Oral Oncology 93 (2019) 8–14

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Altered-fractionation radiotherapy improves local control in early-stage glottic carcinoma: A systematic review and meta-analysis of 1762 patients

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ARTICLE INFO

Keywords:
Radiotherapy
Glottic cancer
Laryngeal cancer
Altered fractionation
Local control
Systematic review
Meta-analysis

ABSTRACT

Objectives: To perform a systematic review of 1762 patients to comprehensively assess the benefit of altered-fractionation radiotherapy (ART) in early stage glottic carcinoma (ESGC).

Materials and methods: Studies were identified in PubMed and EMBASE. Inclusion criteria were: (1) diagnosis of squamous cell ESGC (Tis, T1, T2); (2) ART versus conventionally-fractionationated radiotherapy (CRT); and (3) provision of number of local recurrence events and total numbers per fractionation arm. The random-effects model was fitted to estimate the pooled hazard ratio (HR). Subgroup sensitivity analyses were performed based on ART strategy (hypo- versus hyperfractionation), treatment-day reductions, machine type, tumor stage, and anterior commissure involvement.

Results: Eleven studies met inclusion criteria: 4 randomized controlled trials (RCTs) and 7 two-arm retrospective studies. ART was associated with 38% fewer (HR 0.62; 95% CI: 0.46–0.82, p = 0.0009) and 60% fewer (HR 0.40; 95% CI: 0.24–0.66, p = 0.0003) local failure events in pooled analyses of the RCTs and retrospective studies, respectively. Both hyperfractionation (HR 0.65; 95% CI: 0.43–0.97, p = 0.03) and hypofractionation (HR 0.55; 95% CI: 0.33–0.91, p = 0.02) strategies were superior to CRT. The benefit persisted for all treatment- and tumor-related parameters, including anterior commissure involvement, with the exception of a pooled analysis of studies with predominantly T2 (< 50% T1) cases (HR 0.60, 95% CI: 0.30–1.20, p = 0.15).

Conclusion: Both hypofractionation and hyperfractionation improve local control in ESGC, including T1 tumors and for anterior commissure involvement. However, this benefit may not persist for T2 tumors, for which alternative strategies should be considered.

Introduction

The success of organ preservation with radiotherapy for early stage glottic carcinoma (ESGC) depends on local control of the disease. For patients who ultimately fail locally, surgical salvage may entail a highly morbid total laryngectomy in more than half of cases [1–2].

Regarding radiation therapy, dose-related factors have been associated with better disease control for glottic cancer, possibly by decreasing the repopulation of cancer cells with “more intense” treatment [3]. Initially, a series of reports indicated that the dose increase from 1.8 Gy to 2.0 Gy daily fractions also increased the local control of ESGC substantially [4–10]. After this, further intensification with altered fractionation strategies (ART) that reduce the total treatment time were adopted: either increasing the number of fractions per day

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https://doi.org/10.1016/j.oraloncology.2019.04.007
Received 18 December 2018; Received in revised form 26 February 2019; Accepted 5 April 2019
Available online 08 April 2019
1368-8375/

(hyperfractionation) or increasing the dose per fraction (hypofractionation).

ART is associated with an overall reduction of 21% in local failure when compared with conventional fractionations (CRT), based on the updated results of the meta-analysis of the MARCH collaborative group [11]. However, the MARCH analysis combined several head-and-neck sites and was thus nonspecific for glottic cancer. Furthermore, the predominance of advanced disease (75% stage III/IV) and the use of chemotherapy in the MARCH analysis could also be considered important limitations of applying the results to the ESGC cases treated only with RT.

Although the use of CRT for ESGC has been decreasing over the years, pattern-of-care studies have demonstrated that almost 50% of American patients may still be treated with CRT [12–14], possibly due to provider perceptions of a relative lack of evidence specific for ESGC treated with RT alone.

This systematic review and meta-analysis thus aims to determine the effect of ART on the local control of ESGC treated with radiotherapy alone. Additionally, a series of subgroup sensitivity analyses were conducted to investigate the effect of ART among varying treatment or tumor characteristics.

Methods and materials

Identification of relevant studies

The design of the present study was based on the guidelines that are provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report (PRISMA) [15]. Relevant studies were identified in MEDLINE (PubMed) and EMBASE in English, Spanish, or Portuguese. Further, the ClinicalTrials database, Google website, and reference lists of all included articles were evaluated. Briefly, two authors performed the following steps: search engine, title/abstract evaluation, and full-text evaluation. Discrepancies in the full-text step were solved by a third researcher. The search strategy and terms used are available in Supplementary Material S1.

If the same study was published more than once, the most complete and actualized information was prioritized, but additional information from previous publications or Supplementary Materials were also used if necessary. We did not obtain data on individual patients for this analysis. The data extraction occurred after registration in the PROSPERO database (CRD42018110622).

Prospective trials or retrospective cohorts were considered if they presented all the following inclusion criteria: (1) diagnosis of squamous cell ESGC (Tis, T1, T2); (2) ART compared to CRT (most commonly defined as 1.8–2.0 Gy daily fractions); and (3) number of events of local recurrence and total number of patients per fractionation arm provided. The exclusion criteria were: (1) alternative regimens that increased the overall treatment time (e.g., split course); (2) any chemotherapy used; (3) study populations mixed with moderate or advanced disease (T3, T4, N+, or M1); (4) series including re-irradiation; (5) neck nodal irradiation; (6) fewer than 10 cases per study arm; and (7) absence of any of the inclusion criteria.

Quality assessment

All articles were published as full, peer-reviewed reports, and no additional studies were identified after searching for unpublished material via Internet search engines. The randomized controlled trials (RTCs) that were selected for the meta-analysis were evaluated using a 3-level scale (low, unclear, high) with regard to the risk of bias in grading 7 domains of each outcome per the Cochrane Handbook for Systematic Review of Interventions [16]. For the non-randomized studies comparing ART with CRT, the seven domains of the *Risk of Bias in Non-randomized Studies of Interventions* (ROBINS-I) tool [17] were used. The quality assessment was performed by 2 of the authors.

Statistical analysis

Hazard ratios (risk ratios) and 95% confidence intervals (CIs) were calculated by the Mantel-Haenszel method. The random-effects model was fitted to estimate the pooled hazard ratio (HR) data. Heterogeneity was examined using Q-statistic (Cochran's Q: the chi-square statistic for the test of heterogeneity and measure of inconsistency). Publication bias was verified by funnel plot. Sensitivity analysis was performed to test the influence of individual studies on the summary estimate by plotting the summary estimate in the absence of each study. Statistical analyses were conducted using RevMan 5.0 and R (version 3.2.1) software. All statistical tests were two-sided, and we adopted a significance level of 5%.

Sensitivity analyses

Two types of sensitivity analyses were performed: (I) by excluding one study at a time; and (II) subgroup sensitivity analyses, based on treatment or patient characteristics. The HRs provided by the subgroup sensitivity analyses were also tested, excluding one study at a time. Pooled local control estimates of each subgroup were performed for the following categorized treatment and tumor parameters: ART strategy (hypofractionation versus hyperfractionation), minimum number of treatment-day reductions (MNTDR) (≤ 5 days versus > 5 days), machine type used (only LINAC vs. Cobalt-60 and LINAC vs. only Cobalt-60), tumor stage ($\leq 50\%$ T1 versus $> 50\%$ T1), and anterior commissure involvement ($\leq 40\%$ of the patients with anterior commissure [A-com] involvement versus $\geq 40\%$ A-com involvement). The MNTDR was calculated using the number of treatment days in the CRT arm minus the number of treatment days in the ART arm.

Results

Included studies

The systematic search found 505 articles (after removal of 156 duplicates). One hundred and fifty-seven studies with full-text publications were analyzed after initial abstract screening, and 1 additional relevant publication was found during the evaluation of the references of the included studies (Fig. 1). Additional informations about the systematic search strategy and the publications removed are available in Supplementary Material S1.

After applying inclusion and exclusion criteria to the 157 studies, a total of eleven studies were included in the meta-analysis: 4 RCTs [18–21] and 7 two-arm retrospective studies [22–28]. Of these, eight studies used hypofractionation (3 RCTs and 5 retrospective studies); whereas three studies used twice-daily (BID) hyperfractionation (1 RCT and 2 retrospective studies as the ART arm (Tables 1 and 2). Additional studies' characteristics are presented in Supplementary Material S2. All the RCTs presented > 70% of the domain with low risk of bias. Five retrospective studies were judged to have moderate risk of bias, and two had low risk (Supplementary Material S3). The publication bias was verified by funnel plot and is presented in the Supplementary Material S4. (See-Table 3.)

Impact of ART on local control

Overall, *472* patients were randomized to ART and 473 to CRT. The number of local failure events was 62 and 103 for the ART and CRT arms, respectively. Only two of the four RCT studies (50%) presented a significant reduction in local failure with ART. The combined results of the RCTs demonstrated a reduction of 38% in local failure events with the ART regimens (HR 0.62; 95% CI: 0.46–0.82, $p = 0.0009$) (Fig. 2A). The benefit continued to be significant in all the sensitivity analyses, performed by excluding one of the four studies at a time (Supplementary Material S5).

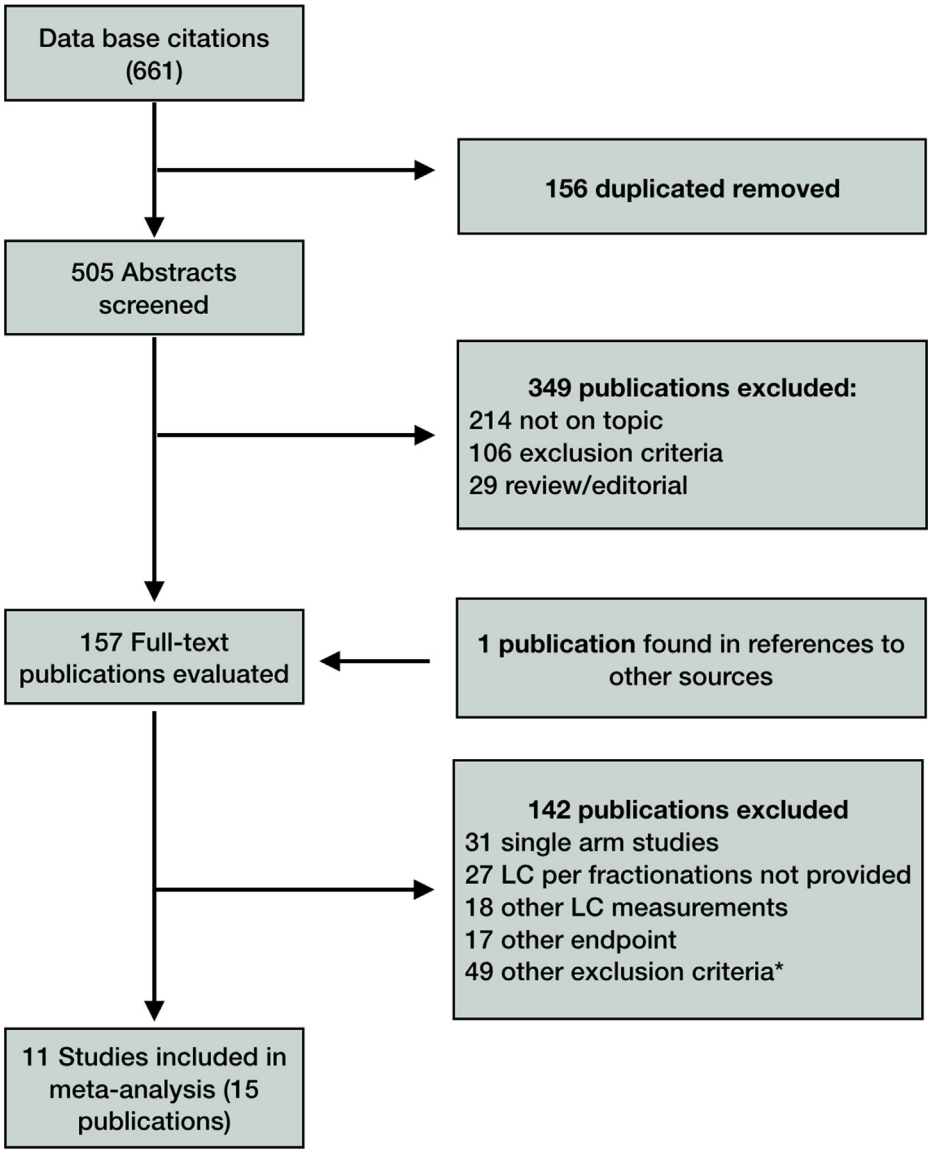

Fig. 1. Study selection flowchart.

In the retrospective studies pool, 534 patients were treated with ART and 283 with CRT. The total number of local failure events was 44 and 64 for the ART and CRT arms, respectively. Only two of the seven retrospective studies (28%) presented a significant reduction in the local failure rate with ART. The combined results of the seven two-armed retrospective studies demonstrated a reduction of 60% in local failure events with the ART regimens (HR 0.40; 95% CI: 0.24–0.66, $p = 0.0003$) (Fig. 2B). The benefit continued to be significant in all the sensitivity analyses, performed by excluding one of the seven studies at a time (Supplementary Material S5).

Subgroup sensitivity analyses

ART was associated with better local control than CRT among the trials that used the hyperfractionation strategy (HR 0.65; 95% CI: 0.43–0.97, p = 0.03) as well as the trials that used hypofractionation (HR 0.55; 95% CI: 0.33–0.91, p = 0.02) (Fig. 3). The benefit of ART remained significant in four of the sensitivity analyses, performed by

Table 1
Characteristics of the randomized clinical trials.

Author/study	Year	N	Stage (%T1)	A-com (%)	Beam energy	ART strategy	Fraction Size		MNTDR
							CRT	ART	
Yamazaki	2006	180	T1 (100%)	14.4%	4 MV	Hypo	2.0 Gy qd	2.25 Gy qd	5 days
KROG 0201	2014	156	T1 (89%) and T2	28.8%	4–6 MV	Hypo	2.0 Gy qd	2.25 Gy qd	5 days
RTOG 9512	2014	239	T2 (0% T1)	NA	Cobalt-60 or 4–6 MV	Hyper	2.0 Gy qd	1.2 Gy bid	2 days
JCOG 0701	2018	370	T1 (74.8%) and T2	3.5%	3–6 MV	Hypo	2.0 Gy qd	2.4 Gy qd	8 days

A-com: anterior commissure involvement. MNTDR – minimum number of treatment days reduced. ART: accelerated radiotherapy. CRT: conventional radiotherapy. Hypo: hypofractionation. Hyper: hyperfractionation.

Table 2
Characteristics of the retrospective cohorts.

Author	Year	N	Stage (%T1)	A-com (%)	Beam energy	ART strategy	Fraction Size		MNTDR
							CRT	ART	
Mendenhall	1988	147	T1 (51%) and T2	NA	Cobalt-60 or 2–8 MV	Hypo	< 2.25 Gy qd	≥2.25 Gy qd	NA
Yu	1997	126	T1 (100%)	53.9%	Cobalt-60 or 4 MV	Hypo	2.0 Gy qd	2.25 or 2.5 Gy qd	13 days**
Sakata	2000	130	T1 (63%) and T2	NA	Cobalt-60	Hyper	2.0 Gy qd	1.72 Gy bid	15 days
Tateya	2006	48	T2 (0% T1)	43.7%	Cobalt-60	Hyper	2.0 Gy qd	1.2 Gy bid	2 days
Gupta	2008	87	T1 (65.5%) and T2	NA	4–6 MV	Hypo	2.0 Gy qd*	3.18 Gy qd*	22 days#
Mourad	2013	250	T1 (77%) and T2	NA	Cobalt-60 or 6 MV	Hypo	2.0 Gy qd	2.25 Gy qd	NA
Alam	2016	29	T1 (41.3%) and T2	48.2%	Cobalt-60	Hypo	2.0 Gy qd	2.5 Gy qd	10 days

A-com: anterior commissure involvement. MNTDR – minimum number of treatment days reduced. ART: accelerated radiotherapy. CRT: conventional radiotherapy. Hypo: hypofractionation. Hyper: hyperfractionation. NA: not available.
* Most common fraction size.
\# Mean time difference.
** Majority (68%) have MNTDR of 13 days.

excluding one study at a time for the hypofractionation studies (4/8), and in one sensitivity analysis similarly performed for the hyperfractionation studies (1/3) (Supplementary Material S5). The benefit of ART also remained significant with respect to the other treatment parameters (machine type and MNTDR) (Supplementary Materials S6 and S7). For tumor-related parameters, the benefit of ART remained significant in the pooled analysis of studies with > 50% of T1 patients (HR 0.49, 95% CI: 0.36–0.65, $p < 0.00001$), but did not retain significance for the pooled analysis of the studies with > 50% of T2 patients (HR 0.60, 95% CI: 0.30–1.20, $p = 0.15$) (Fig. 4). Finally, both analyses of studies with ≤40% or > 40% of patients with anterior commissure involvement detected a benefit with the ART arm (Supplementary Material S8).

Discussion

The purpose of this systematic review and meta-analysis was to determine the effect of ART on the local control of ESGC treated with radiotherapy alone. Only 4 of the 11 studies that compared ART with CRT using our inclusion criteria demonstrated a significant, positive effect of ART in terms of local control. By including both prospective and retrospective studies (and pooling their number of events and relative risks), this analysis permitted sufficient power to address the study question specific to ESGC treated with RT alone. Furthermore, equivalent significant effect sizes were found among each type of the studies in the separate analyses by study design (HR 0.62 for the RCTs and HR 0.40 for the retrospective cohorts), thereby supporting our strategy.

Of note, a previous study published in 2015 [29] compiled the results of the only three RCT trials available at that time and found a HR for LC of 0.59 (p = 0.001, based on a fixed effects meta-analysis). This finding is similar to the HR found in the present analysis with random-effects modeling. However, due to smaller number of studies (and patient numbers), the previous systematic review was not able to perform subgroup sensitivity analyses.

Regarding fractionation, the benefit of ART persisted when each altered-fractionation strategy (hypofractionation and hyperfractionation) was analyzed separately. This finding is in accordance with the single-institution retrospective analysis of 230 patients performed by Garden et al. [1], which indicated that hyperfractionated treatments are similarly effective in terms of local control when compared to hypofractionated regimens with > 2 Gy/fraction. In the same analysis, patients treated with single fractions of ≤2 Gy/day (conventional fractionation range) also presented with greater local failure rates. Taken together, these findings support the notion that either altered fractionation scheme (hypo- or hyper-fractionation) may have a beneficial effect on local control.

In addition to the proposed radiobiological mechanisms, the benefit of ART may in part result from the reduced overall treatment time associated with ART. The impact of treatment time on locoregional

Table 3
Total hazard ratios.

Comparator	N studies	N local failures	N patients	HR [95% CI]	*p*-value	Remained significative on sensitivity analysis*
Overall						
Overall RCT	4	165	945	0.62 [0.46–0.82]	0.0009	4/4
Overall Retrospective	7	108	817	0.40 [0.24–0.66]	0.0003	7/7
ART strategy						
Hyperfractionation	3	101	417	0.65 [0.43–0.97]	0.03	1/3
Hypofractionation	8	172	1345	0.55 [0.33–0.91]	0.02	4/8
MNTDR						
≤5 days	4	120	623	0.57 [0.37–0.88]	0.01	2/4
> 5 days	5	123	742	0.54 [0.39–0.74]	0.0002	5/5
Machine type						
Only LINAC	4	113	793	0.52 [0.36–0.75]	0.0004	4/4
Cobalt-60 and LINAC	4	115	762	0.48 [0.23–0.97]	0.04	2/4
Only Cobalt-60	3	43	207	0.54 [0.30–0.94]	0.03	0/3
T stage						
≤50% T1	3	73	316	0.60 [0.30–1.20]	0.15	0/3
> 50% T1	8	198	1446	0.49 [0.36–0.65]	< 0.00001	8/8
Anterior Commissure Involvement						
≤40% patients	3	104	706	0.54 [0.37–0.79]	0.001	3/3
> 40% patients	3	38	203	0.42 [0.23–0.77]	0.005	2/3

* Sensitivity analysis excluding one study at a time (detailed at Supplementary Material S5).

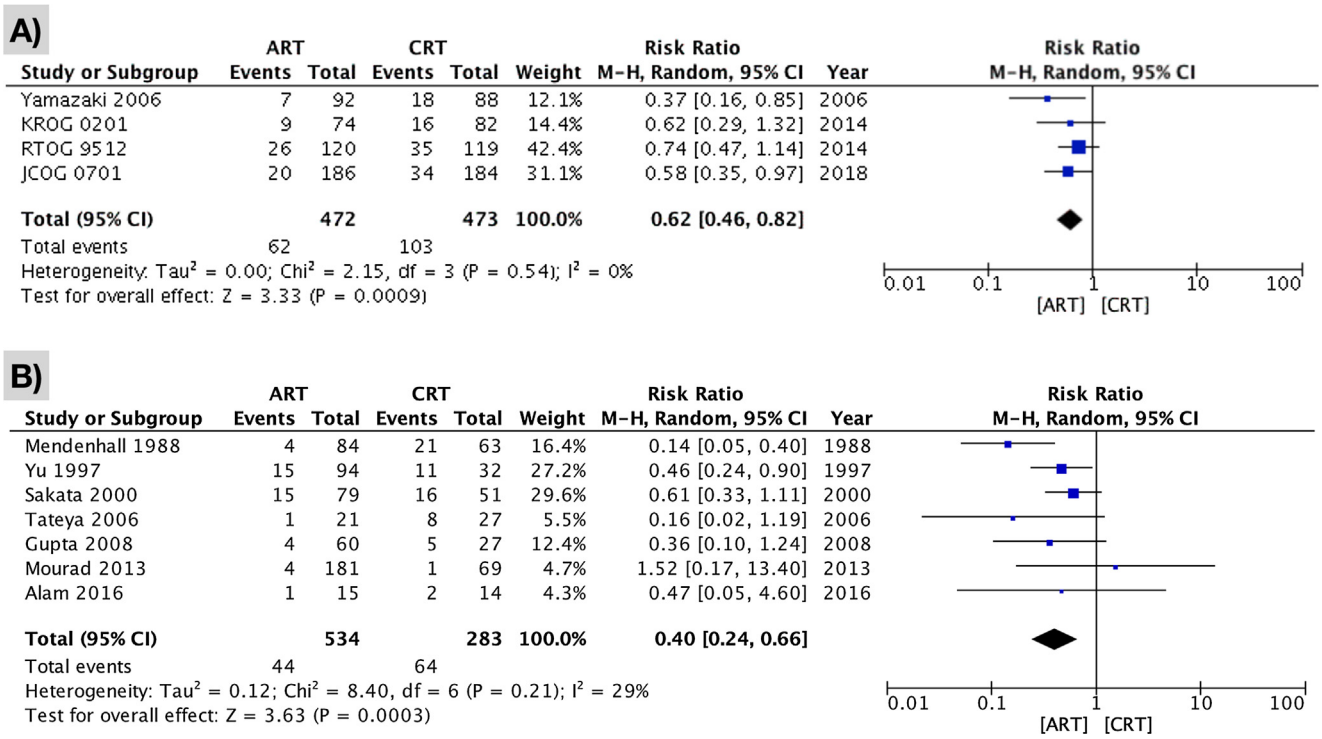

Fig. 2. (A) Overall LC for randomized clinical trials. (B) Overall LC for two-arm retrospective studies.

control of ESGC has been addressed previously by van der Voet et al. [30]. In a large series of 383 consecutive T1N0 patients from Netherlands, the investigators found that the overall treatment time was the most significant factor for disease control, with 95% local control for treatment time between 22 and 29 days and 79% for a treatment time of 40 days or over. Since the altered fractionation schedules used for ESGC generally reduce the overall treatment time (as presented in Tables 1 and 2), the finding that ART improves local control may be related to this notion.

With respect to tumor-related parameters, pooled analyses of the present study clearly demonstrate the beneficial effect of ART on local control for T1 disease and in the setting of anterior commissure involvement. Of note, the Yamasaki et al. trial that recruited only T1 cases (n = 180) similarly demonstrated this significant local control

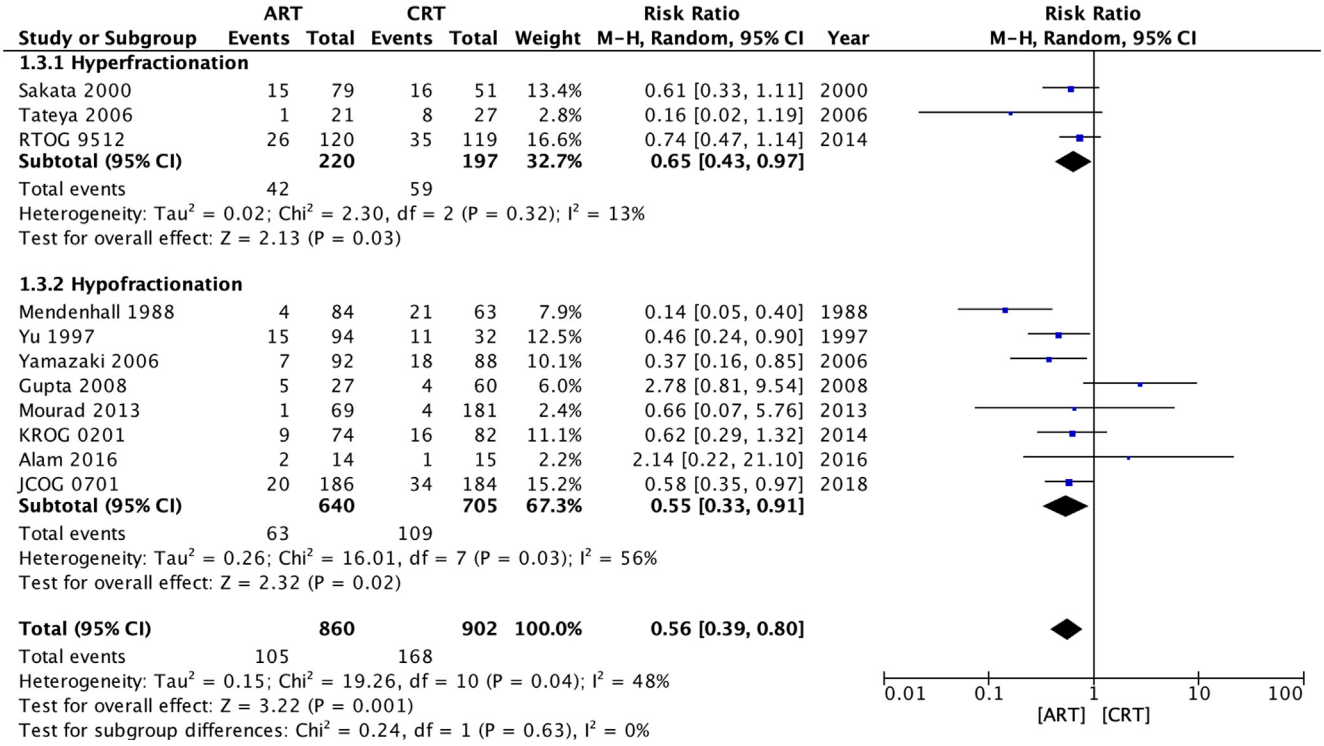

Fig. 3. Pooled local control subgroup analysis based on ART subtype.

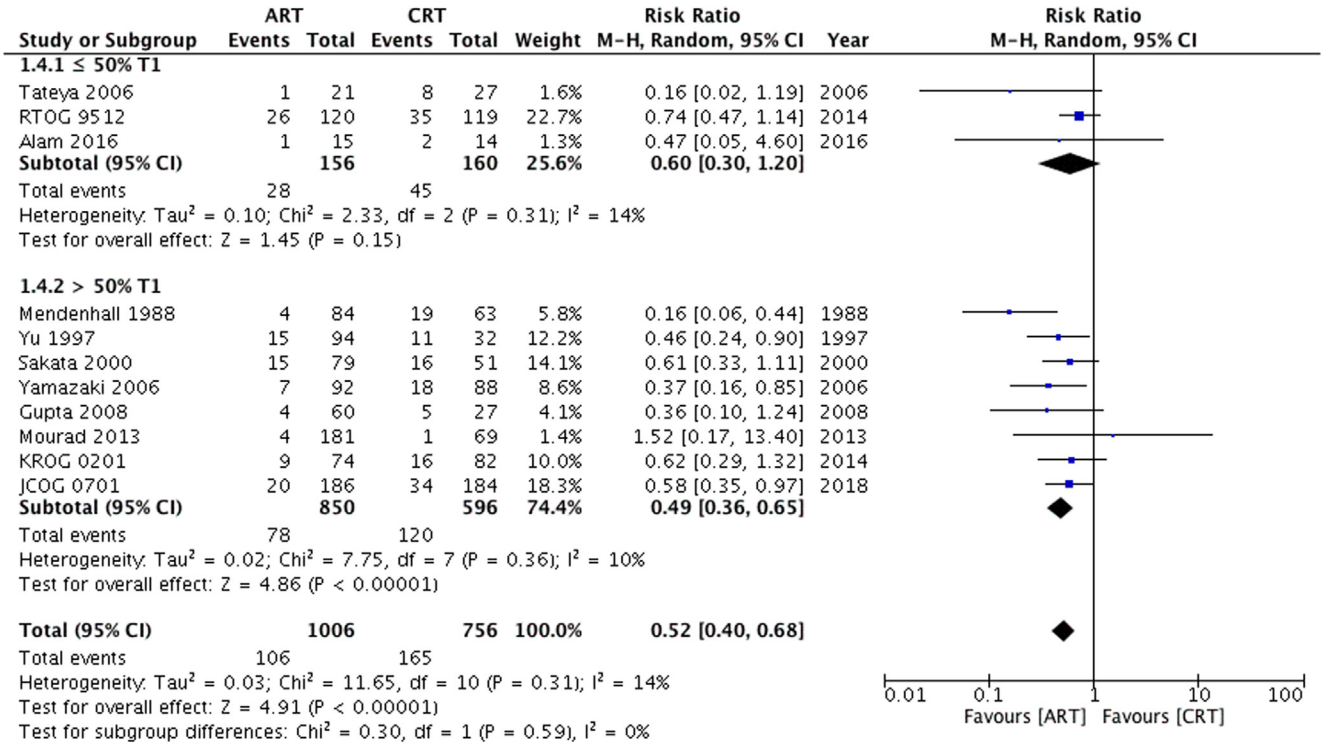

Figure 4. Pooled local control subgroup analysis based on T stage.

gain [18].

In contrast, however, our pooled analyses indicate that this local control benefit of ART may not extend to T2 disease, demonstrating a lack of benefit in studies with predominantly T2 cases. Of note, these studies used a variety of altered dose schedules in their ART arms: 79.2 Gy in 66 fractions bid (RTOG 9512) [20], 72–74.4 Gy in 60–62 fractions bid (Tateya et al.) [25], and 62.5 Gy in 25 daily fractions (Alam et al.) [28] (Supplementary Material S2). Furthermore, the RTOG 9512 trial, which recruited only T2 cases and enrolled even more patients (n = 239) than the Yamasaki trial, failed to show a significant benefit with ART, thereby supporting these findings [20].

Taken together, these findings suggest that ART may not improve LC in the setting of T2 ESGC. Furthermore, these patients are known to have a 20% higher risk of local failure after RT alone compared to patients with T1 tumors (95% CI: 0.73–086, $p = 0.0007$) [31]. Thus, surgical treatment [32–33] and/or other innovative approaches should be considered in this population, such as the use of sensitizing concurrent chemotherapy [34–35] and/or treatment to higher prescription doses more akin to bulkier tumors.

Major limitations of the present study are the fact that few studies comparing the results of ART with CRT were available for inclusion, and the bias inherent within the retrospective designs (including uneven patient number) could adversely affect the impact of our findings. Also, due to the scarce data of T2 stage patients, the approach used of grouping studies with more than 50% of T2 cases has a limited strength to draw definitive conclusions regarding the efficacy of ART in this subgroup of patients. Modern studies with patient-level data using staging CT or MRI to exclude cases with paraglottic space invasion and/or minor thyroid cartilage erosion (T3) are needed to better address the role of ART specifically for T2 ESGC.

In addition, other disease- and treatment-related aspects could not be assessed by our study, including the impact of ART on regional nodal failure, overall survival, and post-treatment quality of voice. The use of ART, especially hypofractionation in particular, could raise concerns about the quality of voice, although multiple studies have demonstrated a lack of significant risk [36–37].

In conclusion, the present study provides summary evidence in favor of the use of ART for ESGC, supporting its utility in standard clinical practice. Irrespective of the acceleration strategy used (hypo- or hyperfractionation), ART improves local control compared to CRT in T1 disease and in the setting of anterior commissure involvement. However, its relative benefit appears to be more pronounced for T1 versus T2 tumors. Further investigation of the role of ART and alternative treatment approaches are warranted for the setting of T2 disease.

Conflicts of interests

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.04.007.

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