Carotid sparing intensity-modulated radiation therapy achieves comparable locoregional control to conventional radiotherapy in T1-2N0 laryngeal carcinoma

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Abstract

Background—Although intensity-modulated radiotherapy (IMRT) is a standard of care for many head and neck cancers, its use for carotid-sparing (CS) therapy in early-stage laryngeal carcinoma is controversial.

Methods—330 consecutive patients with early-stage laryngeal carcinoma were treated from 1/1989 to 5/2011, including 282 CRT and 48 CS-IMRT patients. The median follow-up was 43 (CS-IMRT) and 66 (CRT) months.

Results—There was no difference in local failure rates comparing patients undergoing CS-IMRT with CRT, with 3-year local control rates of 88% vs. 89%, respectively (p=0.938). Using a 1cm circumferential margin, the average dose to the left and right carotid arteries was 48.3 and 47.9 Gy, respectively. 88% of locoregional recurrences involved the ipsilateral true vocal cord, including all local recurrences in the IMRT group.

Conclusions—These results warrant further prospective evaluation of CS-IMRT for early-stage glottic larynx cancer.

Keywords

Early stage laryngeal carcinoma; glottic cancer; IMRT; carotid sparing

INTRODUCTION

Conventional radiotherapy (CRT) delivered with opposed-lateral beams is a mainstay of therapy for early-stage (T1-2N0) glottic carcinoma and achieves excellent rates of larynx preservation and cancer eradication. Long-term local control is achieved in approximately

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90% and 75% of patients with T1 and T2 tumors, respectively, and cancer-specific survival rates over 95% have been reported.[1-4] Given these results and that nearly all patients die of causes unrelated to their laryngeal cancer, further improvement in cancer outcome via technological innovation is unlikely. Rather, the greatest opportunity for advancing therapy is preventing long-term toxicity while maintaining excellent oncologic control, similar to other malignancies with long-term survival.[5-7]

Although early-stage glottic larynx cancers are treated with relatively small radiation fields, longitudinal segments of both common carotid arteries receive radiation doses essentially equivalent to the prescription. Studies have shown increased risk of carotid artery stenosis and stroke for patients receiving radiation for head and neck cancer.[8-13] Additionally, a recent Surveillance, Epidemiology and End Results (SEER) database study reported that T1N0 glottic larynx cancer patients treated with external beam radiation were significantly more likely to experience a fatal cerebrovascular accident than those treated with surgery.[14] As tobacco use is the primary risk factor for developing laryngeal cancer, this population already has increased risk of cerebrovascular morbidity and mortality, and thus techniques minimizing additional cerebrovascular risk are appealing.

Given this background, several institutions have attempted to reduce radiation dose to the carotid arteries with intensity-modulated radiotherapy (IMRT).[14-16] IMRT is capable of delivering highly conformal dose distributions with sharp dose fall-offs, thereby sparing surrounding normal tissue. Thus, IMRT may be able to decrease the dose to the carotid arteries while preserving the excellent oncologic outcomes of CRT. Indeed, several dosimetric studies have shown significantly decreased carotid artery radiation with IMRT compared with CRT for early-stage laryngeal cancer.[14-16]

Nevertheless, the role of IMRT in early-stage larynx cancer is controversial. Increased conformality also increases the risk of marginal misses through contouring errors and organ motion. Further, there have been anecdotal reports of radiation failures from patients undergoing IMRT.[17,18] To investigate these concerns, we assembled a cohort of patients treated with both IMRT and CRT to determine if there was any difference in local control, salvage laryngectomy rates, or survival with either approach.

MATERIAL AND METHODS

Patients

From January 1989 to May 2011, all patients with clinical stage T1 or T2 squamous cell carcinoma of the glottic larynx and clinically negative cervical lymph nodes who underwent definitive radiation at our center were identified from an institutional database. Institutional review board approval was granted prior to data collection.

Staging

All patients underwent evaluation with history and physical exam, including indirect or flexible fiberoptic laryngoscopy. All suspicious lesions were biopsied, and pathology slides were reviewed by an expert in head and neck pathology at our institution. Routine staging computed tomography (CT) of the neck was not performed prior to simulation unless there

were indeterminate cervical lymph nodes on clinical exam or extra-glottic spread was suspected.

Radiation techniques

All patients were treated to the larynx alone without irradiation of elective lymph node volumes. CRT consisted of opposed lateral fields typically spanning 5×5 cm. Borders were the bottom of the hyoid bone superiorly, the bottom of the cricoid inferiorly, the anterior edge of the vertebral bodies posteriorly, and 1 cm of flash anteriorly. For T2 tumors, the field borders for CRT could be expanded to a 6×6cm box, inferiorly extending to include the first tracheal ring, and ensuring that the field borders extended at least 2cm above and below gross disease. Simulation for CRT was either fluoroscopy or CT based. All IMRT patients underwent CT-based simulation. A GTV based on clinical exam was contoured to ensure coverage. The clinical target volume was defined as the entire larynx, including the anterior and posterior commissures, and arytenoids, from the top of the thyroid cartilage to the bottom of the cricoid. The planning target volume (PTV) consisted of a 1.0 cm circumferential expansion of the clinical target volume. The PTV extended to the top of thyroid cartilage superiorly and the bottom of the cricoid inferiorly. Generally, four 6 MV anterior coplanar photon beams were used. The carotid arteries were contoured on slices containing the PTV. Prescriptions were normalized so that 95% of the PTV received 100% of the prescription dose (i.e., PTV D95% = 100%). Additional dose constraints included limiting the maximum dose in the PTV to 105% of the prescription and a soft constraint limiting the mean carotid artery dose to 52 Gy. Coverage was prioritized over carotid artery dose. For both CRT and IMRT, patients with anterior commissure involvement were generally treated with daily bolus as well as anterior flash of the radiation field to ensure coverage of this region.

Follow-up

In general, patients were followed every 3 months for the first 2 years for history, physical exam, and indirect or flexible laryngoscopy, then every 4 months for years 3 and 4, every 6 months for year 5, and then annually. Most patients alternated visits between a radiation oncologist and a head and neck surgeon at our institution. For locoregional patterns of failure, site of first failure was based on clinical exam, laryngoscopy, and pathology report.

Statistical methods

Follow-up was calculated from the start of radiotherapy. All local failures were biopsy-proven disease occurring in the supraglottic, glottic, subglottic larynx, and/or adjacent soft tissue post-radiation. Actuarial estimated survival probabilities were calculated utilizing the standard Kaplan-Meier method, and p values were determined using a log-rank test. Hazard ratios (HRs) and 95% confidence intervals were calculated using a Cox proportional hazards model. All statistics were performed using SPSS version 21 and R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline clinical characteristics are shown in Table 1. Forty eight patients were treated with IMRT and 282 received conventional external beam radiotherapy. The median radiation dose was 63 Gy and 66 Gy for IMRT and CRT, respectively. Overall, 125 patients (38%) were treated with fraction sizes of 2.25 Gy, all 48 undergoing IMRT and 75 (27%) undergoing CRT ($p<0.001$). There were slightly more T2 tumors in the IMRT group than the CRT group, but this did not reach statistical significance (27% vs 20%, $p = 0.462$). Median follow-up was 44 months and 66 months for surviving IMRT and CRT patients, respectively.

Dosimetric characteristics of our patients undergoing IMRT are summarized in Table 2. The median PTV maximum dose was 105%. The mean of the average doses to the left and right carotid artery segments in the region of the PTV were 48.3 and 47.7 Gy, respectively. As shown, the magnitude of carotid sparing varied widely amongst the cohort, with some patients achieving mean carotid doses as low as 20.5 Gy, and others receiving mean carotid doses closer to the prescription. There was a high degree of correlation between the mean doses received to by left and right carotid arteries (correlation coefficient $R^2 = 0.907$)

Three-year local control was 91% for T1 tumors, vs 80% for T2 tumors (HR, 2.38; 95%CI, 1.26 to 4.49; p=0.008) (Figure 1). Additionally, laryngectomy-free survival was significantly better in T1 vs T2 tumors (HR, 1.81; 95%CI, 1.16 to 2.83; $p = .009$). Three-year laryngectomy-free survival was 87% and 74% for T1 and T2 tumors, respectively. Although there was a trend towards increased rates of distant metastasis (1% vs. 8% at 3 years, $p = .057$) with T2 tumors, this did not reach statistical significance.

As shown in Table 3, there was no significant difference in local failure rates comparing IMRT with CRT (HR, 0.96; 95%CI, 0.38 to 2.147; $p = .938$). The 3-year actuarial local control rate was 88% for IMRT and 89% for CRT (Figure 2). After adjusting for tumor stage, there was still no difference in local failure (HR, 0.90; 95%CI, 0.35 to 2.30; $p = .821$). Laryngectomy-free survival (HR, 1.39; 95%CI, 0.73 to 2.65; $p = .318$), distant metastasis (HR, 2.47; 95%CI, 0.48 to 12.65; $p = .247$), and overall survival (HR, 1.85; 95% CI, 0.89 to 3.86; $p = .10$) were not significantly different. Patients with T2 tumors ($p = .008$) and non-smokers ($p = .027$) had decreased local control in univariate analysis. Increasing age and tumor stage predicted for inferior laryngectomy-free survival.

Patterns of locoregional failure are summarized in Table 4. In 41 locoregional recurrences, 36 (88%) involved the ipsilateral true vocal cord, including all 5 in the IMRT group. Among these patients, 18 (44%) had recurrences with subglottic or supraglottic extension and 2 (5%) had simultaneous cervical lymph node recurrence. No patient had contralateral true vocal cord recurrence without ipsilateral true vocal cord recurrence. Of the 5 patients not recurring in the glottic larynx, one recurred in the supraglottic larynx alone, one failed in the hypopharynx and cervical lymph nodes, and three recurred in the cervical lymph nodes alone. Twenty-one patients had salvage total laryngectomy, 13 had organ-preserving salvage surgery, one had laser ablation, one had salvage radiation to a level 6 lymph node recurrence, and 5 did not receive salvage local therapy.

DISCUSSION

We have previously demonstrated that IMRT is feasible and results in excellent locoregional control for locally advanced laryngeal cancer.[19] Here we further demonstrate that IMRT for early glottic cancer results in local control comparable to CRT. Overall, we achieved local control in 91% of T1 tumors and 80% of T2 tumors at 3 years, which is comparable to previous reports.[1-4] Thus, the similar local control outcomes for IMRT and CRT cannot be attributed to unexpectedly poor control in CRT patients. We found only a relatively mild decrease in carotid artery dose with this technique, likely attributable to the relatively generous 1cm circumferential PTV margin we used to the time period of this study and a conservative CTV that included the entire larynx. In contrast, other groups have proposed limiting the treatment volume only to the involved vocal cord to maximize carotid sparing.[20] For example, Janssen and colleagues recently reported excellent local control rates in 39 patients with T1-2N0 glottic carcinoma treated with IMRT, including 21 patients that underwent ipsilateral vocal cord irradiation with bilateral carotid sparing resulting in a mean contralateral carotid dose of 20.2 Gy.[21] Since the time period of this study, we have chosen to employ an intermediate approach, using daily image guidance and decreasing our circumferential margin to 0.5cm, with as little as 0.3cm margin allowable near the carotid arteries in order to achieve a more significant reduction in carotid dose. Notably, in this study we found that the benefit of carotid sparing IMRT varied significantly based on a given patient's anatomy, with mean carotid artery doses ranging from 20.5 Gy to 61.5 Gy. Thus, the benefit of carotid sparing IMRT is likely to depend on patient anatomy.

Although radiation techniques for many anatomic subsites in head and neck cancer have radically evolved over the past 25 years, with IMRT nearly universally replacing older techniques due to its superior dosimetry and decreased long-term morbidity,[22-25] radiation therapy for early-stage glottic cancer has remained essentially unchanged at most institutions. This stems from the fact that early-stage cancer of the glottic larynx, uniquely amongst squamous cell cancers in the head and neck, rarely involves the cervical lymph nodes. Thus, unlike other anatomic subsites, where radiation fields can stretch from the skull base to the clavicle, a relatively small field is used, usually consisting of a 5×5 or 6×6 cm box that excludes the major salivary glands, pharyngeal constrictors, and oral cavity. Thus, although this small field does treat normal structures not included in the target volume, the rationale for employing IMRT for early-stage glottic carcinoma may appear less compelling than for other head and neck sites.

Nevertheless, in a disease where nearly all patients will die of causes unrelated to their cancer, it is important to consider the impact of therapy on long-term morbidity. There is a growing body of literature suggesting that radiation for head and neck cancer induces radiation vasculopathy, thereby increasing the risk of carotid artery stenosis and cerebrovascular morbidity.[26] These adverse effects of radiation on the vasculature can be seen within 1-2 years of treatment.[8,9] Additionally, the effects on carotid artery stenosis appear to continue to progress with longer follow-up after radiotherapy.[10]

These early effects on carotid artery stenosis may have clinically relevant consequences. For example, a study from the Netherlands found that in 367 patients with head and neck cancer

undergoing definitive radiotherapy prior to age 60, including 162 with T1-2N0 laryngeal cancer, the risk of stroke was 5.6 times higher than expected based on age- and sex-matched controls from the general population.[11] A similar study from the University of Pennsylvania found a more than twofold increase in stroke among 413 patients undergoing definitive radiation compared with a population-based estimate derived from unirradiated patients from Stockholm.[12] In a recent SEER database study exclusively of patients with T1N0 glottic larynx cancer radiation was associated with a 75% relative increase in risk of fatal stroke compared with surgery alone, although the absolute increase in risk was relatively small.[13]

Given this reported increased risk of cerebrovascular morbidity, multiple studies have convincingly demonstrated that IMRT is capable of significantly reducing radiation dose to the carotid arteries for patients with early stage glottic cancer.[14-16] Although these studies suggested that IMRT was capable of reducing the carotid dose by approximately 75%, the magnitude of carotid sparing was significantly less in our study for several reasons. First of all, the University of Florida used a 3mm PTV margin,[16] whereas the study from MD Anderson used no PTV margin at all.[15] By contrast, we used a conservative 1cm PTV circumferential margin for the patients included in this study given that we lacked experience with this technique when we first implemented it and wanted to minimize the potential for marginal misses. Additionally, we did not use daily image guidance for the patients included in this study. However, now that our results have demonstrated equivalent local control with IMRT and CRT, we have placed a much stronger emphasis on further reducing the carotid artery dose. Currently, we use daily kV-imaging and a 5mm circumferential PTV expansion around our CTV, with as little as 3mm expansion of the CTV near the carotid arteries, allowing much lower carotid doses to be achieved. Further, it should also be noted that we chose to define the carotid artery structure at risk as only segments of the carotid artery on CT slices containing a PTV contour in order to most fairly compare the carotid dose delivered by our IMRT and oppose lateral beam plans. This is in contrast to the University of Florida study, which defined the carotid artery structure as extending 1cm above and below the PTV.[16] Because this carotid artery definition will artificially lower the reported mean and median carotid doses, dosimetric results from this should not be directly compared to our reported doses.

It should be pointed out that there is no definitive data relating carotid-artery dose to cerebrovascular morbidity, and the impact of carotid-sparing IMRT on vasculopathy remains unproven. Nevertheless, extrapolating from a breast cancer study demonstrating a linear increase of 7.4% in the rate of major coronary artery events for each additional gray of mean heart radiation dose,[7] it seems possible that a clinically significant decrease in carotid-associated adverse sequelae may potentially result from the magnitude of reduction in carotid-artery dose achievable with carotid sparing IMRT, particularly with tighter margins than those employed in our study. However, this is a hypothesis in need of evidence and investigation.

Nevertheless, IMRT for early-stage glottic cancer remains controversial.[17,18] In addition to anecdotal reports of increased failure with IMRT, the major concerns are the potential for underdosing the tumor through target delineation errors, complications resulting from hot

spots, increased cost, and increased treatment complexity leading to prolonged contouring, planning, and treatment time. Although marginal misses resulting from IMRT have been reported in head and neck cancer previously,[27-29] there is no plausible reason to hypothesize that IMRT will result in increased marginal misses when delivering an equivalent radiation dose if a clinical target volume including the entire larynx is properly contoured, a reasonable PTV expansion is employed, and a bolus is used to ensure anterior coverage. In fact, several studies have previously shown that IMRT is capable of producing superior target coverage compared with two-dimensional treatment with a lower maximum dose (i.e., a hot spot),[14,15] In our study, in addition to demonstrating comparable local control for patients undergoing IMRT and CRT, all patients with local recurrence following IMRT had involvement of the ipsilateral true vocal cord, suggesting that the failures occurred mostly within the field itself rather than at the field margins. Further, although there is a theoretical concern that intrafraction motion from mobile organs such as the larynx may be more greatly impacted by IMRT than CRT given the potential interaction of the dynamic multileaf collimator and the target motion, we did not note an increased rate of infield failures with IMRT compared to CRT. It was notable that two of the five local failures in the IMRT arm were in patients initially with anterior commissure involvement treated without bolus, and four of five local recurrences had subglottic extension. Because of this, it is our current practice to employ a 5 mm bolus for all early-stage glottic carcinoma IMRT patients and to carefully check the inferior extent of the field to ensure that it is at least 2cm below gross disease.

Although we believe that tumor control should be similar with carotid-sparing IMRT and CRT, there are some potential dosimetric trade-offs to consider. For example, IMRT planning can lead to a higher integral dose, and increased volume of tissue receiving low radiation doses. The effect of these dosimetric changes on long-term toxicity, especially secondary malignancies, is unclear and warrants careful investigation. However, other arguments against the use of IMRT, such as increased physician time for contouring, increased planning complexity, and increased treatment time, do not preclude its use. Unlike IMRT treatments for other sites in the head and neck, the amount of contouring needed for a glottic larynx IMRT plan is minimal, consisting of defining the larynx, bilateral carotid arteries, and spinal cord. Similarly, although there is some added treatment-planning complexity with IMRT vs CRT, at our institution we use a four-beam technique, and meeting dose-volume constraints is generally straightforward. Analogously, simplified IMRT with opposed tangents is used at our institution routinely for breast cancer given its superior dose homogeneity.[30] Finally, treatment time is not significantly prolonged compared with conventional treatments, and in fact a study from the MD Anderson Cancer Center found that overall time in the treatment room decreased with IMRT for early-stage laryngeal cancer.[15] This may partially be because therapists do not have to enter the treatment room to place wedges with IMRT.

This study has several weaknesses that warrant further discussion. This is a retrospective series, and thus imbalances in unmeasured confounding factors between the IMRT and CRT groups could have affected the results. For example, patients undergoing IMRT, representing a more contemporary cohort, were significantly more likely to receive treatment with 2.25 Gy fraction sizes, a regimen that to improved local control in the randomized trial compared

with 2 Gy fractions.[31] However, in our data set, fraction size did not predict for local control, and thus this imbalance likely did not impact our results. Furthermore, given the small number of local recurrences, we were not able to use multivariate models to adjust for possible confounding variables. However, given that T-stage was the most significant predictor for local control, we adjusted for T-stage and found essentially identical results. A further important limitation to our study is that, in comparison to the group treated with CRT, patients undergoing IMRT had relatively shorter follow-up. However, the majority of local failures in early-stage glottic carcinoma occur during the first 3 years after treatment, and thus it is unlikely that longer follow-up will reveal late local failures that alter the conclusions of this study. Additionally, our results should not be extrapolated to IMRT strategies that target only a single vocal cord or part of the larynx, such as the approach recently reported by the Princess Margaret Hospital that resulted in relatively high rates of local failure for patients with T2N0 laryngeal cancer.[18] Finally, a major weakness of our study is a lack of long-term toxicity data, given the relatively short follow-up of our cohort and incomplete non-oncologic post-radiotherapy medical information in our institution's medical record.

Despite these caveats, and given that IMRT is capable of decreasing radiation dose to the carotid arteries without compromising local control, we believe that a prospective comparison of CRT to IMRT is warranted. However, even if such a study were undertaken in the future, it would require large numbers of patients and many years of follow-up to adequately understand the impact of radiation technique on long-term cerebrovascular morbidity. Given this, prospective studies using surrogate outcomes, like carotid artery stenosis, would be valuable and provide more timely results. Towards this end, we are currently developing a single-arm IMRT protocol at our institution that will prospectively evaluate toxicity and obtain serial carotid ultrasounds following radiotherapy. Nevertheless, we acknowledge that there are many uncertainties regarding its costs and benefits not addressed by our study. Thus, although carotid-sparing IMRT is a safe, effective treatment in this disease and warrants further study, we do not believe that it should broadly replace conventional radiotherapy at this time.
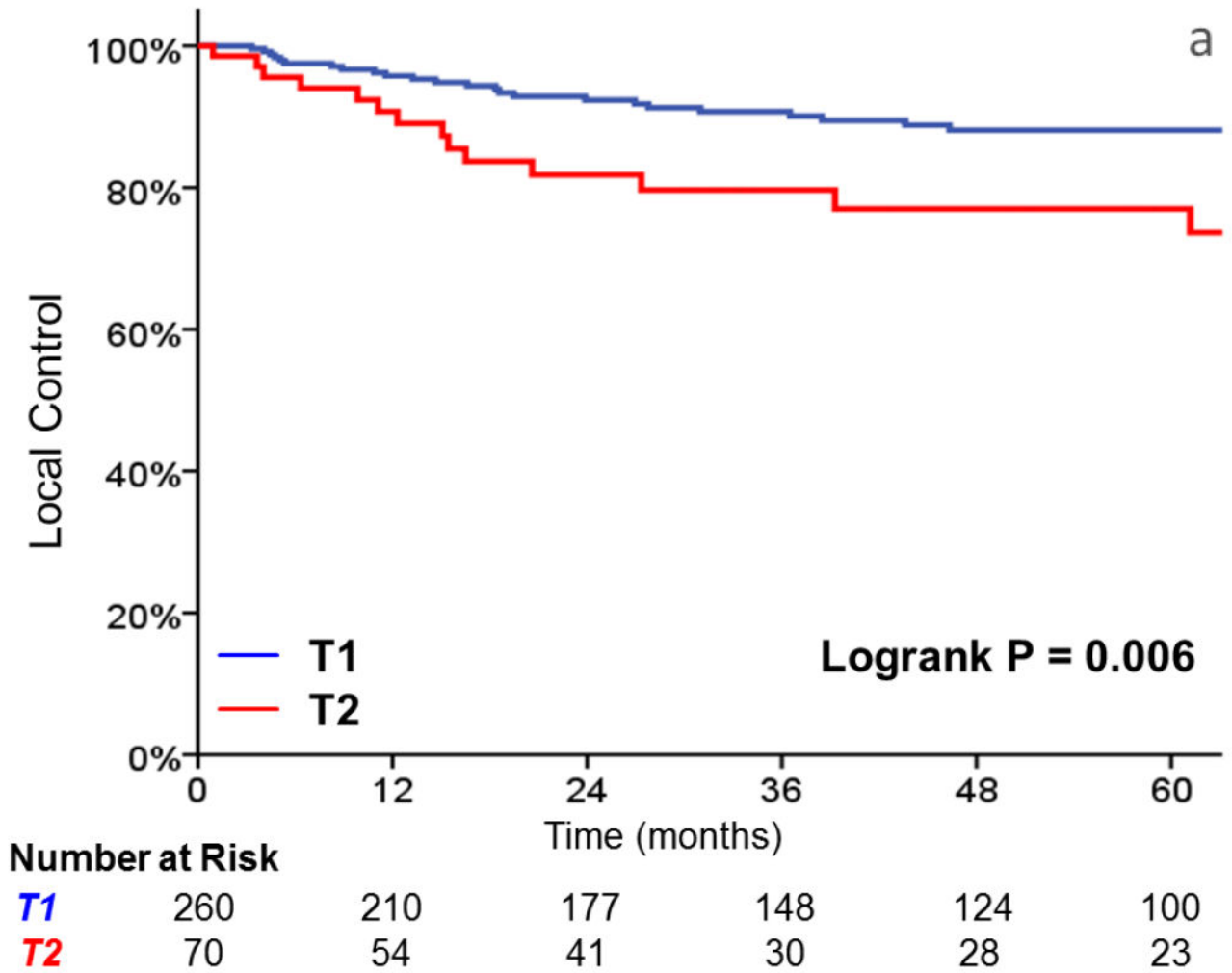
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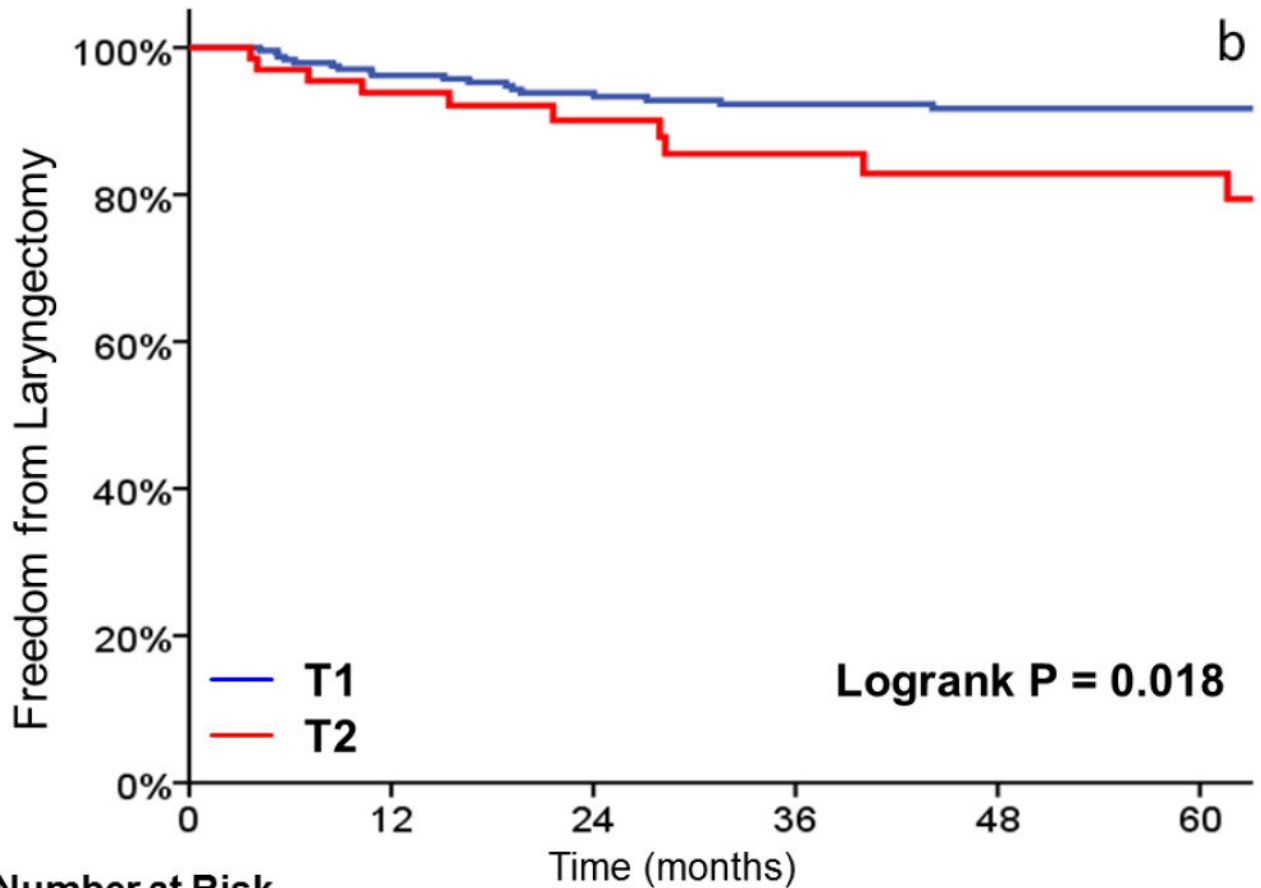
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Highlights

- IMRT produces similar outcomes to conventional radiotherapy in early stage glottic carcinoma.

- All failures in the IMRT group involved the ipsilateral vocal cord.

- Anterior bolus and careful subglottic coverage may reduce the local failure risk with IMRT.

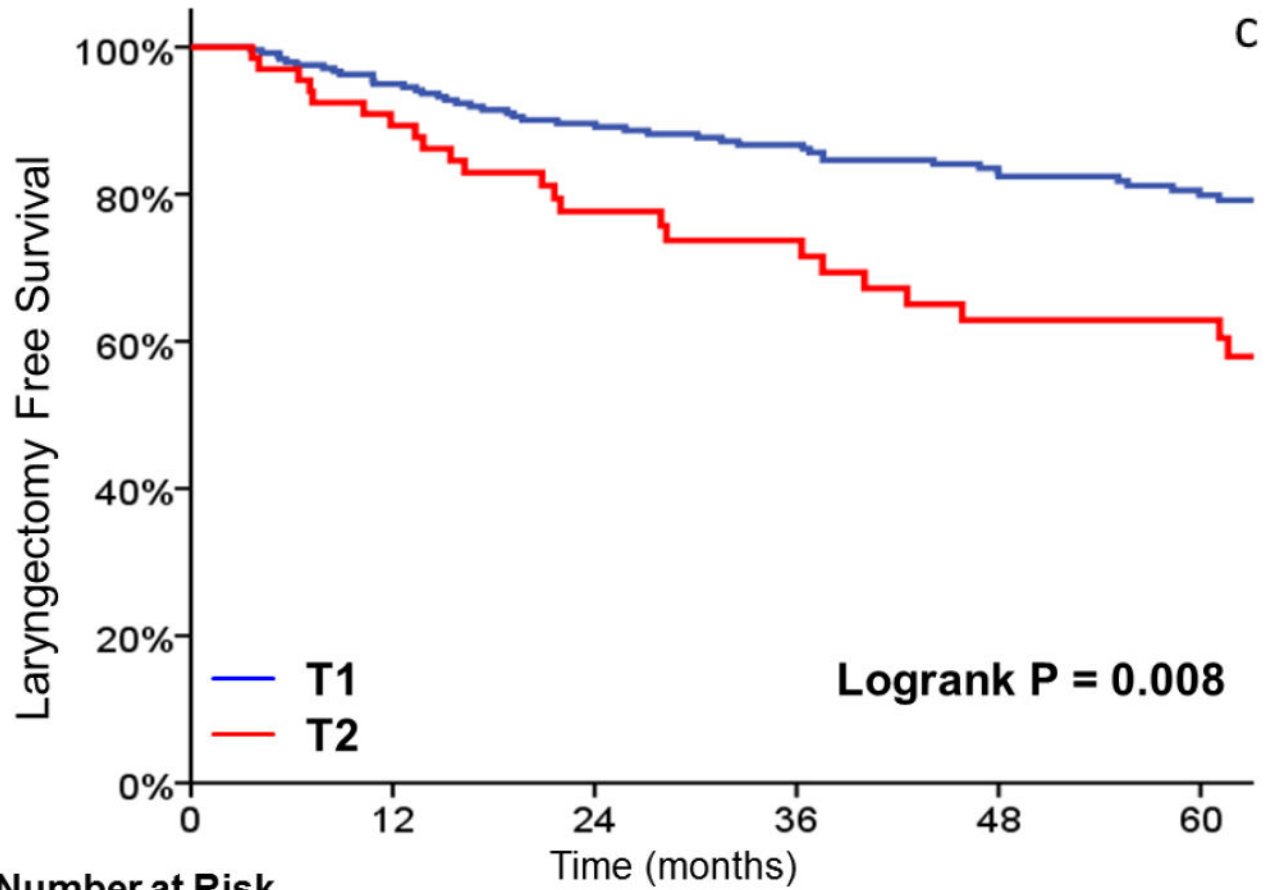- Maximal carotid sparing will likely require tight margins and image guidance.
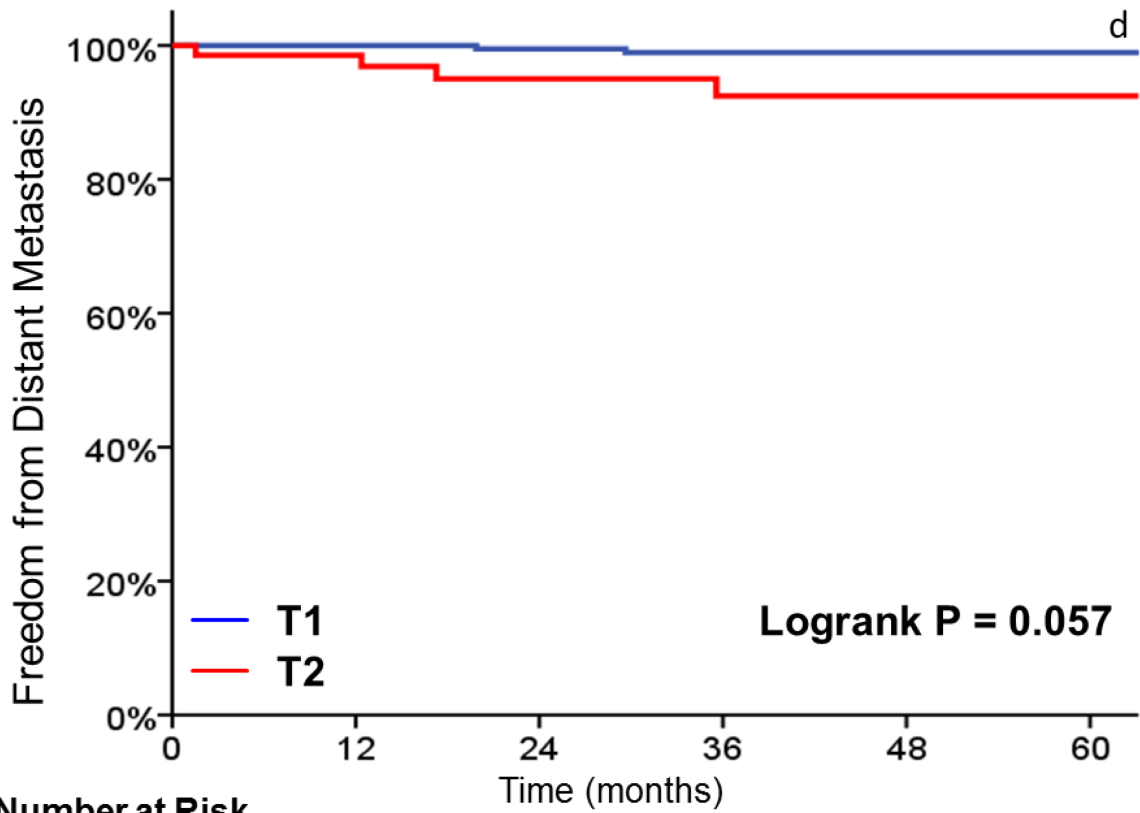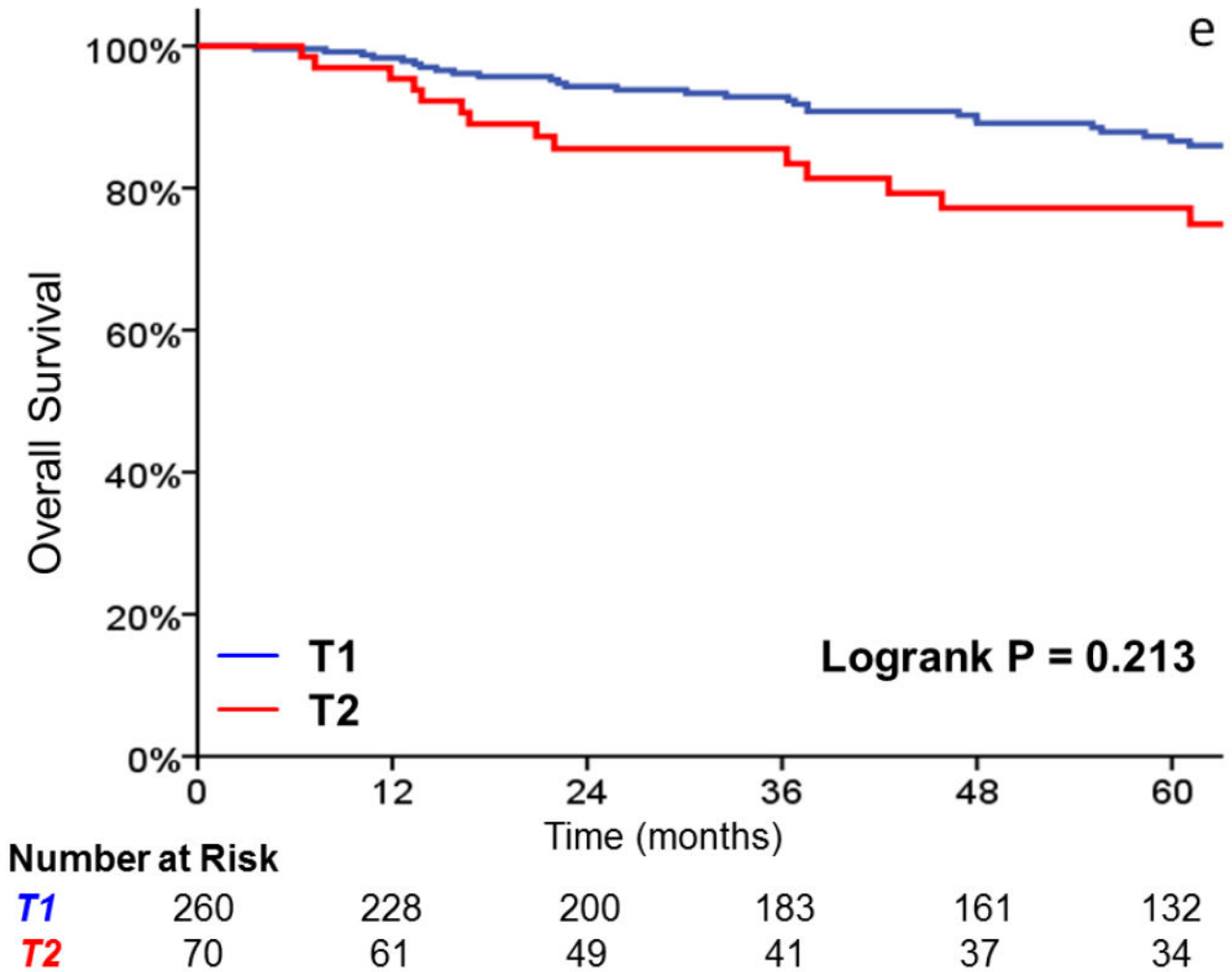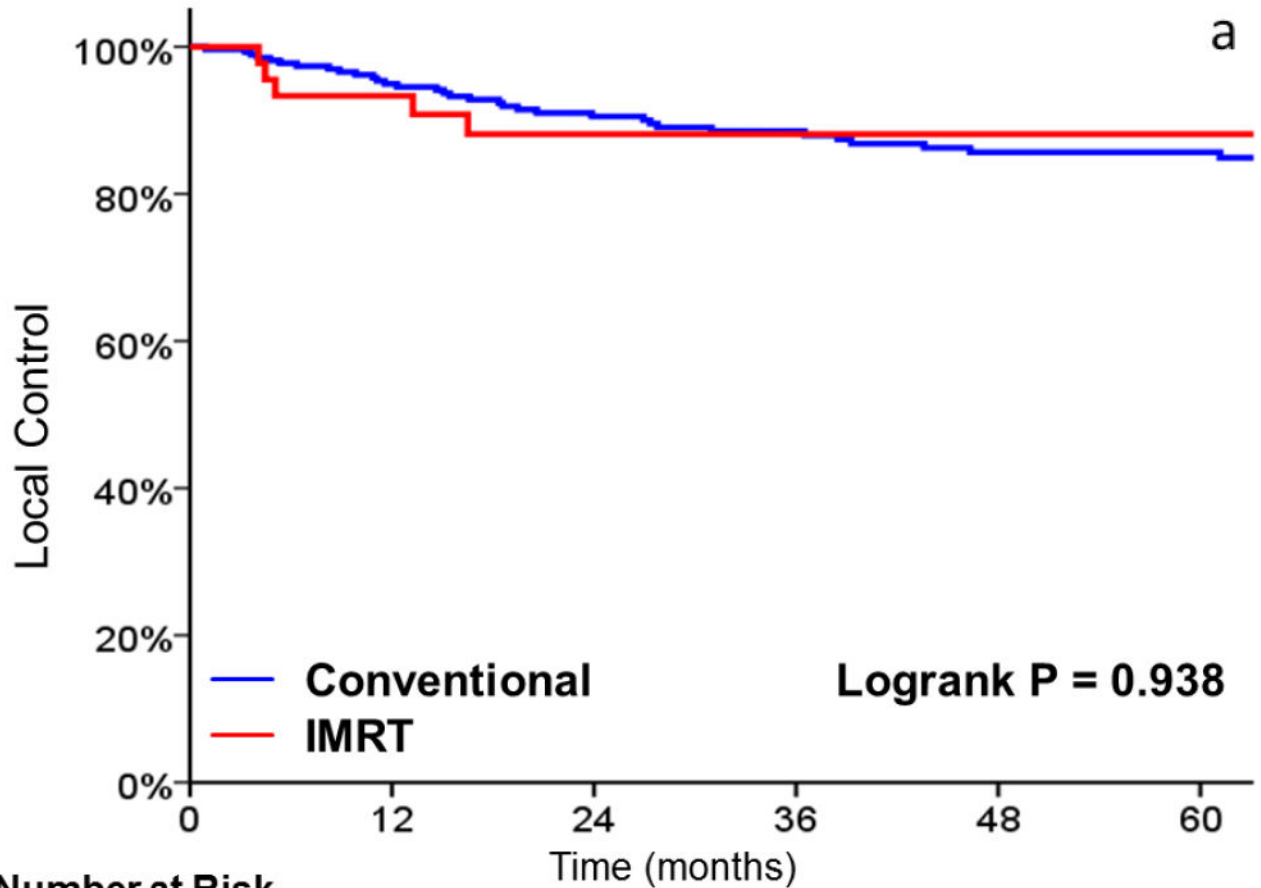
FIGURE 1.
A comparison of A) local control, B) larynx preservation rates, C) laryngectomy-free survival, D) distant metastasis, and E) overall survival in patients with T1 vs T2 glottic carcinoma undergoing definitive radiotherapy.
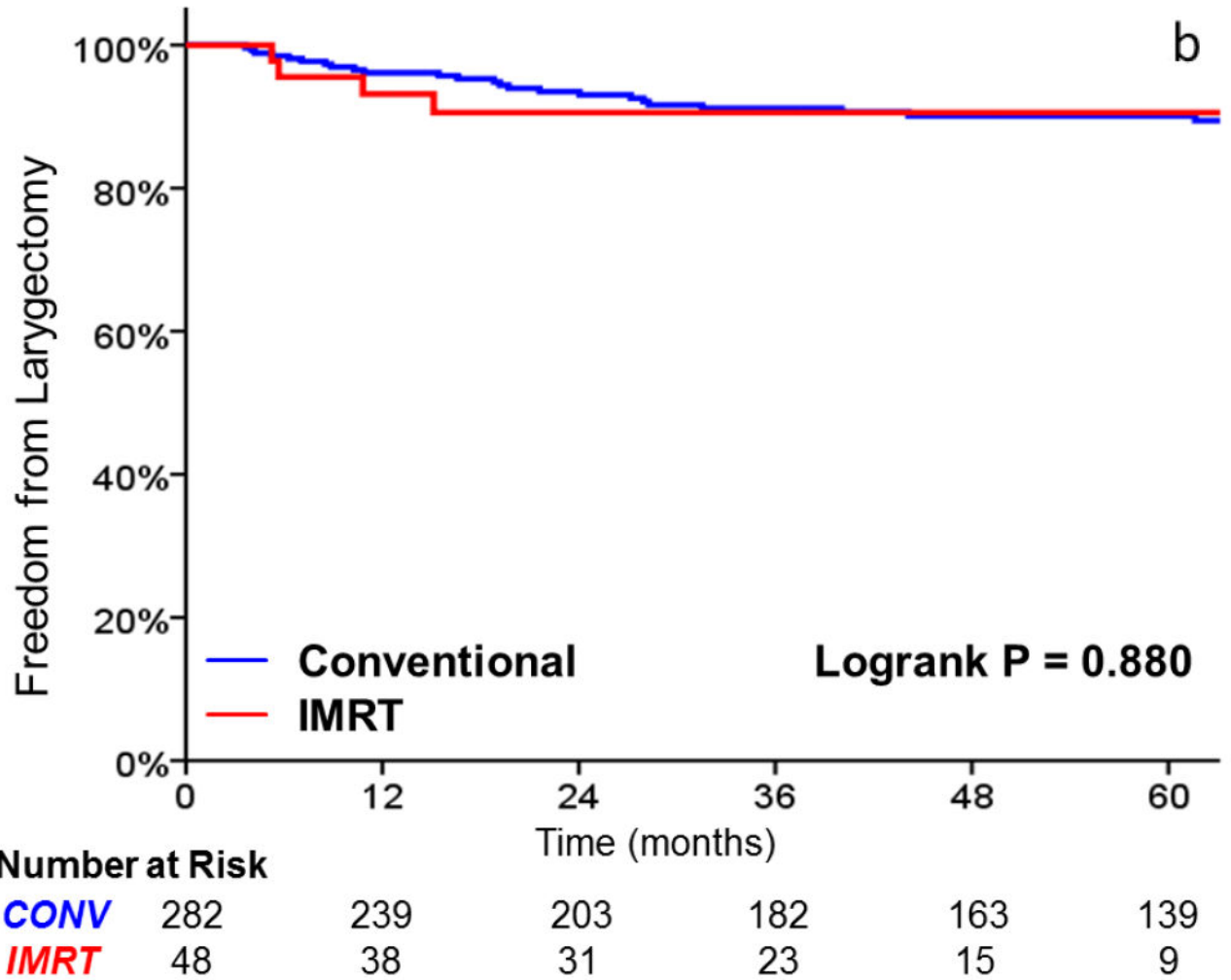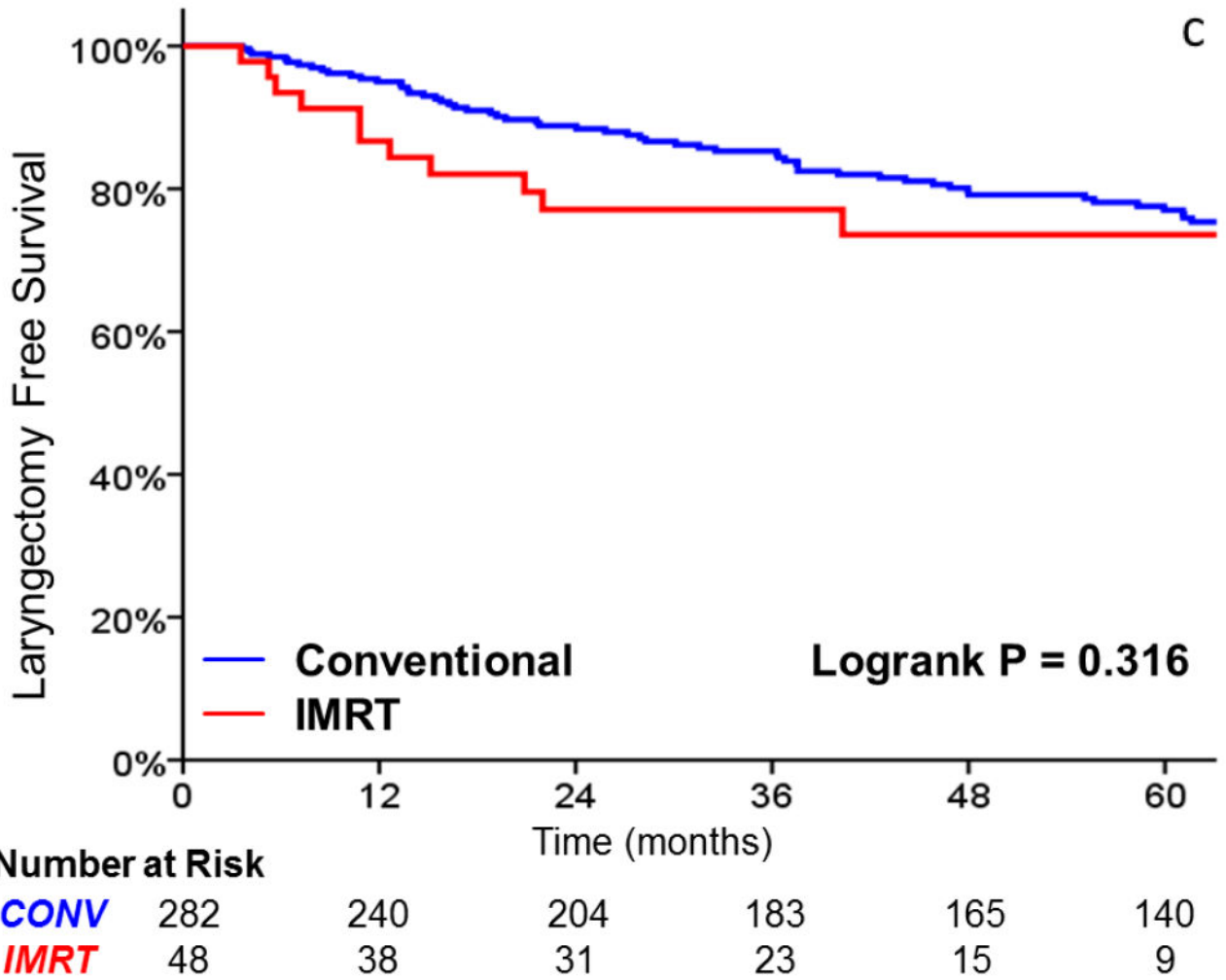
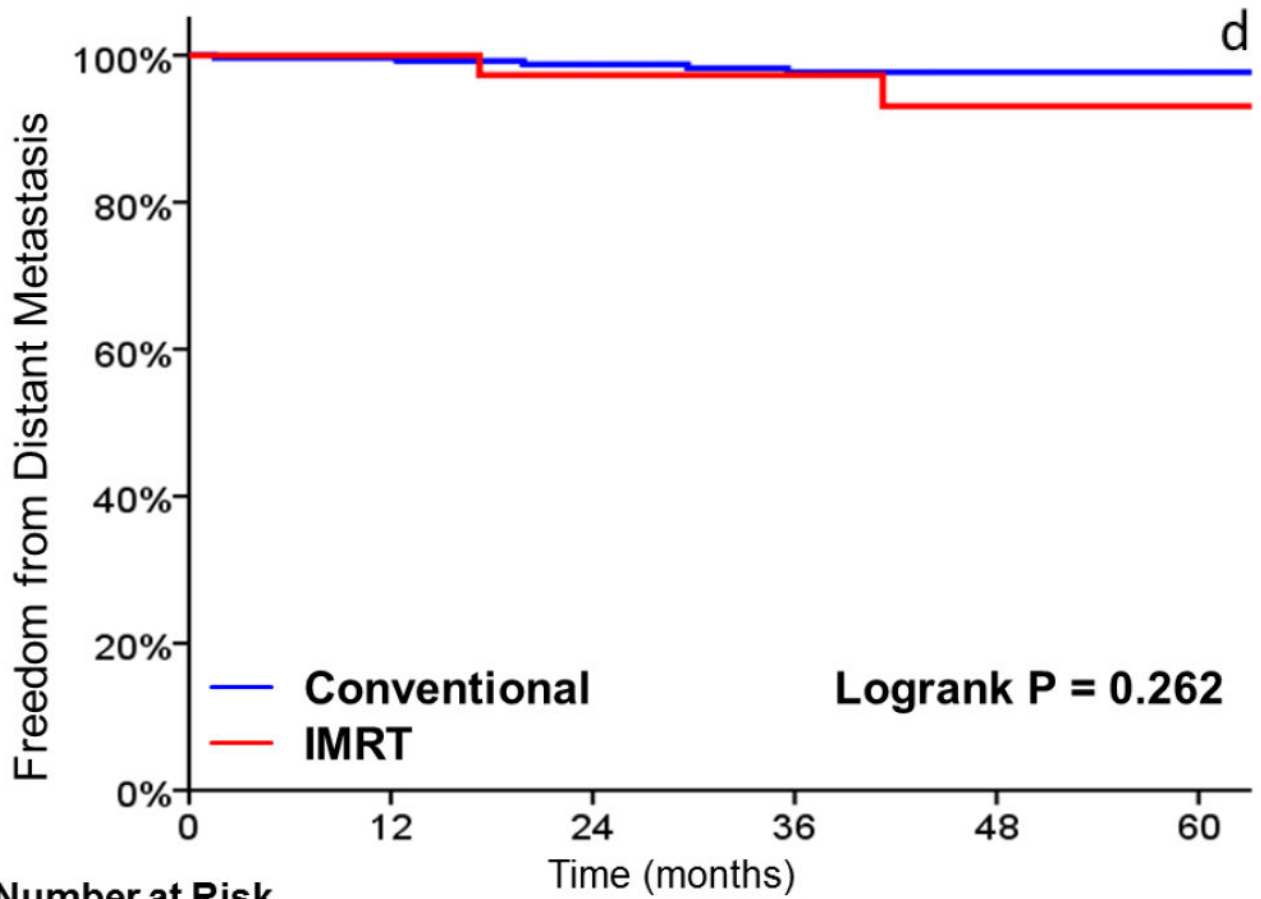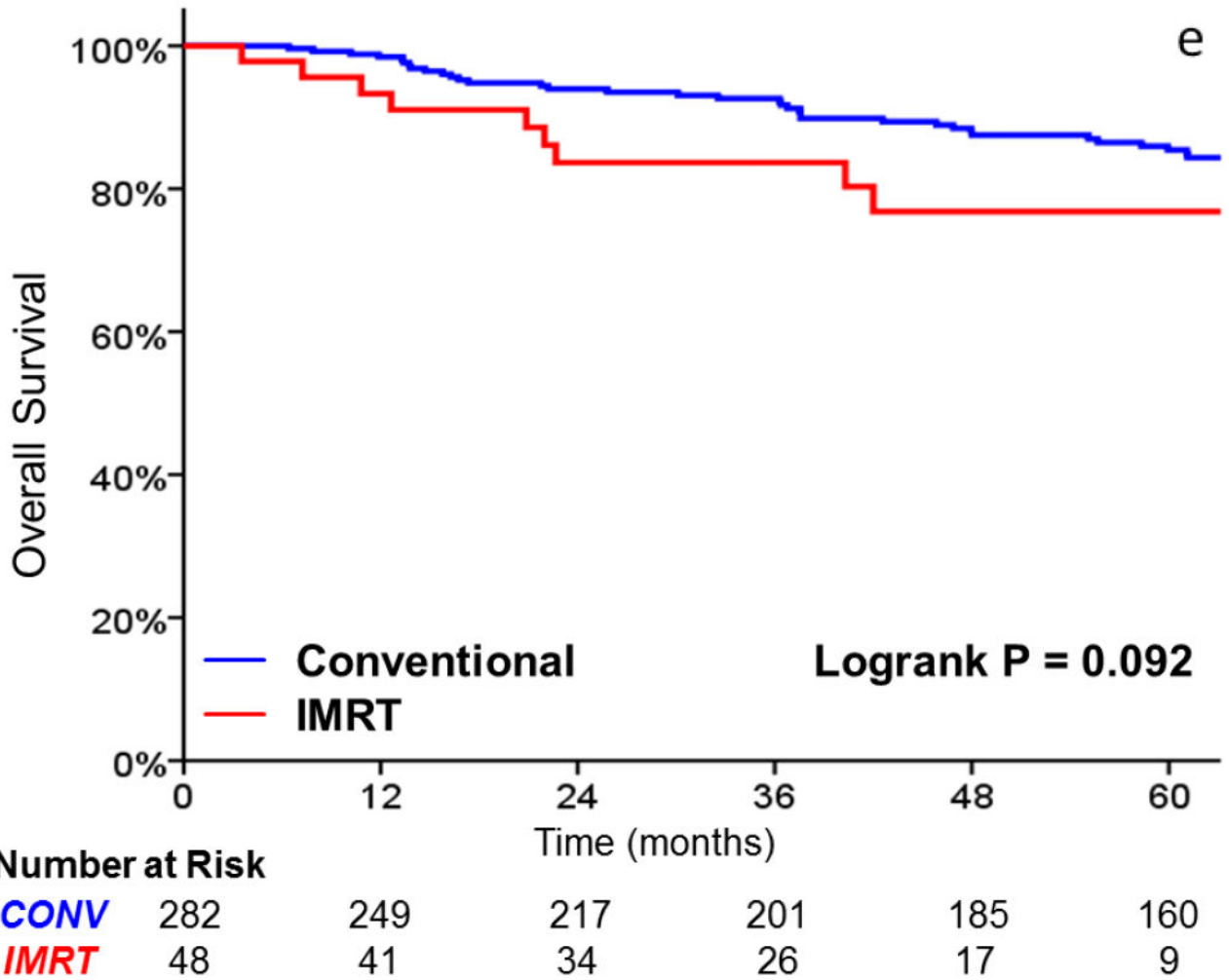**FIGURE 2.**
A comparison of A) local control, B) larynx preservation rates, C) laryngectomy-free survival, D) distant metastasis, and E) overall survival in patients undergoing intensity-modulated radiotherapy (IMRT) and conventional radiotherapy

TABLE 1

Clinical characteristics.

	IMRT	%	Conventional	%	Total	
Number of patients	48		282		330	
Median follow-up surviving (months)	44		66		59	
Time Period						P < .001
1989-1995	0	0%	59	20.9%	59	
1996-2005	0	0%	169	59.9%	169	
2006-2011	48	100%	54	19.1%	102	
Age						P = .237
Median (years)	65		68		68	
65	25	52.1%	121	42.9%	146	
>65	23	47.9%	161	57.1%	184	
Gender						P = .028
Male	37	77.1%	250	88.7%	287	
Female	11	22.9%	32	11.3%	43	
T-stage						P = .462
Tis	3	6.3%	13	4.6%	16	
T1	32	66.7%	212	75.2%	244	
T2	13	27.1%	57	20.2%	70	
T2 Subcategories						
Supraglottic extension	6	12.5%	14	5.0%	20	
Subglottic extension Impaired Cord	4	8.3%	31	11.0%	35	
Mobility	3	6.3%	12	4.3%	15	
Radiation dose						P < .001
Median dose (Gy)	63		66		66	
65.25 Gy or less	47	97.9%	85	30.1%	132	
66 Gy or more	1	2.1%	197	69.9%	198	
Fraction size						P < .001
200 cGy or less	0	0.0%	206	73.0%	206	
225 cGy	48	100.0%	77	27.3%	125	

	IMRT	%	Conventional	%	Total	
						P = .603
Smoking						
Yes	43	89.6%	245	86.9%	288	
No	5	10.4%	37	13.1%	42	

Abbreviation: Gy, Gray; IMRT, intensity-modulated radiotherapy.

Table 2

Dosimetric parameters for the 48 patients undergoing carotid sparing intensity modulated radiotherapy.

PTV Dmax (Relative)	
Median (range)	105% (103%-111%)
Mean	105%
Left Carotid Dose	
Median Dmean (range)	49.9 Gy (21.7-60.5 Gy)
Mean	48.3 Gy
Median V40Gy (range)	78.4% (46.7%-96.6%)
	3.4cc (1.4-7.8cc)
Median V50Gy (range)	64.1% (21.9-93.4%)
	2.8cc (1.0-6.7cc)
Right Carotid Dose	
Median Dmean (range)	47.9 Gy (20.5-61.5 Gy)
Mean	47.7 Gy
Median V40Gy (range)	75.4% (30.9%-96.3%)
	3.9cc (1.4-8.7cc)
Median V50Gy (range)	60% (10.7%-93.7%)
	2.9cc (1.1-6.3cc)

Abbreviations: cc, cubic centimeters; DMax, maximum dose; DMean, average dose; PTV, planning target volume; V40Gy/V50Gy, the volume of the carotid artery receiving at least 40Gy/50Gy.

TABLE 3

Cox proportional hazards univariate analysis of local control, laryngectomy-free survival (LFS), distant metastasis, and overall survival in T1-2N0 glottic carcinoma.

Univariate Analysis	Local Control		LFS		Distant Metastasis		Overall Survival	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
IMRT vs Conventional	0.96 (0.38-2.47)	0.938	1.39 (0.73-2.65)	0.318	2.47 (0.48-12.65)	0.278	1.85 (0.89-3.86)	.100
T2 vs. T1 stage	2.38 (1.26-4.49)	0.008	1.81 (1.16-2.83)	0.009	3.57 (0.88-14.40)	0.076	1.37 (0.83-2.25)	.215
Age	1.00 (0.97-1.02)	0.874	1.04 (1.01-1.05)	<0.001	1.07 (0.99-1.14)	0.068	1.07 (1.04-1.09)	<.001
Smoking (yes vs no)	0.45 (0.22-0.91)	0.027	1.19 (0.64-2.22)	0.583	0.48 (0.10-2.37)	0.365	1.80 (0.83-3.92)	.138
Gender (Male vs female)	1.18 (0.46-3.01)	0.729	1.14 (0.65-2.00)	0.649	0.51 (0.10-2.54)	0.409	1.01 (0.55-1.86)	.977
Fractionation (2.25 vs 2 Gy)	1.03 (0.54-1.96)	0.925	1.077 (0.684-1.696)	0.748	1.32 (0.30-5.77)	0.710	1.31 (0.78-2.22)	.312
Total dose	1.00 (0.999-1.001)	0.796	1.00 (1.000-1.001)	0.690	1.00 (0.998-1.004)	0.377	1.00 (0.999-1.001)	.836
Year of treatment	1.00 (0.95-1.06)	0.973	1.01 (0.97-1.05)	0.720	1.08 (0.93-1.26)	0.291	1.01 (0.97-1.06)	.605

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 4

Patterns of locoregional failures following definitive radiotherapy for early-stage glottic carcinoma.

	IMRT	Conventional
Patients with LRR	5	36
Site of first failure		
True vocal cord (isolated)	5 (1)	31 (17)
Ipsilateral cord only	5	17
Bilateral cords	0	14
Contralateral cord only	0	0
Supraglottic extension (isolated)	3 (0)	10 (1)
Subglottic extension (isolated)	4 (0)	10 (0)
Hypopharynx	0	1
Cervical lymph node (isolated)	2 (0)	4 (3)

Abbreviation: IMRT, intensity-modulated radiotherapy; LRR, locoregional recurrence.