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Head and Neck Tumor Control Probability: Radiation Dose-Volume Effects in Stereotactic Body Radiation Therapy for Locally Recurrent Previously-Irradiated Head and Neck Cancer: Report of the AAPM Working Group

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Abstract

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Purpose: Stereotactic body radiation therapy (SBRT) has emerged as a viable reirradiation strategy for locally recurrent previously-irradiated head and neck cancer. Doses in the literature have varied, which challenges clinical application of SBRT as well as clinical trial design.

Material & Methods: A working group was formed through the American Association of Physicists in Medicine to study tumor control probabilities for SBRT in head and neck cancer. We herein present a systematic review of the available literature addressing the dose/volume data for tumor control probability with SBRT in patients with locally recurrent previously-irradiated head and neck cancer. Dose-response models are generated that present tumor control probability as a function of dose.

Results: Data from more than 300 cases in 8 publications suggest that there is a dose-response relationship, with superior local control and possibly improved overall survival for doses of 35 to 45 Gy (in 5 fractions) compared with <30 Gy.

Conclusion: Stereotactic body radiation therapy doses equivalent to 5-fraction doses of 40 to 50 Gy are suggested for retreatment. © 2018 Elsevier Inc. All rights reserved.

Summary

In a systematic review of the available literature addressing the dose/volume data for tumor control probability with SBRT in patients with locally recurrent previously-irradiated head and neck cancer, data from more than 300 cases in 8 publications suggest that there is a dose-response relationship with superior local control and possibly improved overall survival, for doses of 35 to 45 Gy (in 5 fractions) compared with <30 Gy. Stereotactic body radiation therapy doses equivalent to 5 fraction doses of 40 to 50 Gy are suggested for retreatment.

1. Clinical Significance

Approximately 55,070 new cases of oral cavity, pharyngeal, and laryngeal cancer were diagnosed in the United States in 2014, with an associated approximately 12,000 cancer-related deaths (1). Despite improvements in the multimodality treatment of head and neck cancers, locoregional failure remains the most common cause of head and neck cancer-related death (2), and this pattern of failure persists in the more recently recognized unique subset of human papillomavirus (HPV)-associated head and neck cancers (3).

For patients with locoregionally recurrent head and neck cancer, surgical salvage remains the standard of care. Many such patients present with unresectable recurrences, which carry a poor prognosis (4). Nonoperative strategies, including palliative chemotherapy and conventional reirradiation with or without chemotherapy, are challenged by significant toxicities and suboptimal outcomes (5). Thus, stereotactic body radiation therapy (SBRT) has been embraced as a potentially useful salvage strategy for patients with unresectable locally recurrent head and neck cancers in a previously irradiated field (6, 7). Clinically, the goals are to limit the volume of normal tissue that is reirradiated (thus decreasing toxicity) and shortening the overall treatment time (which is particularly helpful in patients with an overall poor prognosis).

We herein present a systematic review of the available literature addressing the dose/volume data for tumor control probability with SBRT in patients with locally recurrent previously

irradiated head and neck cancer. Dose-response models are generated that present tumor control probability as a function of dose.

2. Endpoints

The primary endpoints considered were local control and overall survival. There was heterogeneity in the local control nomenclature used across studies because some studies included both mucosal and lymph node recurrences. Thus, local control as modeled here represents either local failure or locoregional failure as described in the individual studies. Presumably locoregional failure rates are higher than those of local failure; however, the extent to which this can be distinguished in the included studies is unclear, as outlined in Table 1. The majority of the examined studies used RECIST (Response Evaluation Criteria in Solid Tumors) (16) to define local control assessed from computed tomography (CT) and complementary modalities, such as positron emission tomography (PET)/CT and/or magnetic resonance imaging (MRI) (11–14). One study used a combination of CT and planned repeat endoscopic biopsies (8). Additional challenges in scoring the tumor response included: (1) poor overall survival, which could lead to an underestimation of local failure owing to competing risk; (2) a limited number of studies reporting 2-year and 3-year outcomes; (3) normal tissue distortion from prior therapies (eg, surgery, radiation), which may mask local recurrence or increase interobserver variability in follow-up imaging interpretation; (4) cross-study differences in follow-up imaging modality and frequency (eg, CT vs PET/CT vs MRI); and (5) requirements for histologic confirmation of failure.

In many trials SBRT may have been used to compensate for suboptimal effects of primary therapy (ie, with the patient never reaching a state of “no evidence of disease” after their initial therapy). To address this, the working group segregated patients into 2 groups according to the interval of time between the completion of primary therapy and the SBRT. Those who received SBRT within 6 weeks of completion of primary therapy were considered to have essentially received a “boost” as a part of their initial treatment and were thus excluded from this analysis. Only those patients receiving SBRT more than 6 weeks after completion of primary radiation therapy were included. The 6-week cut-point is somewhat arbitrary, but patients are often seen 3 to 6 weeks after completion of initial therapy to assess for resolution of acute side effects and for resolution of their gross tumor, so this is a reasonable time point to delineate the 2 groups. Further, the working group did not consider patients with benign tumors because these made up a minority of the reported cases. Because HPV status was not available from the majority of the included studies, HPV status was not considered, and thus unrecognized imbalances in HPV positivity could influence outcomes, because HPV has been shown to have strong prognostic impact in recurrent squamous cell carcinoma of the head and neck (SCCHN) (3).

3. Challenges Defining and Segmenting Anatomic Volumes

The examined studies all used intravenous contrast-enhanced CT for target delineation and treatment planning. Several reports incorporated other complementary imaging modalities, such as MRI (8, 13, 15) and/or 18-fluorodeoxyglucose PET/CT (9, 11, 12, 14), to assist with image segmentation. Many of the earlier studies used smaller treatment volumes, whereby

the planning target volume (PTV) was defined by the gross tumor volume (GTV) without any margin (9–12). However, the contemporary studies (that also made up the majority of the studies reviewed) used GTV-to-PTV expansions of 2 to 6 mm (8, 13–15), consistent with published patterns of failure analyses (17). Unlike conventionally fractionated definitive treatment of head and neck cancer, SBRT uses high dose per fraction, often with minimal or no additional margin for subclinical spread, and thus necessitates more accurate target delineation. However, as highlighted by a recent patterns of care analysis and the studies included here, there is no current standard imaging used across all studies, though most use either PET/CT or MRI (18). These differences in volume definition are potential confounders to the presented tumor control models.

4. Review of Outcomes Data

Studies in this review are summarized in Table 1. Several published studies were not included owing to reporting limitations that precluded accurate assessment of the delivered doses and clinical outcomes (19–23). A PubMed search in April 2015 for the keywords “stereotactic” AND “neck” AND “radiation” resulted in 293 articles. The abstracts were searched for peer-reviewed publications containing SBRT retreatment in the head and neck region. Twenty-five candidate articles were found and then examined using the Quantitative Analyses of Normal Tissue Effects in the Clinic review forms adapted for SBRT. The data were not fully evaluable in 16 of the articles; for example, uncertain prescription dose and fractionation, or outcomes (eg, pooling cases with variable degrees of follow-up, or there was overlap in cases among multiple publications). When institutions had multiple publications with overlapping datasets, the most recent or most complete article was selected. Ultimately, 8 articles were found with data that could be used to create the local control dose-response model, as shown in Tables 1–3.

The earliest report with usable dose and outcome data per patient, Chua et al from Hong Kong (8), used an XKnife system (Radionics, Burlington, MA) and relatively modest doses (most received 12.5 Gy in a single fraction; range, 11.2–14 Gy). Eleven of their patients had recurrent disease and were included in our analysis. All subsequent included reports used CyberKnife (Accuray, Sunnyvale, CA) or Trilogy (Varian Medical Systems, Palo Alto, CA) and higher doses.

The next 4 studies were from the UPMC Hillman Cancer Center. The Voynov et al series in 2006 (9) used a slightly higher median biological effective dose of 24 Gy in 5 fractions for recurrent SCCHN, and these patients were known to have minimal overlap with the 2011 University of Pittsburgh Cancer Institute report (11), by virtue of differing time periods and prescription dose levels. From discussions with the original authors it was confirmed that <5% of included cases, estimated to be at most 15 of the included overall total 343 cases or 4.4%, were at risk for overlap; it was the consensus of the group that potential overlap would be ignored within the model because the difference would be small in the context of the presented robust model with hundreds of patients. Results of the Voynov et al study (9) demonstrated the feasibility and safety of SBRT in these patients and justified a prospective phase 1 dose escalation trial (25). Subsequently, Rwigema et al (11), using data from these phase 1 patients and others, were the first to graphically depict the dose, tumor volume, and

treatment response for recurrent, previously irradiated SCCHN on the basis of sigmoidal graphs of local control from 4 prescription dose groups with 1-, 2-, and 3-year follow-up. Rwigema et al (11) suggested that higher dose is required to achieve equivalent 1-year locoregional control of larger tumors; this graph is reproduced in Figure 1. This study makes up one-third of the patient cohort included, thus this article has a substantial impact on the presented dose-response models, especially at 2 and 3 years (11). This is a potential limitation of the presented model; however, the working group included all articles from the initially identified 293 articles that met the HyTEC inclusion criteria necessary to achieve the high level of detail HyTEC was seeking.

Two other articles from UPMC are seen to have minimal overlap, by comparing their various differing nonsquamous cell histologies. The Paravati et al (10) study of 40 patients undergoing endoscopic endonasal surgery followed by SBRT had median target dose biological equivalent dose₁₀ = 48 Gy (equivalent to 25 Gy in 2.7 fractions, Linear Quadratic, $\alpha/\beta = 10$ Gy). We excluded the 26 patients with benign histology, and the 14 cases with malignancies were included in our model. Vargo et al (12) reported on 34 nonsquamous cases with median 40 Gy in median 5 fractions and found that local control was significantly better for tumors smaller than 25 cm³; a higher dose would be required for larger tumors, but the optimal dose was not determined.

The subsequent 3 reports (13–15) used more than 2 fractions. The French series by Lartigau et al (13) used 36 Gy in 6 fractions for all 56 patients. The series from the Ankara Oncology Hospital in Turkey used 4 to 6 fractions (15), Georgetown University Hospital used 3 to 5 fractions (14), and the median number of fractions in both studies was 5. The outcomes from these studies are summarized in Table 3. We acknowledge that it is imperfect to compare data from different retrospective studies, because there are certainly imbalances in patient-specific factors that impact the reported outcomes. For example, Porceddu et al used doses similar to those of Kress et al and Dizman et al yet reported vastly different overall survival rates, possibly owing to differences in the exclusion/inclusion of patients with metastatic disease.

Most of the reviewed reports used the Cyberknife, which aggressively uses multiple noncoplanar beams to deliver a highly conformal dose distribution. Custom thermoplastic mask immobilization was used in all studies, except for 1 study that used an invasive head frame-based immobilization (8). Motion control typically included 6-dimensional skull-based tracking or X-sight spine tracking in studies using the Cyberknife platform (9–15). Other linear accelerator-based radiosurgery delivery systems (eg, TrueBeam, Trilogy, Novalis, Artiste) used daily image guidance, including cone-beam CT or bi-directional X-ray imaging (ExacTrac; BrainLab, Feldkirchen, Germany) (11, 12).

5. Factors Affecting Outcomes

Risk of toxicity to the carotid artery has been shown to be lower when the fractionation is not used on consecutive days (26), although the effects of this on tumor control require further study. The only factor consistently suggested to impact tumor control was total reirradiation prescription dose (8, 11, 12, 15, 27). The dataset from Rwigema et al (11) is the

most robust analysis of the impact of total dose and tumor size on tumor control (Fig. 1). The data in several of the other reports (8, 12, 15, 27) are less convincing because fewer details are provided. With regard to different lesion sizes, several reports suggest that the dose-response relationship continues without plateau across the dose ranges examined (eg, 24–50 Gy) for larger lesions (eg, $>25 \text{ cm}^3$) (11, 12, 15, 27). For smaller tumors (eg, $<25 \text{ cm}^3$) the relationship for crude rate of complete response plateaued at 44 Gy in Table 2 of Rwigema et al at 45.5% (11), although for the smallest tumors and highest dose in Figure 1 the overall local control is seen to approach 100% at 1 year. The simple concept is that lower doses might be able to adequately control smaller tumors, but the exact quantities, particularly for longer duration of control, still need further investigation. Some studies noted the potential importance of reirradiation interval as a function of local control (14, 27). Other factors that potentially could affect tumor control not captured in this analysis are histology (eg, squamous cell carcinoma vs nonsquamous histology), overall treatment time (eg, every day vs every-other-day fractionation), and use of concurrent systemic therapy, most commonly cetuximab (12, 13, 26–28), but insufficient data were available to quantify these effects. Cross-prospective trial comparisons and retrospective matched-pair analyses would suggest a considerable improvement in terms of survival favoring concurrent systemic therapy (28). The working group was also unable to identify reports that addressed outcomes as a function of fraction number, tumor location, tumor growth rate, prescription isodose (eg, dose homogeneity allowed within the target volume), or irradiation technique (eg, margin, immobilization, setup issues, machine) for retreated head and neck tumors. Prior surgery could also affect tumor control probability by virtue of vascular disruption; however, the studies selected unresectable recurrences, thus the authors believed the potential impact to be small. Recently SBRT treatment site has been suggested to potentially affect normal tissue complication probability (NTCP) outcomes (29), though to the authors' knowledge there are no robust data to suggest that primary site influences tumor control probability outcomes, and this limitation further potentially impacts the presented model.

6. Mathematical/Biological Model

For the purpose of dose-response analysis, overall survival and local control data were extracted from the original publications. Specifically, actuarial overall survival at 1- and 2-year follow-up and local control at 1, 2, and 3 years were used for analysis. For reports that did not explicitly state these time points, we digitized them from the published Kaplan-Meier graphs. The dose/fractionation and outcome data from the studies were pooled as follows (Tables 1–3). For each study, the weighted average PTV marginal dose and fraction number were computed and taken to be globally representative for that study (Table 2). If a weighted average PTV marginal dose could not be computed owing to the lack of detailed information, the report's stated prescription dose/fraction number was used. Ideally the weighting would have been from the number of at-risk patients in each time point, but because many of the studies did not include this information, we simply weighted by the total initial number of analyzable patients in each dose group, held constant for each time point. The median number of fractions among all studies was 5, so before performing dose-response modeling, all doses were converted to 5-fraction equivalent dose using the Withers formulation (30) of the linear-quadratic model, $n_2 d_2 (d_2 + \alpha/\beta) = n_1 d_1 (d_1 + \alpha/\beta)$, where $n_2 =$

5 is the desired fractionation, d_2 is the 5-fraction equivalent dose per fraction, n_1 is the originally computed representative number of fractions from Table 2, and d_1 is the corresponding dose per fraction, and α/β was set to a nominal 10 Gy for tumor response. Logistic dose-response modeling of local control rates with maximum likelihood parameter fitting was completed using DVH Evaluator (DiversiLabs, Huntingdon Valley, PA). Confidence intervals for model parameters were calculated using the profile-likelihood method. Confidence intervals for dose-response model were obtained using the bootstrap method with 2000 samples. Figure 2 illustrates the generated model for local control at 1-year, 2-year, and 3-year time points, including P values from the logistic model printed on the graph. Fitted model parameters with confidence interval and P values for median splits, Fisher's exact test, are in Table 4. The data suggest a dose-response, whereby the 1-year local control estimated by the model was 50% for 25.6 Gy over 5 fractions compared with 60% for 40.7 Gy over 5 fractions. However, median split showed that statistical significance was not reached ($P = .069$), and the logistic model also failed to refute the null hypothesis of no dose-response ($P = .096$). The 2-year and 3-year data demonstrate a statistically significant dose-response, $P < .01$ for the model as well as median splits (Table 4). The 3-year local control estimated by the model was 15% for 26.8 Gy over 5 fractions compared with 40% for 44.4 Gy over 5 fractions. Similarly, Figure 3 illustrates the generated model for overall survival at 1-year and 2-year time points. The overall survival probability model at 2 years also suggests a dose-response, with overall survival at the highest examined 5 fraction equivalent doses being almost double that of the lowest. However, statistical significance was not reached for median splits ($P = .13$), as well as the model ($P = .060$), perhaps owing to sparsity of data and the observation that not all of the studies exhibited the same response; therefore other factors may have a role. It should be emphasized that these data do not necessarily demonstrate a causative relationship because patients with a better prognosis might have been treated more aggressively. The slope of both the local control and overall survival curves appear steeper in subsequent years (Table 4), suggesting that dose escalation may be increasingly important for duration of control and length of survival. However, the number of patients at 2 and 3 years is much smaller than the number at the beginning of the studies, and this may affect the significance of the fitted dose responses model.

The dose-response models presented here exclude such variables as target coverage, prescription isodose line, and tumor volumes. Most treatments were planned to achieve a minimum 95% target coverage, but only 3 publications provided this information explicitly (12–14). As indicated by Rwigema et al (11), higher SBRT doses were associated with significantly higher locoregional control rates, and large tumor volume required higher SBRT doses to achieve optimal response rates compared with smaller tumor volume (Fig. 1). The poorer outcomes with larger tumors might be due to suboptimal target coverage, lower prescribed dose, or higher prescription isodose line.

7. Special Situations

The review and the resultant tumor control probability models are unique to reirradiation for malignant head and neck recurrences. They may or may not be applicable to the settings of benign tumors, SBRT used as a planned boost (ie, <6 weeks from the completion of primary therapy), and primary SBRT, that the present analyses do not address.

8. Recommended Dose/Volume Objectives

The analysis of outcomes data from more than 300 cases in 8 publications suggests that there is a dose-response relationship for both local control and overall survival, with statistical significance for local control at 2- and 3- year follow-up. Specifically, data suggest superior local control and possibly improved overall survival for doses of 35 to 45 Gy (in 5 fractions) compared with <30 Gy. Thus, it seems reasonable to suggest SBRT doses equivalent to 5- fraction doses of 40 to 50 Gy according to tumor extent/ volume for retreatment after conventionally fractionated treatments. According to the models presented in Figures 2 and 3, 45 Gy over 5 fractions would give an estimated 2-year and 3-year local control of 50% and 41%, respectively, with a corresponding estimated 2-year overall survival of 47%. The safety of this dose range is supported by a prior prospective phase 1 dose-escalation study for reirradiation with SBRT without concurrent systemic therapy, and a subsequent phase 2 study with SBRT plus concurrent systemic therapy (25, 31). However, it is important to note that the safety of this dose range has not been uniform across the published experiences from other institutions, and fatal complications, most notably carotid blowout syndrome, have been reported in up to 10% to 20% of patients even at lower doses (6, 19, 21). Thus, careful consideration, forethought, and planning is required when applying this high dose per fraction technique in head and neck cancers. A comprehensive description of toxicities and NTCP model for carotid blowout syndrome is précised in the corresponding NTCP working group article (32). Reports of de novo SBRT treatments have used the same dose fractionation as those receiving prior conventionally fractionated radiation therapy (33, 34). Although target volume was not incorporated in our model, for smaller tumors (eg, <25 cm³) doses equivalent to a maximum of 45 Gy over 5 fractions would be recommended, given the flat dose-response above this level, whereas equivalent doses between 45 and 50 Gy over 5 fractions should be considered for larger tumors, with consideration of exploration for novel strategies of escalation (11).

9. Future Studies

Longitudinal studies examining the dose-volume impact on local control and overall survival after SBRT for locally recurrent previously irradiated head and neck cancers are needed. The doses reported in the studies used in this pooled analyses stem from the treatment plans and may not reflect the true delivered dose. Setup errors, including deformation of the neck, anatomic changes especially when missed treatments extend the number of elapsed days, and internal organ motion, can cause target under-dosage and normal tissue over-dosage, thereby reducing local tumor control and increasing side effects. The improved targeting accuracy of SBRT has reduced the size of the offsets, but the steep dose gradients and high dose per fraction have increased the potential consequences, so even small movements of the patient during treatment may have effect, thus further studies relating actual delivered doses to outcomes might be helpful (eg, exploiting image deformation, tracking).

Anatomic/biologic factors may be pertinent as well. Consensus segmentation and margin guidelines are an ongoing effort for treatment of primary tumors (35–37), and reducing the interobserver variability in the reirradiation setting is an even more challenging and important future topic. Additionally, conventional dose-volume statistics (eg, minimum,

maximum, and mean doses) do not consider possible intravolume variation in both tumors and normal tissues. For example, concentration and radioresistance of viable tumor cells in certain regions of the gross tumor volume may be higher (eg, PET-avid areas) or lower (eg, necrotic center). More sophisticated radiobiologically based models (38–40) that consider these sorts of anatomic/ physiologic characteristics may prove to be more predictive of outcomes (41, 42). Future studies could also investigate potential patient-specific differences in radio-sensitivity, as well as comparing behavior, mutations, and genomic diversity of recurrent tumors with that of the original primaries. The findings of this study are dependent on the accuracy of the radiobiological models used to pool the data. The linear-quadratic model was used, with a nominal α/β of 10 Gy. We acknowledge that this model likely is a gross oversimplification but defend its use because there is no clear better alternative.

10. Reporting Standards for Outcomes

A uniform approach to reporting treatment/outcomes data after SBRT for locally recurrent previously irradiated head and neck cancer will facilitate future analysis of pooled data. Most journals (eg, the *International Journal of Radiation Oncology •Biology •Physics*) now allow online appendices where authors can include their raw outcome and dose-volume data. Parameters that should be considered for reporting include the following:

1. Time interval since initial radiation therapy
2. Prior radiation therapy prescription and coverage (eg, D95), as well as dose-volume exposure to pertinent normal tissues, noting which doses corresponded to toxicities
3. Intent of SBRT (boost or salvage)
4. Size of recurrent target lesion (total volume and dimensions)
5. Imaging modality used to define target volumes
6. Proximity to critical normal tissues
7. Planning target volume margins used around the GTV
8. Prescribed PTV doses and associated dose statistics (eg, percent of PTV that is covered by prescription, median, minimum, maximum doses, and prescription isodose level)
9. Number of fractions used. When various prescription dose and fractionation are used in a cohort, separate the reported outcomes by dose and fractionation
10. The use and timing of concurrent systemic therapy
11. Follow-up duration; report outcomes at specific time points, or provide Kaplan-Meier graphs or other means of reporting as a function of time
12. Explicitly state methods used to assess clinical outcomes (eg, RECIST)
13. Better clarify the site of local recurrence (eg, within the treated SBRT volume vs outside; or at the primary or regional nodal site)

14. Tumor cell histology

In general, because modern journals allow electronic supplements, an anonymized database could be provided with many other important quantities per patient for the prior and the reirradiation plan. The database could be a spreadsheet in which each line could be details of an individual deidentified patient, including metrics about the target dose and critical structure doses, as well as age, Karnofsky performance score, gender, lifestyle variables like smoking, alcohol, HPV status, and any other potentially useful information per patient for future analysis.

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Fig. 1. Graphic depiction illustrating an association between dose, volume, and 1-year locoregional control after stereotactic body radiation therapy for recurrent head and neck cancer. Reproduced with permission from reference (11).

Fig. 2.

Pooled data from the literature reporting local control and dose at 1, 2, and 3 years, as shown. Each data point represents 1 data set, and doses are computed (via the linear-quadratic model) as “5-fraction equivalent total doses” (see text and Tables 1–3) (patient numbers of each study are in parenthesis in the keys of each figure panel). Vertical error bars are 68% binomial confidence intervals. Solid line is the logistic model; dashed lines are 95% confidence intervals for the dose-response.

Fig. 3.

Pooled data from the literature reporting overall survival and dose at 1 and 2 years, as shown. Each data point represents 1 data set, and doses are computed (via the linear-quadratic model) as “5-fraction equivalent total doses” (see text and Tables 1–3) (patient numbers of each study are in parenthesis in the keys of each figure panel). Vertical error bars are 68% binomial confidence intervals. Solid line is the logistic model; dashed lines are 95% confidence intervals for the dose-response.

Table 1
Review of outcome data for SBRT retreatment in recurrent head and neck cancer

Study, location (reference)	Patients (n)	Median dose (Gy)	Median fractions (n)	Treatment platform	Median follow-up (mo)
Chua 2003, Queen Mary Hospital, Hong Kong, China (8)	11	12.5	1	XKnife	26
Voynov 2006, UPMC (9)	22	24	5	Cyberknife	19
Paravati 2010, UPMC (10)	14	25	1–5	Cyberknife	24.7
Rwigema 2011, UPMC (11)	96	22.4–44.4*	1–5	Cyberknife or Trilogy	14
Vargo 2012, UPMC (12)	34	40	5	Cyberknife or Trilogy	10
Lartigau 2013, Lille, Nancy & Nice, France (13)	56	36	6	Cyberknife	11.4
Kress 2014, Georgetown (14)	51	30	5	Cyberknife	17.3
Dizman 2014, Ankara, Turkey (15)	24	30	5	Cyberknife	19.5

Histology	Concurrent systemic therapy	Fractionation (QD vs QoD)	Median prior RT dose BED ₁₀ (Gy)	Median reirradiation interval (mo)	Mucosal/nodal treatment sites (%)
SCC	None	QD	81.6	12	100/0
SCC	None	QoD	97.8	NR	45/54
SCC and Non-SCC	None	QoD	NR	NR	100/0
SCC	Cetuximab (41%)	QoD	82.1	NR	76/24
Non-SCC	Cetuximab (15%)	QoD	73.4	53	100/0
SCC	Cetuximab (100%)	QoD	NR	38	NR
SCC	Cetuximab or platinum (74%)	QD	81.6	32	66/33
SCC	None	QD	84	33	75/25

Abbreviations: BED = biological equivalent dose; NR = not reported; QD = consecutive every-day fractionation; QoD = every-other-day fractionation over 1 to 2 weeks; SBRT = stereotactic body radiation therapy; SCC = squamous cell carcinoma; UPMC = UPMC Hillman Cancer Center.

* The Rwigema 2011 study had 4 dose groups ranging from 15 to 50 Gy, with median dose in each group as follows: 22.4 Gy, 33.7 Gy, 40.0 Gy, 44.4 Gy.

Table 2

Summary of local control tumor control probabilities for the included studies

Study (reference)	Patients (n)	Control reported (LC, LRC, or both)	Computed representative dose (Gy)	Computed representative fractions (n)	Fivefraction equivalent dose (Gy)	1-y LC (%)	2-y LC (%)	3-y LC (%)
Chua 2003 (8)	11	LC*	12.5	1	20.1	46	46	-
Voytov 2006 (9)	22	LRC	24	5	24.0	56	26	-
Paravati 2010 (10)	14	LRC	25	2.7	30.1	47	31	16
Rwigema 2011 (11)	29	LRC	22.4	4.375	23.2	48	28	14
Rwigema 2011 (11)	22	LRC	33.7	4.375	35.1	55	37	18
Rwigema 2011 (11)	18	LRC	40	4.375	41.7	67	56	39
Rwigema 2011 (11)	27	LRC	44.4	4.375	46.4	70	60	44
Vargo 2012 (12)	34	LRC	40	5	40.0	59	44	33
Lartigau 2013 (13)	56	LC*	36	6	34.2	43	27	-
Kress 2014 (14)	51	LRC	30	5	30.0	58	28	-
Dizman 2014 (15)	24	LRC	30	5	30.0	64	38	21

Abbreviations: LC = local control; LRC = locoregional control.

* In these studies local control is reported, but the definition of local control is not stated.

Table 3

Summary of overall survival tumor control probabilities for the included studies

Study (reference)	Patients (n)	Calculated equivalent dose (Gy)	Fraction equivalent dose	Fractions (n)	Five- fraction equivalent dose (Gy)	1-y OS probability (%)	2-y OS probability (%)	3-y OS probability (%)
Voytov 2006 (9)	22	24	24	5	24.0	47	22	22
Porceddu 2007 (24)	35	30	30	5	30.0	32	14	-
Vargo 2012 (12)	34	40	40	5	40.0	59	42	16
Lartigau 2013 (13)	56	36	36	6	34.2	47	31	-
Kress 2014 (14)	51	30	30	5	30.0	51	24	-
Dizman 2014 (15)	24	30	30	5	30.0	83	43	31

Abbreviation: OS = overall survival.

Table 4

Summary of dose-response parameters, logistic model, for local control and overall survival calculated for the included studies

Data	D ₅₀ Gy (95% CI)	γ_{50} (95% CI)	P (median splits)
Local control, 1 y	25.5 (3.0, ∞)	0.17 (−0.09, 0.45)	.0685
Local control, 2 y	45.1 (39.1, 71.5)	0.56 (0.27, 0.85)	.0015
Local control, 3 y	49.8 (43.7, 72.8)	0.94 (0.49, 1.43)	.0028
Overall survival, 1 y	30.4 (at limit)	0.17 (−0.32, 0.66)	1
Overall survival, 2 y	46.9 (38.8, ∞)	0.74 (0.25, 1.30)	.1291

Abbreviation: CI = confidence interval; D50 = dose for 50% control or survival; γ_{50} = normalized slope parameter.