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Clinical Investigation

Stereotactic Radiation Therapy for De Novo Head and Neck Cancers: A Systematic Review and Meta-Analysis

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Abstract

Purpose: Stereotactic body radiation therapy (SBRT) for de novo (previously untreated) head and neck cancers (HNCs) is increasingly being used in medically unfit patients. A systematic review of SBRT was conducted for previously untreated HNCs.

Methods and Materials: Medline (PubMed), excerpta medica database, and Cochrane Library databases were queried from inception until July 2020. Comparative outcome data were extracted where available up to 5 years. Results from random-effect models were presented in forest plots, with between-study heterogeneity evaluated by I^2 statistics and Q-tests.

Results: Nine studies met inclusion criteria, representing 157 patients. Local control rates at 1, 2, and 3 years were as follows: 90.7% (95% confidence interval, 80.6%-95.6%), 81.8% (67.2%-90.7%), and 73.5% (40.4%-90.5%), respectively. Overall survival at 1, 2, and 3 years was 75.9% (75.1%-76.6%), 61.1% (60.3%-61.9%), and 50.0% (48.8%-51.4%), respectively. Late grade 3 to 4 toxicity rate was 3.3% (0.2%-10.2%), and late grade 5 toxicity rate was 0.1% (0.0%-1.0%).

Conclusions: SBRT for de novo HNC is safe and effective in providing locoregional control, with acceptable toxicities in most subsites. This finding warrants broader validation to guide its scope.

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Introduction

With modern advances in radiation therapy, stereotactic body radiation therapy (SBRT) is increasingly being used in treating a variety of cancers.[1-4] Taking advantage of increased precision with modern immobilization devices, and together with multiplatform imaging, inverse planning, and cone beam image guidance, SBRT delivers high dose per fraction (typically >5-8 Gy

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per fraction) with steep dose gradients in shorter treatment durations, thereby improving the killing effect on the gross tumor while minimizing radiation-related side effects in surrounding organs at risk (OARs). In some series, SBRT has been shown to have a good efficacy and side effect profile and continues to be an area of interest especially in the novel coronavirus era,[5,6] where minimizing physical contact and in-person presence in care have been identified as a crucial part of controlling the spread of the disease, thereby protecting patients and health care professionals.[7]

Head and neck cancer (HNC) treatment typically includes a protracted course of conventional radiation therapy with or without chemotherapy as a single modality or in the adjuvant setting after a surgical resection. This poses a challenge for frail, elderly patients or patients with multiple comorbidities, often making them poor candidates for standard radiation or systemic options, which may lead to a significant effect on their quality of life and early cancellation of the prescribed radiation course due to prolonged duration of treatment and significant side effects.[8] Given the rising incidence of elderly and otherwise frail patients with HNC, SBRT offers a promising alternative in "de novo" (previously untreated) cancers, with high locoregional control rates and treatment completion rates.[9]

SBRT in the treatment of HNC has been investigated in a variety of settings previously. Retrospective reports indicate it has been used in both curative and palliative intent settings in the treatment of de novo HNCs,[10] as a boost after conventional external beam radiation therapy,[11] retreatment after locoregional recurrence,[12,13] as well as for oligometastatic tumors in the head and neck (HN) region.[14,15] With regards to reirradiation, SBRT has shown to be particularly useful in patients with recurrent or unresectable HN malignancies, leading to more durable control while sparing normal adjacent tissues. Recent published series demonstrate that the local control (LC) outcomes for retreatment with SBRT range from 30% to 80% at 1 to 2 years, with overall survival (OS) rates of 20% to 60%.[12-14,16-18]

Although there have been a few published series of HN SBRT in the de novo setting reporting favorable results, to date there has not been a meta-analysis of outcomes with de novo HN SBRT. The objectives of the present study were to assess the efficacy and safety of HN SBRT in the de novo setting by performing a systematical review of the literature and meta-analysis of patients with HNC presenting with previously untreated disease and treated with either SBRT or stereotactic radiosurgery.

Methods and Materials

This study was conducted as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis of Observational studies in Epidemiology guidelines. The PROSPERO registration number for this study is CRD42020156814. MEDLINE (PubMed), excerpta medica database, and Cochrane Library databases were queried for English literature from inception until July 2020.

Table 1 PICOS

Population	Patients with previously untreated head and neck cancers, including skin cancers and lymphadenopathy treated in the head and neck region and base of skull tumors.
Intervention	Stereotactic radiation therapy, defined as precise and accurate delivery of external beam radiation therapy at high doses per fraction with anatomic targeting accuracy and reproducibility.
Control	No control group, or a study with multiple arms where stereotactic radiation therapy was used
Outcomes	Primary outcome: local control at 1 and 2 y Secondary outcomes: overall survival at 1 and 2 y, progression free survival, late grade $\geq$3 toxicities
Study design	Included prospective or retrospective clinical studies, with greater than 5 patients in the study

Abbreviation: PICOS = Population, Intervention, Control, Outcome, Study design.

Criteria for inclusion defined as per Population, Intervention, Control, Outcome, and Study Design (PICOS) approach are listed in Table 1. For the purpose of this systematic review, SBRT was defined as radiation treatments with hypofractionated schedules using 5 or fewer fractions and 6 Gy or greater per fraction. Based on our prior knowledge, we expected some studies to fall outside this definition given the lack of established dose fractionation regimens for various HN subsites with SBRT. As such, we planned to include studies with greater than 5 fractions and less than 6 Gy per fraction if the intent of treatment was to "hypofractionate" and deliver treatment in "SBRT-like" fashion to explore toxicities and outcomes. In addition, this was intended to broaden the number of included studies for analysis given the paucity of data published regarding HN SBRT to date. Records underwent title, abstract, and full text review independently by 2 authors (NM, MK), and discrepancies were resolved by a third author (IK). The details of the search strategy are included in Appendix EA.

Non-English literature, guidelines, review papers, editorials, abstracts, case reports, and non–peer-reviewed correspondence were excluded. Studies on benign HN tumors and distant metastatic disease outside the HN region were also excluded, as were those that did not report data on oncologic outcomes or toxicities. If studies reported SBRT in HNC in different patient populations,

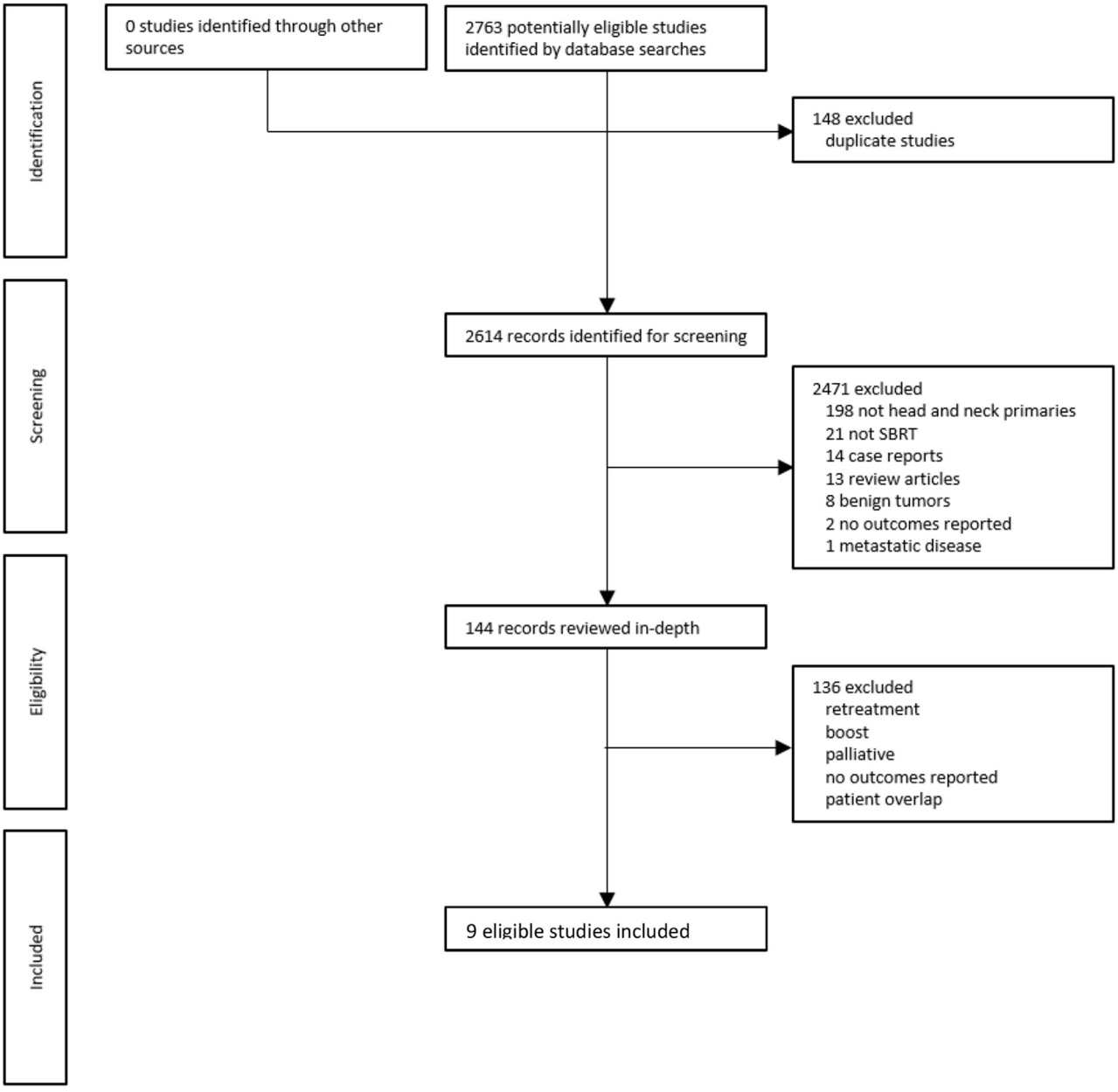

Figure 1 Flow diagram as per Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) convention.

such as SBRT as primary treatment, boost, or retreatment in previously irradiated patients, they were only included if outcome data were reported separately for each patient population, allowing for meta-analysis. Studies with fewer than 5 patients were excluded from the meta-analysis. If multiple publications were found from the same institution, with potentially overlapping patients, we included the most recently published study and/or with the largest sample size.

The initial search strategy yielded 2763 results. Studies underwent initial screening based on inclusion criteria, exclusion of nonhuman and basic science studies, as well as removal of duplicates. After initial screening, 144 studies were further assessed for eligibility, 136 studies were eventually excluded, and 9 studies included (Fig 1). References of eligible studies were reviewed for possible inclusion, and expert review of the final list of included studies was done to ensure completeness of search. The Newcastle Ottawa Scale for cohort studies[19] was used to assess risk of bias among included studies, which were all nonrandomized. Studies were evaluated on 3 criteria of selection, comparability, and outcome to a maximum possible score of 9. Studies were considered high quality if they scored 7 or higher on the scale.

Extracted data included study factors such as design; sample size; median follow-up duration; treatment

Table 2 Studies evaluating de novo stereotactic radiation therapy for head and neck primary cancers

Study	Subsite	Study design	Sample size (n)	Median follow-up (mo)	Dose in Gy, median (range)	Fractions, median (range)	Median BED_{10}* ($\alpha/\beta = 10$)	Median BED_3† ($\alpha/\beta = 3$)	EQD2‡(Gy, $\alpha/\beta = 10$)
Kang[29]	Larynx	Prospective	13	26.6	59.5 (55-59.5)	17 (11-17)	80.3	128.9	66.9
Sher[25]	Larynx	Prospective	29	43.6	45 (42.5 − 50)	10 (5-15)	65.3	112.5	54.4
Karam[26]	Parotid	Retrospective	13	14	33 (25-40)	6 (5-7)	51.2	93.5	42.6
Kodani[27]	Mixed	Retrospective	13	16	30 (19.5-42)	5 (3-8)	48.0	90.0	40.0
Amini et al[10]	Mixed	Retrospective	2	6	25-30	5	42.6	77.9	35.5
Vargo[28]	Mixed	Retrospective	12	6	44 (20-44)	5 (1-6)	82.7	173.1	68.9
Khan et al[9]	Mixed	Retrospective	17	8	40 (35-48)	5 (5-6)	72.0	146.7	60.0
Siddiqui et al[15]	Mixed	Retrospective	10	32.7	36 (18-48)	6 (1-8)	57.6	108.0	48.0
Al-Assaf[30]	Mixed	Retrospective	48	10.5	41.6 (35.6 − 53.8)	5 (4-6)	76.2	157.0	63.5

Abbreviation: BED = biologically effective dose.
* BED_{10} is biologically effective dose for tumor ($\alpha/\beta = 10$).
† BED_3 is biologically effective dose for tumor ($\alpha/\beta = 3$).
‡ EQD2 is the total equivalent dose in 2 Gy fractions.

parameters such as SBRT technique, radiation therapy prescription data, and OAR constraints; late grade 3 to 5 toxicities; OS; LC; and progression free survival (PFS) up to 5 years.

Primary comparative outcome data were extracted with 95% confidence intervals (CIs) where available up to 5 years. Secondary endpoints were also extracted wherever available up to 5 years. For studies that did not explicitly report outcomes, but included Kaplan-Meier curves, outcomes were estimated from figures using methods and tools described by Tierney et al.[20] Toxicity grading was as per Common Terminology Criteria for Adverse Events reported by authors. Late grade 3 to 4 toxicities were analyzed separately from grade 5 toxicities.

A variety of fractionation methods were employed, which were converted to a standardized biologically effective dose ($BED_{\alpha/\beta}$), defined as $BED_{\alpha/\beta} = nd\ (1 + d/[\alpha/\beta])$, where n is the total number of fractions, d is the dose per fraction, and α/β is the alpha/beta ratio of the tumor. The value of 10 was used for α/β in $BED_{\alpha/\beta}$ calculations for tumors, and 3 for normal tissues. Study characteristics and outcomes were summarized with medians and ranges.

Log-negative-log-transformed inverse variance-weighted linear mixed-effects models were used to summarize Weibull-distributed OS and LC curves over time (*lme4* v1.1-21).[21] This method was previously described in Arends et al.[22] CIs of the final estimates from the mixed-effects models were calculated with a bootstrap method using 1000 resamplings. Individual studies were modelled as random effects on both intercepts and slopes for OS and on only intercepts for LC due to limited sample size.

Second, inverse variance-weighted DerSimonian-Laird random-effects meta-analyses of arcsine-transformed proportions were used to summarize PFS at 1 year and crude late toxicity rates (>6 months from treatment) (*metafor* v2.1-0).[23] Results from random-effect models were presented in forest plots, and between-study heterogeneity was evaluated by I^2 statistics and Q-tests. Leave-1-out sensitivity analysis was used to discover unduly influential studies that might have contributed to increased between-study heterogeneity. Funnel plots and Egger tests were used to evaluate publication bias visually and quantitatively. A P value threshold of .05 was used for statistical significance. Restricted maximum likelihood estimation was used for all mixed and random-effects models. The R statistical environment was used for all statistical analysis (*x64* v3.6.2).[24]

Results

Study characteristics

A total of 9 studies (2 prospective, 7 retrospective) were identified for inclusion, representing 157 mutually exclusive patients.[9,10,15,25-30] Individual study characteristics are summarized in Table 2. The 2 prospective larynx studies were included despite some patients receiving more than 10 fractions. Sher et al[25] used 3 different fractionation schedules, with 50 Gy in 15 fractions, 45 Gy in 10 fractions, and 42.5 Gy in 5 fractions. Kang et al[29] had 2 fractionation schedules, with 59.5 Gy and 47.5 Gy in 17 fractions to gross tumor volume (GTV) and

remaining larynx, or 55 Gy and 40.7 Gy in 11 fractions to the GTV and remaining larynx.

The Newcastle Ottawa Scale for the assessment of quality of each study is summarized in Appendix EB. This showed most of the studies were at high risk of bias, with 3 studies scoring 7 and the rest 5 or 6 out of the highest possible score of 9.

Patient characteristics

The countries represented in the studies were Korea (n = 1), Japan (n = 1), Canada (n = 2), and the United States (n = 5). The largest included study was by Al-Assaf et al[30] and included 48 patients. The studies ranged from 2009 to 2020, and the median follow-up ranged from 6 to 43.6 months. The pooled median patient age across studies was approximately 76 years. The 2 prospective studies were of larynx cancers,[25,29] with remaining retrospective studies parotid (n = 1)[26] and mixed (n = 6) subsites.

Four of the studies included mixed populations of primary and retreatment patients[9,15,27,30] but reported their data separately, and as such it was possible to include them in the meta-analysis. For these studies, sample size was that of the patients treated with primary intent.

Treatment planning and radiation data

Four studies reported using CyberKnife for treatment delivery,[25-28] 1 used Elekta Synergy linear accelerator,[30] and the rest did not report. Three studies reported using computed tomography (CT) simulation alone with thermoplastic mask. One study used 4D-CT, 1 CT with magnetic resonance imaging (MRI) simulation, and another reported using CT, MRI, and positron emission tomography/CT simulation. Treatment frequency was every other day in 5 studies, with 2 studies doing daily treatments, twice weekly in 1, and 1 not reporting.

Contouring protocols were heterogeneous. Three studies used 0 mm clinical target volume margins, 2 studies indicated 2 to 10 mm clinical target volume margins, 2 studies reported overdrawing from the GTV, whereas the remaining 2 did not report. For planning target volume (PTV) margins, 3 studies indicated using 0-mm margins, 2 studies used 3-mm margins, 3 studies used a range of margins from 2 to 5 mm, and 1 study did not report.

Doses ranged from 25 to 59.5 Gy in 3 to 17 fractions, with median BED_{10} values ranging from 42.63 to 82.72 Gy_{10} and equivalent dose in 2Gy fractions ($\alpha/\beta = 10$) ranging from 35.53 to 68.93, as summarized in Table 2. Only 2 studies provided prescription volume details, with 1 prescribing to 90% of the PTV and 1 to 86% isodose line (range, 57%-90%). Only 1 study reported OAR constraints, with goals of keeping thyroid mean dose <50%, max carotid dose <10%, spinal cord <10%, and skin <10% of prescribed doses, while another reported constraints were used as reported in the survey of current practices for HNC SBRT.[31] None of the studies mentioned brachial plexus dose constraints.

Only 3 studies reported on follow-up imaging, with 1 study using MRI and positron emission tomography/CT for follow-up, whereas 2 used CT and MRI 6 to 12 weeks posttreatment. With regards to systemic treatments, a minority of patients were reported to have received systemic treatments with SBRT, with 1 study reporting no systemic therapy,[30] 1 reporting carboplatin before, during, and after SBRT for a parotid gland tumor,[26] and 3 studies reporting weekly cetuximab.[9,10,28]

Outcomes

With regards to primary endpoints, LC rates (with 95% CI) at 1 year were 90.7% (80.6%-95.6%), 2 year 81.8% (67.2%-90.7%), and 3 year 73.5% (40.4%-90.5%) (Fig 2B). OS across all studies were as follows: 1 year 75.9% (75.1%-76.6%), 2 year 61.1% (60.3%-61.9%), 3 year 50.0% (48.8%-51.4%), and 41.5% (39.7%-43.3%) at 4 years (Fig 2A). The 1-year PFS rate was 76.3% (59.2%-89.9%), with no data available for longer follow-up (Fig 3). There was good agreement among the studies regarding 1-year PFS ($I2 = 45.6\%$, $P = .149$). There was no significant publication bias for PFS (Fig E1).

Toxicity

Among all studies, reported late grade 3 to 4 toxicity rate was 3.3% (0.2%-10.2%). There was moderate to high heterogeneity among studies regarding reported grade 3 to 4 toxicity rates ($I2 = 61.2\%$, Q-test $P = .02$), with leave-1-out sensitivity analyses showed Kang et al[29] had the most influence on heterogeneity, but there remained moderate heterogeneity even with its exclusion (2.1% [0.0-7.2%], $I^2 = 50.2\%$, Q-test $P = .07$). The 2 prospective larynx studies[25,29] both reported grade 3 laryngeal inflammation and edema as side effects, with 1 patient having grade 3 arytenoid necrosis. One study closed early due to higher than expected toxicity.[29] Two retrospective studies reported grade 3 toxicities including dysphagia, mucositis, facial pain, and cataracts.[15,30] Grade 5 toxicity rate was 0.1% (0.0%-1.6%), with 1 patient dying after treatment from complications related to aspiration pneumonia[26] (Fig 4). There was minimal heterogeneity for the grade 5 toxicity results ($I^2 = 0\%$, Q-test $P = .81$). There was no significant publication bias for toxicity results (Fig E2).

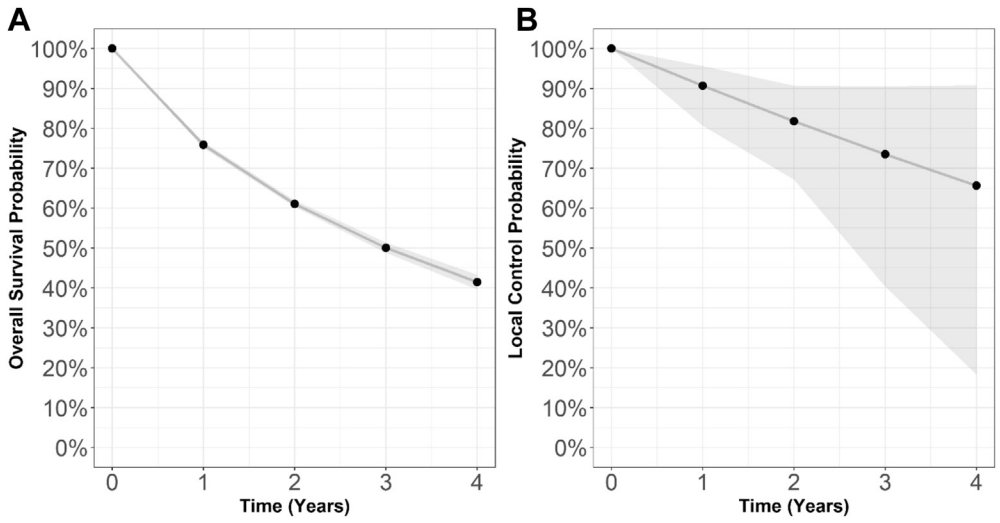

Figure 2 Summary of (A) overall survival and (B) local control probability over time. Estimates from mixed-effects models at each time point (black) are shown with their 95% confidence intervals (grey).

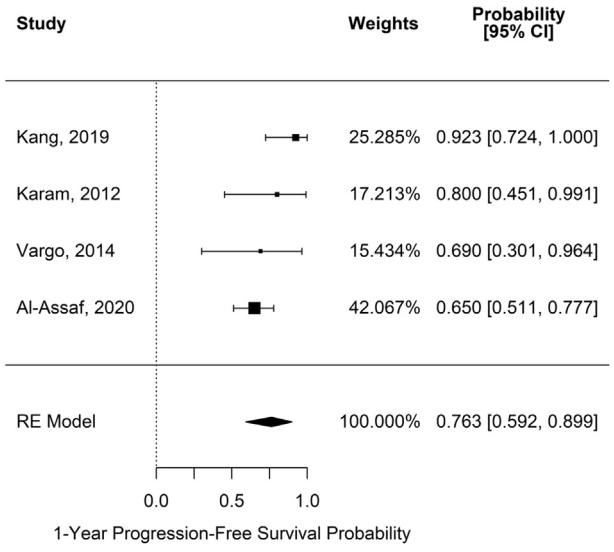

Figure 3 Forest plot of the meta-analysis of 1-year progression-free survival probability. Weights were calculated with the inverse-variance method.

Discussion

This is the first contemporary meta-analysis to report on the use of SBRT for de novo HNC. SBRT appears to be effective and safe in the management of previously untreated HNCs, with LC rates of approximately 91% and 82% at 1 and 2 years, and any grade 3 or higher toxicity at approximately 3%, with the most common toxicities being dysphagia, mucositis, laryngeal edema, and inflammation.

The current analysis included 7 retrospective studies and 2 prospective larynx trials, and as such, further prospective randomized studies are needed. None of the studies had a comparator arm, and only 1 study explicitly mentioned that patients undergoing SBRT were discussed in a multidisciplinary setting and deemed unable to tolerate conventional combined modality treatment. Given the heterogeneity of data and the paucity of long-term follow-up data, our LC estimate had a large CI at longer follow-ups. For PFS, only 4 studies reported 1-year estimates, limiting conclusions regarding that data. Although the short-term data are certainly encouraging, the overall sample size of the review herein included 157 cases, treated with variable techniques and dose fractionation schedules. Therefore, the relative role of de novo HNC SBRT needs to be better defined through well-conducted prospective and comparative studies to inform broader adoption of this technique, as in other disease sites where it is more common.

There were 2 prospective studies investigating SBRT in larynx cancer. Sher et al[25] reported 5 local failures and 2 dose-limiting toxicities in their trial of 29 patients with a modified "3 + 3" design investigating dose-escalation in Tis to T2 glottic larynx cancer. One patient receiving 45 Gy in 10 fractions (3 fractions per week) with PTV of 17 cm^3 developed grade 4 laryngeal edema, and the authors note that, in retrospect, this patient had actually presented with T4 disease with cricoid involvement. The second patient received 42.5 Gy in 5 fractions, PTV 21.3 cm^3, and developed grade 3 arytenoid necrosis. Kang et al[29] reported in their phase I dose escalation study grade 3 toxicities in 2 of 6 patients in the 55 Gy in 11 arm (every other day or twice a week), arytenoid necrosis, and vocal cord ulceration. Further dose escalation was planned in this study up to 45 Gy in 5 fractions, but the trial was terminated early due to toxicity. These results highlight sensitivity of the larynx to hypofractionation, as well as consideration of the unique anatomic challenges with larynx SBRT, which are determining tumor extent, added

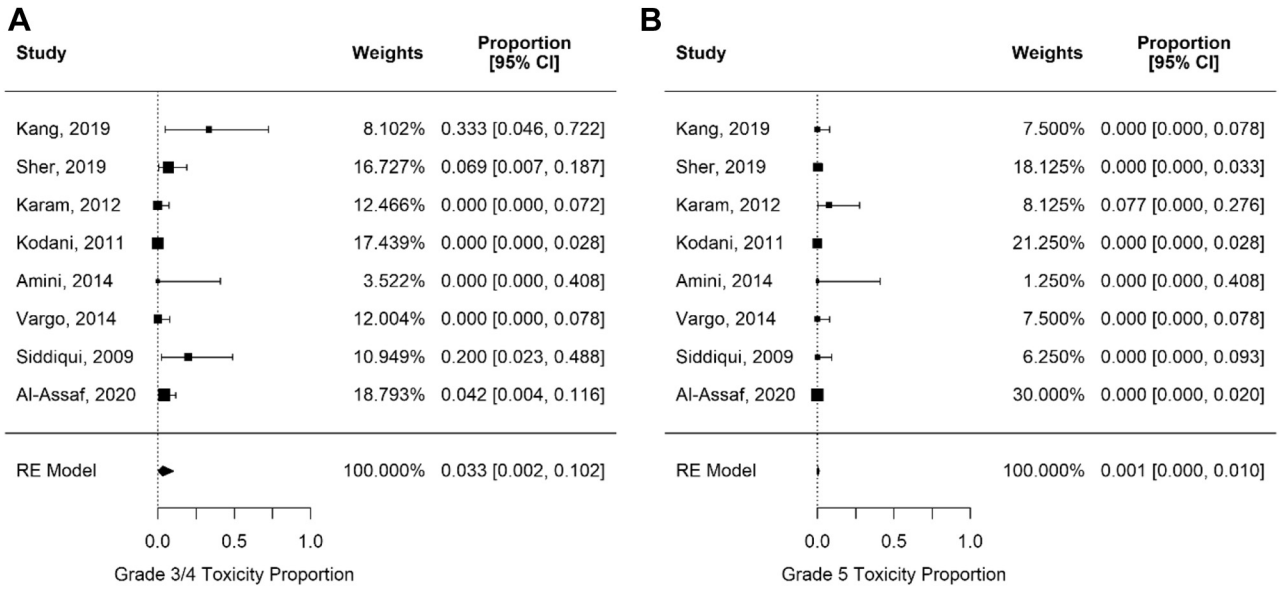

Figure 4 Forest plot of the meta-analyses of grade (A) 3 to 4 toxicity and (B) grade 5 toxicity proportions. Weights were calculated with the inverse-variance method.

margins, radiation dose, and timing of SBRT fractions. Given the challenges in this subsite, consideration of SBRT for glottis tumors in the curative setting is not routinely recommended and should be carried under a clinical trial setting.

To date, SBRT for HNC has been explored most in the retreatment setting, given its relative OAR sparing. However, SBRT may have benefits beyond this application in a population of radioresistant tumors. It has been postulated that SBRT acts via distinct radiobiological mechanisms, contributing to an enhanced biological result not seen with standard fractionation.[9,32] A enlarging body of evidence suggests that the distinct mechanisms involve vascular collapse, upregulation of immunomodulatory surface molecules, and other effects on the tumor microenvironment.[33] Irradiation of tumors with single-doses of more than 8 Gy lead to activation of endothelial cell acid sphingomyelinase–mediated generation of proapoptotic second messenger ceramide, leading to apoptosis initiation in endothelial cells, which generates microvascular dysfunction or ablation and ultimately death of the tumor cell.[34,35] This hypothesis was demonstrated in early clinical trials by Sathishkumar et al,[36] revealing that elevated ceramide levels in sera correlated with tumor response to hypofractionation. As such, further work for the identification and validation of novel genomic predictive and prognostic biomarkers is of interest in HNC SBRT clinical trials.

As of May 2020, National Comprehensive Cancer Network (NCCN) guidelines report there is insufficient evidence to recommend SBRT for de novo HNC but do acknowledge that it may be beneficial in palliative cases or for elderly patients.[9,37] The referenced study in NCCN was in this meta-analysis, including 17 patients with a median age of 87 with a 1-year LC rate of 87%. The current meta-analysis provides further evidence to support NCCN guideline recommendations. Across all included studies, a pooled median age of 76 years certainly points to SBRT being used in such a fashion, although it is uncertain how many were unsuitable for radical intent chemoradiotherapy and were discussed in a multidisciplinary setting beforehand. However, the lower 2-year OS estimate of about 61% is in keeping with optimization of locoregional control over survival. This level of weak recommendation is also in keeping with an international survey of current practices, which revealed SBRT for de novo HNC is used 0% to 10% of the time, with doses ranging from 15 to 22 Gy in 1 fraction to 30 to 50 Gy in 5 or 6 fractions, with some centers using SBRT postoperatively as well.[31] To our knowledge, there are no active randomized clinical trials on SBRT as a primary modality of treatment for de novo HNCs. One trial attempted to study SBRT in the setting of newly diagnosed, high-risk, locally advanced HNC but terminated due to slow accrual.[38]

Indeed, there has been a growing interest in SBRT use for its ability to provide shorter treatment durations, with a renewed push for hypofractionated regimens to reduce patient exposure risks due to the novel coronavirus disease pandemic (severe acute respiratory syndrome coronavirus-2; coronavirus disease 2019) given the higher observed mortality in patients with cancer.[39,40] Additionally, this push is expected to continue given the predicted postpandemic surge of patients with cancer. As such, careful use of hypofractionated and SBRT regimens is increasingly being investigated, and many centers have

called for and adopted shorter protocols, including for HN malignancies in a palliative setting,[31] where durable control remains a priority.

Although the current study remains the first meta-analysis on the use of SBRT in HNC, a recent publication reported a systematic review of HNC SBRT in both de novo and retreatment settings, with 4 publications and 1 abstract in the de novo setting.[18] The authors concluded there is a lack of evidence regarding SBRT as a de novo treatment option in HNC, and safety and efficacy questions remain. This meta-analysis builds on this important topic, and we conclude SBRT is safe and efficacious in this setting, with some important caveats.

Our study has some limitations. First, individual patient-level data were not available. Patients with HNC are a heterogeneous group due to the number of subsites, and therefore data on patient demographics, subsite, staging, and comorbidities are key in determining the role of SBRT in this setting. Most of the included studies were retrospective and reported data not stratified by subsites. A variety of dose fractionations were employed with both curative and palliative intent, and dose prescription data were inconsistently reported across studies. Contouring and planning strategies were heterogeneous and data on OAR constraints used and dose delivered to OARs were also largely missing. Most patients did not receive systemic therapy, and for those that did, data were limited on the type of medication, dosing, and timing relative to radiation therapy. In some studies, only CT simulation was reported to have been used, limiting the accuracy of target delineation required in HN SBRT where MRI simulation would be highly recommended. There may also be publication bias, with more favorable results more likely to be published.

Patients with minimal comorbidities are more likely to be offered standard types of treatments, including surgery and postoperative radiation therapy, or definitive radiation plus or minus systemic therapy, whereas frail patients or those with multiple medical comorbidities are more likely to receive treatments that allow for shorter treatment durations. Poor performance status may preclude these patients from attending follow-up appointments, or from having meaningful follow-up periods after their treatment, which may help explain the fact that a number of the retrospective studies included in this analysis suffered from short follow-up after their treatments. This would also account for the lack of data on systemic treatments for patients on SBRT, as they would also be precluded from systemic therapies that depend on age or comorbidities. Another point to consider is use of systemic treatments in this patient population, given perhaps less need for radiosensitization with SBRT.

In summary, the current meta-analysis shows that HN SBRT has been used in restricted settings and selected subsites, where patients were ineligible for other therapies due to their frailty or comorbidities or in palliative cases. Retrospectives studies show that the treatment is effective in providing good LC, with few serious side effects, but these are limited by a short follow-up period. There is a paucity of high-level data to guide the use of HN SBRT, and this meta-analysis consists mostly of retrospective data. Therefore, HN SBRT would be best done in the context of prospective randomized studies, with strict protocols and registries in place to systematically evaluate for toxicities, response assessment, quality of life, and survival. Studies should also consistently report on radiation therapy delivery details such as simulation and image guidance, margins, dose constraints, dose fractionation, techniques, and patient selection. The practice of HN SBRT is promising, but it should be performed with rigorous quality assurance, in a center experienced in SBRT. As such, international collaboration and prospective data registries to systemically evaluate toxicities among centers of expertise in HN SBRT to establish treatment guidelines should be a priority.

Conclusions

SBRT in de novo HN malignancies has been shown to be safe and effective in providing locoregional control, with acceptable toxicities in the short term. However, there is a gap in the evidence and practical application, which needs to address multiple aspects including consistent protocols, margins, dose fractionation and constraints, techniques, and patient selection. Particular caution is warranted with use in larynx cancer, and this should be explored in a clinical trial setting. For HN SBRT to be implemented as a viable treatment option, an international consortium with rigorous treatment guidelines will need to be generated.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.11.013.

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