the parotids alone has inconsistently translated into improvements in xerostomia [15-19]. Since the submandibular glands (SMG) contribute two-thirds of unstimulated saliva flow and its saliva is rich in mucins [20], patients could potentially benefit from SMG sparing. However, concerns have been raised that SMG sparing could compromise adequate coverage of target volumes, with an increased risk of marginal recurrences [refs Eisbruch 16, Mendenhall 21]. As shown in **chapter 3**, we were able to reduce the dose to contralateral SMG to 33.2 Gy and 34.4 Gy (using an elective dose of 57.75 Gy (21 patients) and 54.25 Gy (10 patients) respectively) in patients undergoing elective irradiation to clinically negative contralateral level II-IV nodes. Planned PTV coverage was not compromised, with an average V95% of 99.2% and 98.7% for the PTV_{boost} and $PTV_{elective}$, respectively. In contrast, a planning study by Houweling et al. of contralateral SMG-sparing IMRT, reported that in order to reduce the mean contralateral SMG dose from 54 Gy to 40 Gy, it was necessary to accept an underdosage of target volumes in the vicinity of the gland to 90% of prescribed dose [22]. It is unclear if this is due to the difference in planning technique, or choice of optimization objectives. Several studies have reported no relapses in the vicinity of the spared SMG, demonstrating that SMG sparing can be achieved without increasing the risk of marginal failures [23,24].

Tumors arising in the paranasal sinuses remain a challenge in radiotherapy treatment planning due to the proximity of many critical OARs. In **chapter 4** we investigated the possible dosimetric gain of a non-coplanar arc technique in patients treated locally to a dose of 66 Gy in 2 Gy fractions. Since the sinonasal region is box-shaped and located in between the optic nerves, it makes sense to incorporate a craniocaudal beam to avoid the optic system. Using a dual arc strategy (360° counterclockwise and 160-180° craniocaudal), we were able to achieve a dose reduction of 3 to more than 10 Gy in the clinically relevant 55-60 Gy area in one of the optic nerves in 50% of patients without compromising PTV coverage, conformity or the homogeneity index. Comparable findings were recently reported by Orlandi et al., with a superiority of non-coplanar VMAT over static IMRT and coplanar VMAT plans [25]. Compared to (non-)

coplanar static IMRT, VMAT makes use of unrestricted beam directions over the range of the arcs, and using a non-coplanar setup increases the degrees of freedom, which can allow for steeper dose gradients to be achieved in an axial plane. The integral dose may be higher with a non-coplanar setup. This has led some authors to prefer a coplanar VMAT technique, since in their series OAR sparing is only marginally better with a non-coplanar technique [26].

Swallowing problems as a result of (chemo)radiotherapy treatment for HNC have a significant impact on quality of life, possibly even more than xerostomia [27-29]. Eisbruch et al. was one the first to describe that muscular components of the swallowing apparatus, critical to the development of dysphagia in irradiated patients, could be spared by IMRT [30]. Numerous studies have found significant correlations between dysphagia and various dose–volume parameters for the pharyngeal constrictor muscles, esophageal inlet muscle and glottic and supraglottic larynx [31-37], leading to IMRT based strategies to limit the dose to the swallowing structures. Since sparing of more structures leads to increasingly complex treatment plans, there is a potential risk for unexpected negative consequences like an increase in dose to other OARs and/or healthy structures or less conformity. When introducing new techniques into the clinic it is important to guard against unintended consequences. In **chapter 5**, we examined the introduction of successive technologies and planning techniques in our department and the consequent impact on dosimetric parameters. To do so, clinical treatment plans of 120 comparable patients with oropharynx cancer were selected from 4 IMRT time periods with increasing sparing of OARs and/or newer techniques. Significant gains in OAR sparing over time, especially for the swallowing muscles and submandibular gland, did not come at the cost of increasing dose deposition in other OARs like the parotid glands or elsewhere, nor at the cost of decreasing PTV coverage/homogeneity. In our opinion, this is mostly due to increasing planner skill and experience in VMAT planning followed by stricter planning protocols, and to a lesser part by improved optimization algorithms. This emphasizes the importance of high quality planning protocols and implementation/training techniques that minimize the learning curve and equip the planner with the skills needed to optimize plan quality [38]. Results also show that it is unlikely that the optimal planning solutions have been reached. Tol et al. reported on the tradeoff between an increasing number of arcs (leading to a better OAR sparing) and increased delivery time, and a modest increase in MU. Although dual arc treatments are mostly used in clinical practice, they concluded that four arc plans seemed to provide a good balance between increased delivery time and improved plan quality [39]. Another important factor is the (inverse) relation between increasing PTV coverage/homogeneity and the resulting OAR sparing, showing the need for interdepartmental consensus on planning criteria [40,41].

With the advent of IMRT and the resulting conformal dose distributions, some authors have cautioned about the potentially increased risk of marginal tumor miss [42]. Proper delineation of both primary tumor and elective lymph node regions using multi-modal imaging modalities, combined with a robust treatment setup protocol is of paramount importance [43-46]. A recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database, pooling individual data from HNC patients treated with radiotherapy between 1999 and 2007, demonstrated that the use of IMRT was associated with a significant improvement in cause-specific survival compared with non-IMRT techniques [47]. This differs from the results of Nutting et al. who found no difference in locoregional control or survival in the PARSPORT-trial, comparing 3D conformal and IMRT radiotherapy (n=94, with 47 patients receiving IMRT) for HNC [48].

Organ at risk sparing

In addition to maximizing tumor control, the goal of IMRT and VMAT is to reduce radiation-induced complications to improve the quality of life of patients. Xerostomia and swallowing problems are the most important side effects after radiotherapy and have been the subject of numerous investigations. Since it is intuitive that a lower dose in an OAR (potentially) leads to a lower normal tissue complication probability (NTCP), there are only a few studies in which a direct comparison between different techniques in HNC has been performed. One randomized controlled clinical study showed that at 12 months post-radiation therapy, QOL scores were significantly higher in the IMRT group than the conventional radiation therapy group for patients with nasopharyngeal carcinoma [49]. The prospective randomized PARSPORT trial showed similar results: at 12 and 24 months, significant benefits were seen in recovery of saliva secretion with parotid sparing IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global quality of life scores [48]. A retrospective study of 114 patients showed significantly lower xerostomia rates in the contralateral SMG sparing group compared to the non-sparing group, independent of parotid sparing [50]. Van der Laan et al. compared in their planning study 30 standard IMRT treatment plans with swallowing-sparing IMRT plans that aimed to reduce the dose to organs at risk for swallowing dysfunction in the same patients. Adequate coverage of target volumes and dose to critical structures were comparable, whereas the mean doses to the various swallowing-related structures were significantly reduced. Applying predictive models for swallowing dysfunction, a mean reduction of 9% (range 3-20%) in predicted physician-rated Radiation Therapy Oncology Group (RTOG) grade 2-4 swallowing dysfunction was achieved [37]. A recent comparative effectiveness systematic review investigated whether one treatment modality (i.e. 3DCRT, IMRT, proton therapy, and stereotactic body RT) would be more effective than the others in (among other things) reducing normal tissue toxicity and adverse events, and improving quality of life. Late xerostomia was shown to be reduced and QOL domains related to xerostomia were improved in patients treated with IMRT compared with 3DCRT. Although evidence was identified on other key toxicities like dysphagia, the reported rates compared between modalities were inconsistent [51].

The balance between striving for improvements in tumor outcomes and not increasing toxicity is delicate. Although a burdensome treatment, with an absolute survival benefit of 6.5% for the combination of [52] concurrent platinum-based chemotherapy and radiotherapy (CRT), this is nowadays considered the standard of care for non-surgical treatment of locally advanced HNC. Since several randomized trials testing sequential approaches with induction docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by concurrent CRT versus concurrent CRT alone have failed to demonstrate a statistically significant difference in OS and PFS [53-56], the exact role of induction chemotherapy (IC) remains controversial. Nevertheless, all studies showed an important reduction in tumor volumes after IC, presenting opportunities for modification (i.e. reduction) of the pre-IC target volumes, with a possible resulting decrease in OAR dose and toxicity. Although consensus guidelines advocate using the pre IC tumor volume projected on the post-IC planning CT scan [57], it is unclear if it is imperative to give the whole pre-IC tumor volume the full boost dose. **Chapter 6** describes a planning study in a uniform cohort of patients with oropharynx cancer, comparing OAR doses calculated on the pre- and post-IC planning CT scan, using 2 different delineation strategies on the post-IC scan: one based on pre-IC (consensus) and the other on

post-IC (visible) target volumes. As expected, substantial reductions in primary tumor and nodal volumes after TPF-IC were achieved with both contouring strategies. Unfortunately, subsequent reductions in OAR doses were rather modest and only statistically significant for the contralateral parotid gland with the consensus delineation approach. When using the post-IC visible target volumes, differences were larger, especially for some of the swallowing muscles, for which the reduction in doses were possibly clinically relevant. Radiotherapy strategies delivering a full dose on the post-IC visible tumor but a lower dose to the pre-IC volume (in order to decrease the dose in some OARs) merit investigation.

Historically, a dose (equivalent) of 46-50 Gy has been given to the elective lymph node regions to eradicate possible microscopic disease. This dose is rather empirical, and based on historical studies, when staging was primarily done by clinical examination and radiotherapy was given using large open 2D fields. With the advent of modern imaging techniques including contrast enhanced CT scan, (diffusion weighted) MRI (DW-MRI), PET-CT scan, ultrasound with fine needle aspiration or a combination of techniques, it is likely that affected lymph nodes that were missed in earlier days, are now diagnosed and treated to a high dose, and that a lower dose to the clinically negative neck would be sufficient. This hypothesis is in part supported by some (retrospective) studies, showing a very low rate of isolated regional recurrences of only a few percent [58-60]. Since the dose to the swallowing muscles and the salivary glands is at least in part due to the elective lymph node irradiation, dose de-escalation to the elective neck would reduce the resulting dose to these OARs and could probably reduce toxicity and improve quality of life after treatment. Nuyts et al. recently reported on the VLAK trial, a prospective randomized study investigating whether a reduction of the dose to the elective nodal sites from 50 to 40 Gy would result in a reduction of acute and late side effects without compromising tumor control [61]. In the 40 Gy arm, extra dose constraints to the swallowing apparatus were set, which makes it somewhat difficult to appreciate the true benefit of an elective dose decrease. Follow up was too short to report on (late) tumor control, but grade 3 dysphagia was significantly reduced and at the time of reporting, no patients had a recurrence in the electively treated neck. In the Netherlands, the UPGRADE-RT study (Uniform FDG-PET guided GRAdient Dose prEscription to reduce late Radiation Toxicity), giving a lower dose to the $PTV_{elective,}$ will soon start accruing patients [NCT02442375].

Although parotid gland sparing (and more recently SMG sparing) IMRT is now current practice, up to 40% of patients still experience moderate to severe xerostomia after treatment [62]. It would be useful to be able to identify the patients at risk for developing xerostomia, so truly individualized interventional and/or therapeutic strategies could be developed. An earlier report from Dirix et al. suggested that DW-MRI before and after treatment might be a promising tool for investigating changes due to radiotherapy [63]. In our study, DW-MRI data before, early during treatment and after treatment were analyzed to evaluate the effect of CRT on salivary gland function **(Chapter 7)**. To overcome possible geometric distortions, both echo planar imaging (EPI) and half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences were used. Since there is evidence that the parotid gland is not a parallel organ and that irradiation of the central region containing the highest number of stem cells resulted in the greatest loss of salivary output [64], sub-regions in all individual salivary glands were evaluated. Although the magnitude of effect differed between both techniques, a rise in salivary gland apparent diffusion coefficient (ADC) values during and after treatment was observed, indicating a lower cell density. Although still weak, using

HASTE sequences showed a better correlation between dose and ΔADC between baseline and during/after CRT. ADC values with both techniques were higher in the SMG than the parotid gland which is in line with previous data [63]. Since two-thirds of the saliva is produced by the SMG in the unstimulated state, the expected higher amount of water in the extracellular space of the submandibular glands could explain the higher ADC. With both techniques there appeared to be regional differences within the salivary glands, possibly reflecting the regional dose differences. Animal studies showing that the dose to the sub-volume of the parotid gland containing the stem cells is a better predictor for dysfunction than the mean dose to the whole gland were recently confirmed in a retrospective analysis of treated patients [65]. Therefore, a reduction of dose in this sub-volume might further reduce the risk of parotid gland dysfunction and xerostomia. A better understanding of possible heterogeneity in the response to treatment within the individual glands could help to develop optimal treatment plans with preferential sparing of important sub-regions, in an effort to further reduce treatment morbidity. At the University Medical Centre Groningen, a prospective randomized trial evaluating parotid gland stem cell sparing IMRT is currently recruiting [NCT01955239].

Standardization

Although general guidelines are well formulated in national and consensus treatment protocols, specific treatment recommendations are sometimes vague or open to interpretation. This can be the result of conflicting reports, historically different treatment approaches or a lack of data. With concomitant CRT nowadays considered standard non-surgical treatment for locally advanced HNC, there seems to be little chance of new studies directly comparing CRT against alternative fractionation schedules like for example hypofractionated radiotherapy (compared to standard fractionation, with an absolute survival benefit at 5 years of 6.5% and 8% respectively [52,66]). The result of this could be that some patient subgroups are now treated too intensively and exposed to higher risks of toxicity. T3 larynx cancer, especially when not-bulky, could be considered intermediate stage HNC, and guidelines are less clear in the approach that should be taken with this disease. In the Netherlands, the treatment of HNC is relatively well organized and centralized, and comprehensive guidelines exist, so we conducted a survey to identify how T3 laryngeal carcinoma is currently being managed in the Netherlands **(Chapter 8)**. Results show that although there were areas of agreement, differences were identified. For example, for T3N0 cancer, 3/12 centers use RT only, while other centers define a 'bulky' disease state or use a volume criterion above which chemotherapy (CT) is added. For T3N+ laryngeal cancer, nodal stage is considered more important than primary tumor volume for the addition of CT: with N2-3 disease, 10/12 centers use CRT. The two leading centers in the ARCON trial do not use a nodal volume criterion, which is in line with the results of their study [67]. Total (boost) doses were comparable (i.e. 68-70 Gy), whereas elective doses differed more, with a higher dose in the simultaneous integrated boost (SIB) schemes compared to the sequential schemes and accelerated scheme only (ASO) scheme. The higher dose in the SIB schemas was given to compensate for a longer total treatment time of the elective regions (from 4-5 weeks to

6-7 weeks). Since no robust data exist, elective doses and/or fractions vary between the centers. The results of this study emphasize the need for further standardization of treatment in general, and dose and fractionation schedules in particular. The National Platform RT HNC, an assembly of radiation oncologists and physicists treating HNC in the Netherlands, therefore aims to harmonize RT dose, fractionation and delivery techniques. A current project of the Platform is an evaluation of the variation in treatment plan objectives, leading to a possible improvement of treatment planning by increased OAR sparing and reduction of variation between institutes. First results show that after targeted feedback on their initial plans, average composite salivary/swallowing mean doses (±SD) decreased from 30.3±5 / 36.6±8Gy to 26.1±3.2 / 29.6±6.7Gy [Verbakel, personal communication].

Looking to the future

Treatment of locally-advanced HNC is complex, and although progress has been made, both conceptually and technically, more than one-third of patients eventually succumb to their disease [68,69]. Furthermore, effective but aggressive treatments have a major impact on quality of life issues like xerostomia and dysphagia.

Several approaches to improving the therapeutic ratio are currently being investigated. The ARTFORCE study (adaptive RT for HNC: a phase III randomized study with cisplatin and conventional or adaptive high dose RT for advanced HNC [NCT01504815]) and the EORTC1219/DAHANCA29 trial (a blind randomized multicenter study of accelerated fractionated CRT with or without nimorazole, [NCT01880359]) investigate the possibility of treatment intensification with no/modest increase in toxicity for selected patient groups. Other studies focus on treatment de-intensification, looking for a consequent decrease in toxicity: the UPGRADE-RT is a randomized controlled trial with dose reduction to the elective neck in head and neck squamous cell carcinoma [NCT02442375]. The De-ESCALaTE study compares cetuximab versus cisplatin early and late toxicity events in HPV+ oropharyngeal squamous cell carcinoma in patients treated with combined therapy [NCT01874171].

To enable a more tailored approach to treatment selection, new predictive and prognostic (bio)markers are being investigated: the PREDICTION study explores the predictive value of PET-CT and PET-DW-MRI early during CRT for locoregional control of advanced stage HNC (local VU University Medical Center study). The EORTC1219/DAHANCA29 study uses a 15-gene signature for hypoxia to pre-randomize the patients and investigate if the hypoxic gene profile is a predictive factor for the benefit of hypoxic sensitization. Furthermore, the integration of new diagnostic and molecular imaging modalities for more precise delineation and technical advances like improved imaging during treatment could optimize RT treatment [70,71].

Despite a tendency toward standardization of techniques and increasing plan quality despite additional OAR sparing, it is unlikely that current plans are optimal and it remains difficult, if not impossible, to predict a specific dose distribution for each individual patient. However, technical improvements are being made in a number of areas. For example, in order to estimate the achievable OAR doses and to improve the overall plan quality and consistency, knowledge-based planning strategies have been developed. RapidPlan®, the Varian solution makes use of a large set of previously generated OAR dose volume histograms (DVH) to build a model. This is used to predict a range of achievable DVH-lines for OARs of new patients and then to generate a plan. However, the quality of the model's output for any given new patient depends on the plans used to build the model, and the number and relevance of the structures and DVHs used [72]. Other vendors are also developing comparable solutions like Pinnacle Auto-Planning® (Philips Radiation Oncology Systems, Best, Netherlands) and multi-criteria optimization strategies (RaySearch Laboratories, Stockholm, Sweden). In addition, the extent of OAR sparing has been shown to be related to the desired PTV coverage and dose homogeneity, providing additional opportunities to refine PTV-OAR trade-offs [40].

Adaptive radiotherapy, an approach to correct for anatomical changes during RT treatment through modification of original target volumes and plans is an interesting intellectual concept [73]. However technical limitations have hampered its integration into routine care, and it is difficult to predict which patients are likely to benefit in a clinically meaningful way [74]. With increasing computational power, more accurate deformation algorithms and better pre-treatment selection criteria, it is likely that adaptive radiotherapy will be implemented in routine clinical practice.

Planning studies have shown a reduction in OAR dose using proton planning in HNC [75], which is expected to translate into less side effects. Because of the higher costs of proton therapy, the model based approach is a potential tool to select patients who would benefit most of this treatment [76].

References

1. Brahme A, Roos JE, Lax I. Solution of an integral equation encountered in rotation therapy. Phys Med Biol. 1982;27:1221-9
2. Yu CX. Intensity-modulated arc therapy with dynamic multileaf collimation: an alternative to tomotherapy. Phys Med Biol. 1995;40:1435-49
3. W.F. Verbakel, J.P. Cuijpers, D. Hoffmans, M. Bieker, B.J. Slotman, S. Senan. Volumetric intensity-modulated arc therapy vs. conventional IMRT in head-and-neck cancer: a comparative planning and dosimetric study. Int J Radiat Oncol Biol Phys. 2009;74:252–9
4. E. Vanetti, A. Clivio, G. Nicolini, A. Fogliata, S. Ghosh-Laskar, J.P. Agarwal, et al. Volumetric modulated arc radiotherapy for carcinomas of the oro-pharynx, hypo-pharynx and larynx: a treatment planning comparison with fixed field IMRT Radiother Oncol. 2009;92:111–7
5. Dai X, Zhao Y, Liang Z, Dassarath M, Wang L, Jin L, Chen L, Dong J, Price RA, Ma CM. Volumetric-modulated arc therapy for oropharyngeal carcinoma: a dosimetric and delivery efficiency comparison with static-field IMRT. Phys Med. 2015;31:54-9
6. Holt A, Van Gestel D, Arends MP, Korevaar EW, Schuring D, Kunze-Busch MC, Louwe RJ, van Vliet-Vroegindeweij C. Multi-institutional comparison of volumetric modulated arc therapy vs. intensity-modulated radiation therapy for head-and-neck cancer: a planning study. Radiat Oncol. 2013;8:26
7. Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys. 2003; 56:83-8
8. Stathakis S, Roland T, Papanikolaou N, Li J, Ma C. A prediction study on radiation-induced second malignancies for IMRT treatment delivery. Technol Cancer Res Treat. 2009;8:141-8
9. Ardenfors O, Josefsson D, Dasu A. Are IMRT treatments in the head and neck region increasing the risk of secondary cancers? Acta Oncol. 2014;53:1041-7
10. Wiezorek T, Brachwitz T, Georg D, Blank E, Fotina I, Habl G, Kretschmer M, Lutters G, Salz H, Schubert K, Wagner D, Wendt TG. Rotational IMRT techniques compared to fixed gantry IMRT and tomotherapy: multi-institutional planning study for head-and-neck cases. Radiat Oncol. 2011;6:20
11. Bortveld T, Webb S. Single-Arc IMRT? Phys Med Biol. 2009;54:N9-20
12. Otto K. Letter to the Editor on 'Single-Arc IMRT?'Phys med Biol. 2009;54:L37-41
13. Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys. 2009;74:1-8
14. Scorsetti M, Fogliata A, Castiglioni S, Bressi C, Bignardi M, Navarria P, et al. Early clinical experience with volumetric modulated arc therapy in head and neck cancer patients. Radiat Oncol. 2010;5:93
15. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;50:695–704
16. Eisbruch A. Reducing xerostomia by IMRT: what may, and may not, be achieved. J Clin Oncol. 2007;25:4863–4
17. Kam MKM, Leung S, Zee B, Chau RM, Suen JJ, Mo F, Lai M, Ho R, Cheung KY, Yu BK, Chiu SK, Choi PH, Teo PM, Kwan WH, Chan AT. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol. 2007;25:4873–9

18. Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Impact of radiation induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;69:751–60

19. Dijkema T, Terhaard CH, Roesink JM, Braam PM, van Gils CH, Moerland MA, Raaijmakers CP. Large cohort dose-volume response analysis of parotid gland function after radiotherapy: intensity-modulated versus conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2008;72:1101-9

20. Tabak LA. In defense of the oral cavity: structure, biosynthesis, and function of salivary mucins. Annu Rev Physiol. 1995;57:547–56

21. Mendenhall WM, Mendenhall CM, Mendenhall NP: Submandibular gland-sparing intensity-modulated radiotherapy.Am J Clin Oncol 2014; 37:514-6.

22. Houweling AC, Dijkema T, Roesink JM, Terhaard CH, Raaijmakers CP. Sparing the contralateral submandibular gland in oropharyngeal cancer patients: a planning study. Radiother Oncol. 2008;89:64–70

23. Collan J, Kapanen M, Mäkitie A, Nyman H, Joensuu H, Tenhunen M, et al. Submandibular gland-sparing intensity modulated radiotherapy in the treatment of head and neck cancer: sites of locoregional relapse and survival. Acta Oncol. 2012;51:735-42

24. Gensheimer MF, Liao JJ, Garden AS, Laramore GE, Parvathaneni U. Submandibular gland-sparing radiation therapy for locally advanced oropharyngeal squamous cell carcinoma: patterns of failure and xerostomia outcomes. Radiat Oncol. 2014;9:255

25. Orlandi E, Giandini T, Iannacone E, De Ponti E, Carrara M, Mongioj V, et al. Radiotherapy for unresectable sinonasal cancers: dosimetric comparison of intensity modulated radiation therapy with coplanar and non-coplanar volumetric modulated arc therapy. Radiother Oncol. 2014;113:260-6

26. Zhong-Hua N, Jing-Ting J, Xiao-Dong L, Jin-Ming M, Jun-Chong M, Jian-Xue J, et al. Coplanar VMAT vs. noncoplanar VMAT in the treatment of sinonasal cancer. Strahlenther Onkol. 2015;191:34-42

27. Goguen LA, Posner MR, Norris CM, Tishler RB, Wirth LJ, Annino DJ, et al. Dysphagia after sequential chemoradiation therapy for advanced head and neck cancer. Otolaryngol Head Neck Surg. 2006;134:916-22

28. Nguyen NP, Frank C, Moltz CC, Vos P, Smith HJ, Karlsson U, et al. Impact of dysphagia on quality of life after treatment of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2005;61:772-8

29. Jensen K, Lambertsen K, Grau C. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity and correlation with dose and volume parameters. Radiother Oncol. 2007;85:74-82

30. Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT?.Int J Radiat Oncol Biol Phys. 2004;60:1425–39

31. Dornfeld K, Simmons JR, Karnell L, et al. Radiation doses to structures within and adjacent to the larynx are correlated with long-term diet- and speech-related quality of life. Int J Radiat Oncol Biol Phys. 2007;68:750–75

32. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2007;68:1289–98

33. Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2008;72:1110–8

34. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol. 2009;90:189-95

35. Christianen ME, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR, Doornaert P, Koken PW, Leemans CR, Rinkel RN, de Bruijn MJ, de Bock GH, Roodenburg JL, van der Laan BF, Slotman BJ, Verdonck-de Leeuw IM, Bijl HP, Langendijk JA. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. Radiother Oncol. 2012;105:107-14

36. Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol. 2007;85:64–73

37. van der Laan HP, Christianen ME, Bijl HP, Schilstra C, Langendijk JA. The potential benefit of swallowing sparing intensity modulated radiotherapy to reduce swallowing dysfunction: an in silico planning comparative study. Radiother Oncol. 2012;103:76-81

38. Tol JP, Dahele M, Peltola J, Nord J, Slotman BJ, Verbakel WF. Automatic interactive optimization for volumetric modulated arc therapy planning. Radiat Oncol. 2015;10:75

39. Tol JP, Dahele M, Slotman BJ, Verbakel WF. Increasing the number of arcs improves head and neck volumetric modulated arc therapy plans. Acta Oncol. 2015;54:283-7

40. Tol JP, Dahele M, Doornaert P, Slotman BJ, Verbakel WF. Different treatment planning protocols can lead to large differences in organ at risk sparing. Radiother Oncol. 2014;113:267-71

41. Tol JP, Dahele M, Doornaert P, Slotman BJ, Verbakel WF. Toward optimal organ at risk sparing in complex volumetric modulated arc therapy: an exponential trade-off with target volume dose homogeneity. Med Phys. 2014;41:021722

42. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. J Clin Oncol. 2006;24:2618–22

43. Eisbruch A, Gregoire V. Balancing risk and reward in target delineation for highly conformal radiotherapy in head and neck cancer. Semin Radiat Oncol. 2009;19:43-52

44. Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol. 2014;110:172-81

45. Qi XS, Hu AY, Lee SP, Lee P, DeMarco J, Li XA, et al. Assessment of interfraction patient setup for head-and-neck cancer intensity modulated radiation therapy using multiple computed tomography-based image guidance. Int J Radiat Oncol Biol Phys. 2013;86:432-9

46. Graff P, Kirby N, Weinberg V, Chen J, Yom SS, Lambert L, Pouliot J. The residual setup errors of different IGRT alignment procedures for head and neck IMRT and the resulting dosimetric impact. Int J Radiat Oncol Biol Phys. 2013;86:170-6

47. Beadle BM, Liao KP, Elting LS, Buchholz TA, Ang KK, Garden AS, Guadagnolo BA. Improved survival using intensity-modulated radiation therapy in head and neck cancers: A SEER-Medicare analysis. Cancer. 2014;120:702–10

48. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011;12:127-36

49. Pow, E. H. et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int. J. Radiat. Oncol. Biol. Phys. 2006;66:981–91

50. Gensheimer MF, Liao JJ, Garden AS, Laramore GE, Parvathaneni U. Submandibular gland-sparing radiation therapy for locally advanced oropharyngeal squamous cell carcinoma: patterns of failure and xerostomia outcomes. Radiat Oncol. 2014;9:255

51. Ratko TA, Douglas GW, de Souza JA, Belinson SE, Aronson N. Radiotherapy Treatments for Head and Neck Cancer Update. Comparative Effectiveness Review No. 144. (Prepared by Blue Cross and Blue Shield Association Evidence-based Practice Center under Contract No. 290-2007-10058.) AHRQ Publication No. 15-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2014

52. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4–14

53. Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol. 2014;25:216–25

54. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013;14:257–64

55. Cohen EE, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol. 2014;32:2735-43

56. Budach W, Bölke E, Kammers K, Gerber PA, Orth K, Gripp S, Matuschek C. Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials. Radiother Oncol. 2015 Nov 14. pii: S0167-8140(15)00563-0. doi: 10.1016/j.radonc.2015.10.014

57. Loo SW, Geropantas K, Wilson P, Martin WM, Roques TW. Target volume definition for intensity-modulated radiotherapy after induction chemotherapy and patterns of treatment failure after sequential chemoradiotherapy in locoregionally advanced oropharyngeal squamous cell carcinoma. Clin Oncol (R Coll Radiol). 2013;25:162-7

58. Duprez F, Bonte K, De Neve W, Boterberg T, De Gersem W, Madani I. Regional relapse after intensity-modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2011;79:450-8

59. Lambrecht M, Dirix P, Van den Bogaert W, Nuyts S. Incidence of isolated regional recurrence after definitive (chemo-) radiotherapy for head and neck squamous cell carcinoma. Radiother Oncol. 2009;93:498-502

60. Vergeer MR, Doornaert PA, de Bree R, Leemans CR, Slotman BJ, Langendijk JA. Postoperative elective nodal irradiation for squamous cell carcinoma of the head and neck: outcome and prognostic factors for regional recurrence. Ann Oncol. 2011;22:2489-94

61. Nuyts S, Lambrecht M, Duprez F, Daisne JF, Van Gestel D, Van den Weyngaert D, et al. Reduction of the dose to the elective neck in head and neck squamous cell carcinoma, a randomized clinical trial using intensity modulated radiotherapy (IMRT). Dosimetrical analysis and effect on acute toxicity. Radiother Oncol. 2013;109:323-9

62. Marta GN, Silva V, de Andrade Carvalho H, de Arruda FF, Hanna SA, Gadia R, et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol. 2014;110:9-1

63. Dirix P, De Keyzer F, Vandecaveye V, Stroobants S, Hermans R, Nuyts S. Diffusion-weighted magnetic resonance imaging to evaluate major salivary gland function before and after radiotherapy. Int J Radiat Oncol Biol Phys. 2008;71:1365-71

64. Pringle S, Van Os R, Coppes RP. Concise review: Adult salivary gland stem cells and a potential therapy for xerostomia. Stem Cells. 2013;31:613-9

65. van Luijk P, Pringle S, Deasy JO, Moiseenko VV, Faber H, Hovan Aet al. Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. Sci Transl Med. 2015;7:305ra147

66. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet. 2006;368:843-54

67. Janssens GO, van Bockel LW, Doornaert PA, Bijl HP, van den Ende P, de Jong MA, et al. Computed tomography-based tumour volume as a predictor of outcome in laryngeal cancer: results of the phase 3 ARCON trial. Eur J Cancer. 2014;50:1112-9

68. Cancer Facts and figures 2014, American Cancer society, Atlanta, GA, USA

69. Grégoire V, Lefebvre JL, Licitra L, Felip E; EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v184-6

70. Arens AI, Troost EG, Hoeben BA, Grootjans W, Lee JA, Grégoire V, et al. Semiautomatic methods for segmentation of the proliferative tumour volume on sequential FLT PET/CT images in head and neck carcinomas and their relation to clinical outcome. Eur J Nucl Med Mol Imaging. 2014;41:915-24

71. Hoeben BA, Bussink J, Troost EG, Oyen WJ, Kaanders JH. Molecular PET imaging for biology-guided adaptive radiotherapy of head and neck cancer. Acta Oncol. 2013;52:1257-71

72. Tol JP, Dahele M, Delaney AR, Slotman BJ, Verbakel WF. Can knowledge-based DVH predictions be used for automated, individualized quality assurance of radiotherapy treatment plans? Radiat Oncol. 2015;10:234

73. Schwartz DL, Dong L. Adaptive radiation therapy for head and neck cancer-can an old goal evolve into a new standard? J Oncol. 2011.pii: 690595

74. Brouwer CL, Steenbakkers RJ, Langendijk JA, Sijtsema NM. Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help? Radiother Oncol. 2015;115:285-94

75. van der Laan HP, van de Water TA, van Herpt HE, Christianen ME, Bijl HP, Korevaar EW, et al. The potential of intensity-modulated proton radiotherapy to reduce swallowing dysfunction in the treatment of head and neck cancer: A planning comparative study. Acta Oncol. 2013;52:561-9

76. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol. 2013;107:267-7