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Original Article

Outcomes of Radiotherapy for Early–Stage Laryngeal Cancer: A 12–Year Retrospective Review.

Shehzad K [1,3], Alrajhi N [1]., Alwhaid M [1], Alnagmy A [1,4], Shehadeh M [1], Alsemali A [2], Gamal M [2], Aldehaim M [1,3]

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Simple Summary

This single–institution retrospective study from King Faisal Specialist Hospital and Research Center in Riyadh examined radiotherapy outcomes in 62 patients with early–stage laryngeal cancer (Tis, T1–T2 N0M0) treated between 2009–2021. The investigation compared three fractionation schedules: 60 Gy/25 fractions, 63 Gy/28 fractions, and 66 Gy/33 fractions, with hypofractionated regimens predominating (>90% of patients). Tomotherapy emerged as the preferred treatment technique (66.1% of cases). At 5–year follow–up, the study demonstrated promising outcomes with overall survival of 80.2%, local control of 80.5%, regional control of 96.77%, and cancer–specific survival of 84.6%. Despite the cohort's high smoking prevalence, these results align with international reports, supporting external beam radiotherapy as an effective and safe approach for early–stage laryngeal malignancies.

Background: Laryngeal cancer commonly originates in the glottic region and frequently presents at early stage (cT1–T2 N0M0, AJCC 8th edition). Both external beam radiation therapy (EBRT) and surgery demonstrate excellent efficacy as single–modality treatments for these early–stage malignancies.

Methods: We conducted a retrospective analysis of patients with early laryngeal carcinoma (Tis, T1–T2 N0M0) treated exclusively with External beam radiation therapy EBRT at King Faisal Specialist Hospital and Research Center in Riyadh from 2009–2021. Treatment consisted of one of three fractionation schedules (60Gy/25, 63Gy/28, or 66Gy/33) delivered via Tomotherapy, 3DCRT, or IMRT/VMAT. We evaluated demographic characteristics, risk factors, and multiple survival endpoints including local control, regional control, overall survival, and cancer–specific survival.

Results: The study comprised 62 patients (mean age: 60.4 years), predominantly male (90.3%) with high smoking prevalence (74.2%). All patients presented with voice hoarseness. Hypofractionated regimens were administered to over 90% of patients, with Tomotherapy being the most utilized technique (66.1%), followed by IMRT/VMAT (25.8%) and 3DCRT (8.1%). Treatment was well–tolerated with no grade 3–4 toxicities and manageable early side effects. The 5–year outcomes demonstrated favorable results: local control (80.5%), regional control (96.77%), overall survival (80.2%), and cancer–specific survival (84.6%).

Conclusion: Definitive radiotherapy has demonstrated efficacy and safety as a primary treatment modality for early–stage laryngeal cancer, consistent with prior studies. The outcomes from our cohort, despite the notably high prevalence of smokers, are comparable to international benchmarks, further confirming external beam radiotherapy's role as an effective therapeutic option for early–stage laryngeal carcinoma. Nonetheless, the significant smoking rates observed in our patient population highlight the critical need to incorporate smoking cessation strategies into comprehensive management plans to further enhance treatment outcomes and reduce risks

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Introduction

Malignant tumors of the larynx represent approximately 2% of all cancers worldwide, with an annual global incidence estimated around 151,000 new cases [1]. Although relatively uncommon compared to other malignancies, laryngeal cancer poses significant clinical and therapeutic challenges due to its potential impact on speech, swallowing, and quality of life. Epidemiological data indicate regional variations in the prevalence of laryngeal carcinoma. In Saudi Arabia, a retrospective review examining the distribution of head and neck (H&N) malignancies found that laryngeal cancer comprised approximately 6.7% of all head and neck cancer diagnoses[2]. Additionally, according to the Saudi Cancer Registry report from 2022, laryngeal carcinomas accounted for nearly 1.2% of all malignancies reported nationwide [3].

Laryngeal cancers, particularly those diagnosed at early stages involving the glottic region, typically demonstrate limited local invasiveness and low rates of regional or distant metastases at presentation. This characteristic makes early–stage glottic cancers particularly amenable to organ–preserving treatment strategies. Radiotherapy has emerged as a cornerstone of treatment, offering substantial advantages in preserving laryngeal function, voice quality, and overall quality of life for patients. When managed with radiotherapy alone, early–stage glottic carcinomas have consistently shown favorable survival rates, comparable to surgical interventions. Several treatment options are currently available for early–stage laryngeal cancer, including surgical approaches such as transoral laser microsurgery (using CO2 laser) and open partial laryngectomy, as well as non–surgical therapies primarily involving radiation treatment. A recent Cochrane systematic review evaluating outcomes of early–stage glottic cancer highlighted no definitive evidence favoring surgical procedures over radiotherapy in terms of local control or survival outcomes, suggesting that these modalities may be considered equivalent in terms of effectiveness [4].

In clinical practice, hypo–fractionated radiotherapy regimens—that is, radiotherapy delivered in fewer, larger–dose fractions—have become increasingly common for the treatment of early–stage glottic laryngeal carcinomas. Hypo–fractionation regimens offer convenience, shorter treatment duration, and potentially comparable efficacy to conventional fractionation schedules [5,6]. However, clinical outcomes, including local and regional control rates, vary according to the specific radiotherapy fractionation schedule used, necessitating further research to identify optimal strategies.

In the present study, we performed a retrospective review of patients diagnosed with early–stage (stage I and stage II) laryngeal carcinoma treated with radiotherapy at King Faisal Specialist Hospital and Research Center (KFSH & RC) in Riyadh, Saudi Arabia, from January 2009 through January 2021. Our primary objective was to analyze the outcomes of radiotherapy in terms of local and regional disease control, with specific attention given to comparing three distinct radiation fractionation regimens commonly employed in clinical practice. Through this analysis, we aim to provide valuable insights into the efficacy of different radiotherapy schedules, thereby contributing to evidence–based decisions in optimizing the management of early–stage laryngeal carcinoma.

Study Design and Methods

Study Setting and Population

This retrospective cohort study was conducted at King Faisal Specialist Hospital and Research Centre (KFSH&RC), a tertiary referral center located in Riyadh, Saudi Arabia. The study included 62 adult patients (age ≥18 years) diagnosed with early–stage squamous cell carcinoma (SCC) of the larynx (stage I and stage II) between January 2009 and January 2021. Patients were identified through the hospital's electronic medical records system. Selection criteria focused on patients who had comprehensive documentation available, including details regarding initial diagnosis, therapeutic interventions, and follow–up evaluations carried out at KFSH&RC.

Inclusion Criteria

Patients were eligible for inclusion if they met all the following criteria:

- Age ≥ 18 years at diagnosis.
- Pathologically confirmed diagnosis of squamous cell carcinoma (SCC) of the larynx.
- Received primary radiotherapy treatment at KFSH&RC.
- Availability of complete medical history, treatment data, and follow–up information in the hospital's medical records.

Exclusion Criteria

Patients were excluded from the analysis if any of the following conditions were met:

- Age < 18 years at diagnosis.
- Previous radiotherapy to the head and neck region for any reason.
- Presence of distant metastatic disease at the time of initial diagnosis.

- Diagnosis of a synchronous or prior second primary malignancy.

Data Collection and Variables

Patient demographic information (including age at diagnosis, gender, and smoking history), clinical characteristics (tumor stage, subsite, and histopathological details), radiotherapy treatment specifics (fractionation schedules, treatment techniques, and total radiation dose), and clinical outcomes (treatment response, acute side effects, local and regional control, survival status, and follow–up duration) were retrospectively collected from electronic medical records. Data extraction was conducted systematically by reviewing detailed medical charts, pathology reports, radiotherapy treatment plans, radiology reports, and laryngoscopy findings.

Statistical Analysis

Descriptive statistics were utilized to summarize baseline demographic and clinical characteristics of the patient cohort. Continuous variables were presented using means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate, while categorical variables were summarized using frequencies and percentages. Survival analyses, including local and regional control rates and overall survival (OS), were estimated using the Kaplan–Meier method, with survival curves constructed accordingly. To identify potential prognostic factors associated with survival outcomes, univariate and multivariable analyses were performed utilizing Cox proportional hazards regression models. Results were reported as hazard ratios (HR) with corresponding 95% confidence intervals (95% CI), and statistical significance was set at a p–value <0.05.

Treatment Details and Follow–up

Radiotherapy Techniques and Target Volume Definition:

A detailed retrospective review was conducted on 62 patients diagnosed with early–stage (stage I and II) laryngeal carcinoma who underwent definitive EBRT at KFSH&RC during the study period (2009–2021). All patients received EBRT delivered with head–and–neck thermoplastic masks to ensure consistent immobilization and reproducible positioning in the supine orientation. Radiotherapy techniques utilized primarily included intensity–modulated radiotherapy (IMRT) and tomotherapy. Additionally, a smaller subgroup of patients received three–dimensional conformal radiotherapy (3D–CRT).

Target volumes were defined according to standard institutional protocols and international guidelines for radiotherapy in early–stage laryngeal cancer. The gross tumor volume (GTV) included all visible gross disease



Figure 1: Tomotherapy planning image demonstrating optimal dose distribution with 95% of the prescribed 60 Gy (green isodose line) conformally covering the planning target volume, while bilateral carotid arteries receive 50% or more of the total dose (purple isodose line).

present at the level of the true vocal cords. The clinical target volume (CTV) was delineated to encompass the entire laryngeal structure, extending superiorly from the thyroid notch down to the inferior margin of the cricoid cartilage, thus covering all potential microscopic disease spread. Planning target volume (PTV) margins were subsequently added to account for setup uncertainties and internal organ motion: typically, margins were 3–5 mm in medial, lateral, and anterior–posterior directions, and slightly larger (5–10 mm) in the superior–inferior direction.

Fractionation Schedules:

Patients were stratified by tumor stage for radiation fractionation regimen selection:

Patients with T2 tumors received conventional fractionation at a total dose of 66 Gy delivered in 33 fractions (2 Gy per fraction).

Patients diagnosed with T1 tumors predominantly received hypo–fractionated radiotherapy at 60 Gy delivered in 25 fractions (2.4 Gy per fraction). A single patient with a T1 tumor received an alternative hypo–fractionation schedule of 63 Gy delivered in 28 fractions (2.25 Gy per fraction).

Carotid Artery Sparing Technique

Whenever feasible, carotid artery sparing techniques were applied prospectively during radiotherapy planning to minimize radiation exposure to the carotid vessels and reduce the risks of long–term cerebrovascular complications. For patients treated without initial carotid sparing, the carotid doses were retrospectively calculated by contouring bilateral carotid arteries on original radiation treatment plans.

Treatment Duration and Response Assessment:

The total duration of radiotherapy was calculated from the first day of radiation delivery to the final fraction. Any unplanned interruptions during radiotherapy were recorded, including their duration and reasons.

Clinical assessment of treatment response and acute toxicity was conducted weekly throughout the radiotherapy course. Post–treatment evaluation was systematically performed approximately 2–4 months after completing EBRT, utilizing either computed tomography (CT) imaging, direct laryngoscopic examination, or a combination of both modalities. Response criteria were based on radiological and endoscopic assessments, with complete response defined as the absence of any radiologic or endoscopic evidence of residual disease.

Patients underwent structured follow–up visits every 3 months for the first two years, every 6 months until 5 years, and annually thereafter. During follow–up, clinical examinations, direct laryngoscopy, and imaging studies were performed as indicated clinically, to assess disease recurrence, late toxicity, and overall patient status.

Toxicity and Outcome Measures:

Treatment–related toxicities, both acute and late, were assessed and graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) standard toxicity criteria. Acute toxicity was defined as side effects occurring during or within three months after completion of radiotherapy, while late toxicity was defined as side effects appearing or persisting beyond three months following treatment completion.

Clinical outcomes evaluated included treatment response, loco–regional control (LRC), and overall survival (OS). A complete response (CR) was defined as the absence of any clinical, radiological, or endoscopic evidence of residual disease after completion of radiotherapy. For patients presenting with lesions suspicious for persistent or recurrent disease, definitive diagnosis was confirmed through biopsy and subsequent histopathological examination.

Overall survival (OS) was calculated from the starting date of radiotherapy until the date of death from any cause or the date of the last follow–up visit for patients still alive. Loco–regional control (LRC) duration was calculated from date of radiotherapy until the first documented date of local or regional recurrence or disease progression. Patients without evidence of recurrence or progression were censored at the time of their last follow–up visit.

Prognostic Factors: The following prognostic factors were prospectively selected and analyzed for their potential influence on treatment outcomes (including overall survival and loco–regional control): Patient–related factors: age at diagnosis, gender and smoking history (current/former smoker vs. never smoked). Tumor–related factors: disease stage (T1 vs. T2), histopathological grading (well–differentiated, moderately differentiated, or poorly differentiated carcinoma), and anterior commissure involvement (present vs. absent). Treatment–related factors: radiotherapy fractionation regimen (fraction size: conventional vs. hypofractionated), total radiation dose delivered (Gy), and overall treatment duration (days)

Statistical analysis

Descriptive statistics summarized patient characteristics. Continuous variables were reported as means ± standard

deviations (SD), and categorical variables as frequencies and percentages. Time–to–event outcomes (overall survival, recurrence, and progression) were analyzed using Kaplan–Meier and Cox proportional hazards regression methods.

Kaplan–Meier Survival Analysis: Survival probabilities and rates at specific time points were calculated using the Kaplan–Meier estimator. Log–rank tests compared survival curves between groups carried out.

Cox Proportional Hazards Regression: to identify potential predictors of survival outcomes. Hazard ratios (HRs) and 95% confidence intervals (CIs) to quantify the effect of each predictor on the risk of events (e.g., death or recurrence). Both univariate (assessing each predictor individually) and multivariate (adjusting for confounders to assess independent effects) Cox regression analyses were performed.

Results

A total of 62 patients diagnosed with early–stage (stage I–II) laryngeal carcinoma who received definitive radiotherapy were included in this retrospective analysis. The mean age at diagnosis was 60.4 years. The majority of patients were males (90.3%, n=56), while females accounted for only 9.7% (n=6). Most patients (74.2%, n=46) reported a significant smoking history. Alcohol consumption was relatively uncommon, reported in only 3.2% (n=2) of patients.

Clinically, all patients (100%) initially presented with voice hoarseness as the primary symptom. Less common presenting symptoms included dysphagia in 4.8% (n=3), and odynophagia in 1.6% (n=1) of patients. All included cases were pathologically confirmed as squamous cell carcinoma (SCC), except for one patient (1.6%) who had carcinoma in situ (CIS). Histopathological differentiation revealed that 12.9% (n=8) of tumors were well–differentiated, 58.1% (n=36) were moderately differentiated, and 9.7% (n=6) were poorly differentiated. Anterior commissure involvement was present in 11.3% (n=7) of patients.

Upon clinical staging, all patients had no evidence of regional lymph node involvement (N0) or distant metastases (M0). Tumor stage distribution was as follows:

- Tis (carcinoma in situ): 1.6% (n=1)
- T1 tumors: 80.6% (n=50)
- T2 tumors: 17.7% (n=11)

Radiation Therapy Dose and Techniques

More than 90% of patients received hypofractionated radiotherapy regimens. Tomotherapy was the predominant radiation delivery technique, utilized in 66.1% (n=41) of cases, while the remainder underwent intensity–modulated radiotherapy (IMRT) or 3D conformal radiotherapy.

Patients received one of three radiotherapy fractionation schedules based on tumor stage and clinical considerations:

60 Gy delivered in 25 fractions (2.4 Gy per fraction): Administered to 80.6% of patients (n=50), predominantly those with T1 tumors.

66 Gy delivered in 33 fractions (2 Gy per fraction): Administered exclusively to patients with T2 tumors, comprising 17.7% of the cohort (n=11).

63 Gy delivered in 28 fractions (2.25 Gy per fraction): Administered to a single patient (1.6%) with a T1 tumor.

Side effects

In total, 62 patients underwent definitive radiotherapy and generally tolerated the treatment well, with manageable acute and late toxicities.

Acute Side Effects: The most frequently observed acute side effects included mucositis, dysphagia, and dermatitis, all predominantly mild to moderate in severity and within clinically acceptable ranges. Specifically, mucositis occurred in 93.4% (n=58) of patients and was graded as follows:, Grade 1 (mild): 67.7% (n=42), Grade 2 (moderate): 24.1% (n=15), Grade 3 (severe): 1.6% (n=1). Dysphagia was identified in 95.1% (n=59) of patients, with severity distribution: Grade 1 (mild): 80.6% (n=50), Grade 2 (moderate): 14.5% (n=9), No patient experienced dysphagia exceeding Grade 2. Dermatitis was documented in 95.2% (n=59) of cases, primarily mild: Grade 1 (mild): 88.7% (n=55), Grade 2 (moderate): 6.5% (n=4). Additionally, nearly half of the cohort (48.4%, n=30) experienced acute voice deterioration characterized by increased hoarseness during radiation therapy.

Late Side Effects: Late toxicities, defined as those occurring or persisting beyond three months after completion of radiotherapy, were infrequent but included:, Neck fibrosis: 1.6% (n=1), Persistent late dysphagia: 1.6% (n=1), Carotid artery stenosis: 1.6% (n=1), Radiation–induced hypothyroidism: 38.7% (n=24).

Secondary Malignancies

During routine clinical follow–up, which included imaging studies such as contrast–enhanced computed tomography (CT) or positron emission tomography–CT (PET–CT) prompted by clinical suspicion or symptoms, secondary malignancies were diagnosed in 19.4% (n=12) of patients. Among these secondary cancers, the following were observed: Lung cancer: 7 patients (all with a documented history of smoking and ongoing tobacco use), Thyroid cancer: 2 patients, Hepatocellular carcinoma: 2 patients, Urothelial carcinoma (bladder): 1 patient

Gender	Frequency (Percent)
Male	56 (90.3)
Female	6 (9.67)
Smoking	**Frequency (Percent)**
No	16 (25.8)
Yes	46 (74.19)
Hoarseness	**Frequency (Percent)**
Yes	62 (100)
Performa Status	**Frequency (Percent)**
0	18 (29)
1	34 (55)
2	10 (10)
Histopathology	**Frequency (Percent)**
Well differentiated Squamous cell carcinoma	8 (12.96)
Moderately differentiated Squamous cell carcinoma	36 (58.1)
Poorly Differentiated Squamous cell carcinoma	6 (9.7)
Squamous cell carcinoma with Sarcomatoid differentiation	2 (3.22)
Squamous cell carcinoma with no mention of differentiation	10 (16)
Tumor Stage (AJCC T staging)	**Frequency (Percent)**
Carcinoma in Situ (Tis)	1 (1.6)
T1	50 (80.6)
T2	11 (17.7)
Radiation Technique	**Frequency (Percent)**
3 D Conformal Radiation Therapy	5 (8.06)
IMRT and Rapid Arc	16 (25.8)
Tomotherapy	41 (66.1)
Fractionation schedules	**Frequency (Percent)**
60Gy in 25 fractions @ 2.4 Gy per fraction	50 (80.6)
63Gy in 28 fractions @2.25 Gy per fraction	1 (1.6)
66Gy in 33 fractions @2.0Gy per fraction	11 (17.7)

Table1: Baseline characteristics

Acute radiation effects	
Mucositis Grades	**Frequency (Percent)**
Grade 0	3 (4.83)
Grade 1	42 (67.74)
Grade 2	15 (24.1)
Grade 3	1 (1.6)
Dysphagia Grades	**Frequency (Percent)**
Grade 0	3 (4.83)
Grade 1	50 (80.6)
Grade 2	9 (14.5)
Dermatitis Grades	**Frequency (Percent)**
Grade 0	3 (4.83)
Grade 1	55 (88.7)
Grade 2	4 (6.45)
Hoarseness	**Frequency (Percent)**
No	32 (51.6)
Yes	30 (48.4)
Late Side effects	
Neck Fibrosis	**Frequency (Percent)**
No	61 (98.4)
Yes	1 (1.6)
Hypothyroidism	**Frequency (Percent)**
No	38 (61.3)
Yes	24 (38.7)
Carotid Stenosis	**Frequency (Percent)**
No	61 (98.4)
Yes	1 (1.6)
Second cancer	**Frequency (Percent)**
No	50 (80.6)
Yes	12 (19.4)

Table 2: Acute and late toxicity profile

Survival analysis

The median follow–up duration was 5.8 years, with an interquartile range of 3.7 to 8.3 years.

Survival outcomes for the cohort were analyzed using Kaplan–Meier methodology. The estimated 5–year overall survival (OS) rate was 80.2% (95% CI: 67.7%–88.3%). The local control rate at 5 years, defined as freedom from local recurrence, was 80.5% (95% CI: 67.0%–88.8%). Regional control rates were excellent, with a 5–year estimate

of 96.8% (95% CI: 87.7%–99.0%). Similarly favorable results were observed regarding distant metastasis–free survival, with a 5–year freedom from distant failure rate of 96.0% (95% CI: 85.0%–99.0%).

In terms of laryngeal preservation, the 5–year laryngectomy–free survival (LFS) was 80.0% (95% CI: 66.7%–88.6%). The cancer–specific survival (CSS) at 5 years was similarly favorable at 84.6% (95% CI: 72.5%–91.7%). Overall, these data indicate robust disease control and favorable long–term survival outcomes within this patient population.

Kaplan–Meier Overall Survival

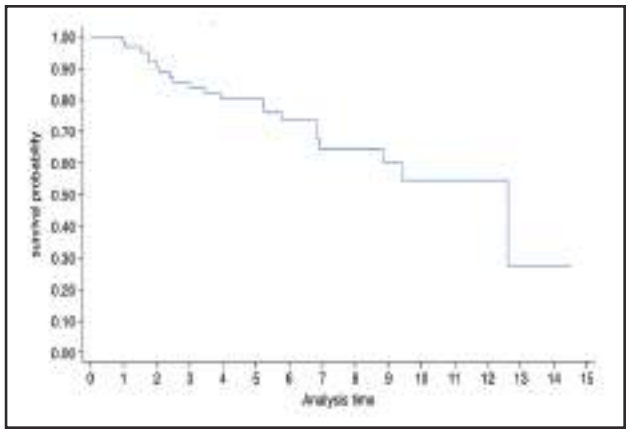


Figure 1: Showing overall survival (OS)

Kaplan–Meier Local Survival

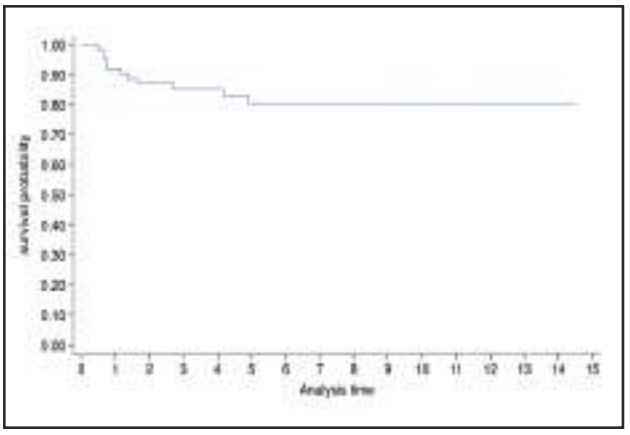


Figure 2: Showing Local control

Kaplan– Meier Regional Survival

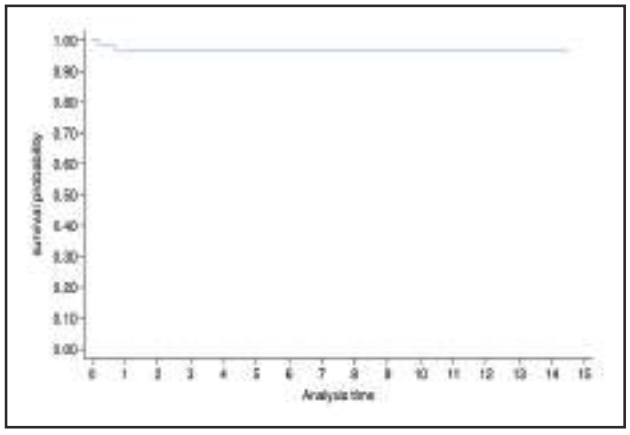


Figure 3: Showing regional control

Kaplan – Meier distant failure free Survival

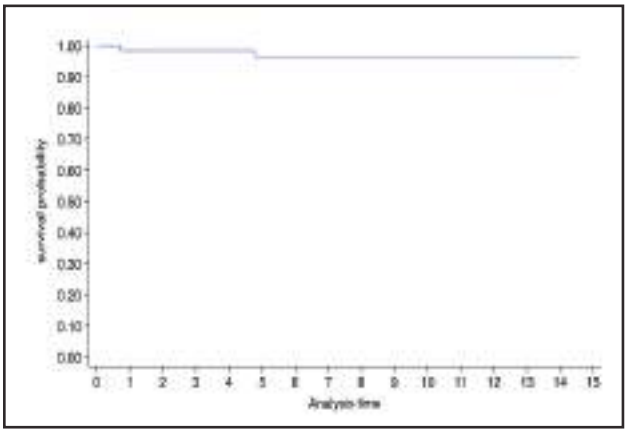


Figure 4: Showing distant control

Kaplan–Meier Laryngectomy free Survival

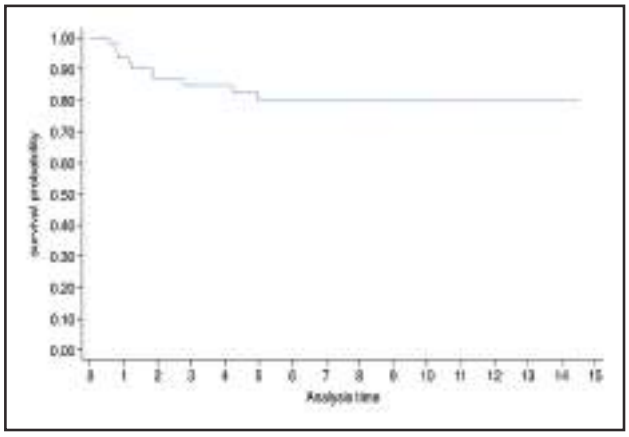


Figure 5: Showing Laryngectomy free survival

Kaplan–Meier Cancer Specific Survival

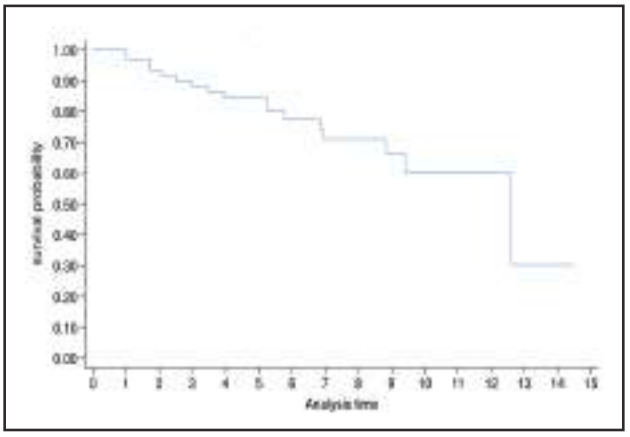


Figure 6: Showing Cancer specific survival

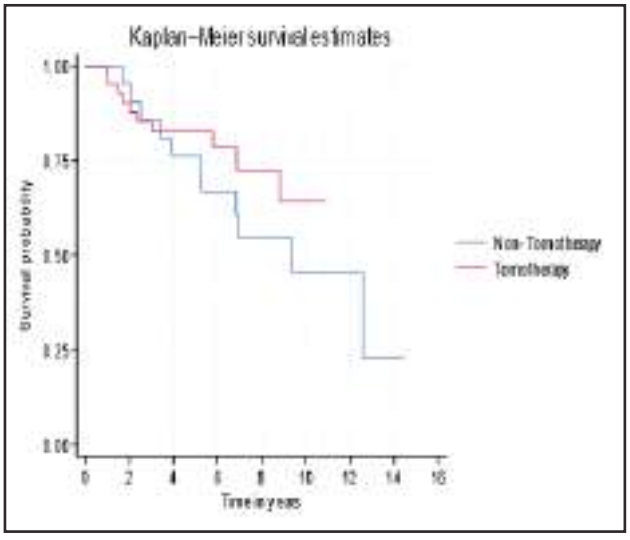
Comparison of Overall Survival by Radiotherapy Technique

The comparison of the impact of radiotherapy technique (Tomotherapy versus non–Tomotherapy) on overall survival outcomes was done using the log–rank test, no statistically significant difference was found between the two groups (Log–Rank chi–square = 1.05, p = 0.3062).

Figure below plots the estimated survival function for patients receiving the two treatments. The survival curves clearly show that Tomotherapy had slightly better survival experience than non–Tomotherapy patients.

Radio Therapy Technique	N	25th percentile	Median	75th percentile	p–value
Non–Tomo	21	5.2	9.4	12.6	0.3062
Tomo	41	6.9	–	–	

Table 3: Log–Rank Test Comparison of Overall Survival by Radiotherapy Technique



Discussion

Radiotherapy remains a cornerstone in the management of early–stage glottic cancer, offering excellent disease control while preserving organ function, particularly voice quality [8]. Unlike locally advanced laryngeal cancer, which typically requires combined modalities such as chemoradiation or extensive surgery, early–stage glottic carcinomas can be effectively managed with radiotherapy alone, achieving high rates of larynx preservation and favorable survival outcomes [9].

In the current study, the majority of patients (approximately 80%) received moderate hypo–fractionation regimens (specifically 60 Gy in 25 fractions), and nearly two–thirds (66%) underwent treatment utilizing Tomotherapy, reflecting contemporary practice patterns favoring advanced radiotherapy techniques.

Our study utilized three main fractionation schedules: 60 Gy in 25 fractions (predominantly for T1 tumors, n=50), 66 Gy in 33 fractions (exclusively for T2 tumors, n=11), and 63 Gy in 28 fractions (for a single T1 patient, n=1). While comparing outcomes between different fractionation schedules is of interest, a direct and statistically robust comparison within our cohort is significantly limited by several factors inherent to this retrospective analysis.

Firstly, the choice of fractionation schedule was almost entirely dictated by the tumor stage (T1 vs. T2), representing significant confounding by indication. The conventional fractionation (66 Gy/33 fractions) was reserved for the higher–risk T2 tumors, while hypofractionation (60 Gy/25 frcations) was used for the lower–risk T1 tumors. Consequently, any observed differences in outcomes between these groups would likely reflect the inherent prognostic differences between T1 and T2 stages rather than an independent effect of the fractionation schedule itself.

Secondly, the group sizes are highly imbalanced (50 vs. 11 vs. 1), severely limiting the statistical power required for meaningful comparative analyses, especially concerning toxicity profiles, which were generally low–grade across the entire cohort.

Thirdly, other potential confounding factors exist. While Tomotherapy was the predominant technique overall (66.1%), its precise distribution across the T–stage/fractionation groups was not uniform, potentially influencing outcomes independently. Furthermore, the high baseline smoking prevalence (74.2%) across the cohort is a known significant factor impacting local control and survival, making it difficult to isolate the effect of fractionation alone.

Therefore, while we report the outcomes achieved with these regimens, we caution against interpreting these results as a direct comparison of the fractionation schedules' efficacy due to these substantial confounding factors. The study's strength lies in demonstrating the overall effectiveness and safety profile of definitive radiotherapy, primarily utilizing hypofractionated Tomotherapy, within a real–world cohort characterized by a high prevalence of smokers.

Tomotherapy represents an innovative approach within the radiotherapy field, characterized by its unique capability to deliver intensity–modulated radiotherapy (IMRT) in a helical fashion. This technology employs intensity–modulated fan beams delivered continuously as the treatment gantry rotates around the patient (helical mode) or at fixed angles (direct mode), while the treatment couch simultaneously translates the patient through the beam. Tomotherapy–generated plans consistently

demonstrate high conformity to the target volumes, excellent dose homogeneity within tumor regions, and reduced radiation exposure to adjacent healthy structures and critical organs.These advantageous dosimetric characteristics are likely key contributors to improved local control rates, reduced toxicity, and enhanced quality of life observed in patients treated with this method.

Since its inception, Tomotherapy has undergone significant technological advancement. That includes, integration of sophisticated computational algorithms and image–guided radiotherapy (IGRT) capabilities [17]. Recent evidence highlights its significant role in organ preservation strategies for laryngeal cancer [18]. Chatterjee and colleagues, in a phase II prospective study, reported a 5–year local control rate of approximately 75.1% in early–stage laryngeal cancer patients treated with helical radiotherapy [19]. Bolukbas et al. similarly demonstrated favorable outcomes, reporting 3–year overall survival (OS) and disease–free survival (DFS) rates of 71.7% and 60.4%, respectively, in a heterogeneous group of laryngeal cancer patients treated definitively with helical Tomotherapy, regardless of tumor stage [20].

In our cohort, the 5–year local control rate of 80.5% aligns closely with previously published data, although slightly lower than some reported figures (85–95%) from studies evaluating definitive radiotherapy or conservative surgical treatments, such as transoral laser microsurgery and partial laryngectomy [4].As discussed, this modest discrepancy could be attributed primarily to the inclusion of T2 tumors (approximately 18% of our cohort, receiving 66 Gy/33 fx), as these lesions inherently carry a higher risk of local recurrence compared to T1 disease. Additionally, the high smoking prevalence (74%) and ongoing tobacco use among some patients during and after treatment likely contributed negatively to local control and potentially increased the risk of secondary malignancies, irrespective of the specific fractionation schedule used.

The 5–year overall survival of 80.2% observed in this study is consistent with previously published series, reflecting the favorable prognosis of early–stage glottic carcinoma. It is important to note that several deaths in our study were unrelated to the primary malignancy, reflecting competing comorbidities and the occurrence of secondary cancers. Cancer–specific survival at 5 years was favorable at 84.6%, comparable to other studies evaluating similar patient populations [9, 10].

Prophylactic irradiation of regional lymph nodes is typically omitted in early–stage glottic cancers due to their low propensity for regional spread. Consistent with this approach, our cohort received radiotherapy focused solely on the laryngeal glottic region, without elective nodal irradiation. Nevertheless, regional recurrences were infrequent, occurring in only two patients (3.3%), underscoring the validity of this selective approach. One patient with regional recurrence also experienced local recurrence, and another had a T2 lesion at initial presentation, suggesting a possible higher risk of nodal involvement with more advanced primary lesions. Our findings align closely with prior studies by Ermiş et al. [11] and Lim et al. [12], who reported regional recurrence rates of approximately 2–8% following definitive radiotherapy for early–stage glottic carcinoma.

Moderate hypofractionation (fraction sizes between 2.2 and 2.5 Gy) has been increasingly adopted due to convenience and reported efficacy, although potential concerns regarding increased acute toxicity remain [13, 14]. Contrary to this concern, our patient cohort demonstrated excellent tolerability. with acute toxicities predominantly classified as Grade 1 or 2, including dermatitis, dysphagia, and mucositis. Only one patient experienced severe (Grade 3) mucositis. Furthermore, late toxicities were minimal, and radiation–induced hypothyroidism emerged as the most frequent late effect, affecting approximately 39% of patients. This finding is noteworthy given the relatively small irradiated volume and absence of elective nodal irradiation. Kumar et al. previously reported hypothyroidism rates of 24% (subclinical) and 6% (clinical) following radiotherapy for early–stage glottic cancer [15]. The relatively higher rate observed in our study underscores the importance of routine endocrine follow–up and thyroid function screening post–treatment.

Conventional opposed–lateral beam radiotherapy historically used for early–stage laryngeal cancer, inherently exposes part of the thyroid gland and carotid arteries to relatively high radiation doses, potentially increasing the risk of hypothyroidism and cerebrovascular disease over time. Recent advances, including Volumetric Modulated Arc Therapy (VMAT), have demonstrated dosimetric advantages in sparing critical structures such as the thyroid gland and carotid arteries, potentially reducing long–term toxicities [16]. Given our findings, future studies investigating comparative dosimetry and clinical outcomes between Tomotherapy, VMAT, and other IMRT–based approaches may provide valuable insights to optimize treatment selection.

The limitations of our study merit acknowledgment. First, the retrospective nature of the analysis inherently introduces selection bias and limitations in data completeness and accuracy. As highlighted earlier, this design also prevents definitive conclusions regarding the comparative efficacy of the different fractionation schedules due to significant confounding by T–stage. Second, our cohort size was relatively small, potentially limiting statistical power to detect subtle differences

or identify additional prognostic factors. Third, comprehensive long–term data on certain late toxicities, particularly functional outcomes such as voice quality and swallowing ability, were not systematically collected, highlighting future areas for prospective investigation.

In conclusion, definitive radiotherapy, particularly using advanced techniques such as Tomotherapy with moderate hypofractionation for T1 lesions and conventional fractionation for T2 lesions, provides robust local and regional control, favorable survival outcomes, and acceptable toxicity profiles in patients with early–stage glottic carcinoma, even within a population with high smoking rates. Continued efforts toward patient education, smoking cessation, and regular post–treatment surveillance are critical components of comprehensive care, aimed at improving long–term outcomes and quality of life for this patient population.

References

1. Feng Y, Wang B, Wen S. Laser surgery versus radiotherapy for T1–T2N0 glottic cancer: a meta–analysis. *ORL J Otorhinolaryngol Relat Spec*. 2011;73(6):336–42. doi: 10.1159/000327097. Epub 2011 Oct 15. PMID: 22005723.
2. Akhtar SS, Ijaz AI, Fadl FA, Oyetunji NM. Head and neck cancer in the central region of Saudi Arabia. *Saudi Med J*. 2003 Jun;24(6):688–90. PMID: 12847610.
3. Bazarbashi S, Al Eid H, Minguet J. Cancer Incidence in Saudi Arabia: 2012 Data from the Saudi Cancer Registry. *Asian Pac J Cancer Prev*. 2017 Sep 27;18(9):2437–2444. doi: 10.22034/APJCP.2017.18.9.2437. PMID: 28952273; PMCID: PMC5720648.
4. Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1–T2 glottic carcinomas. *Cancer*. 2004 May 1;100(9):1786–92. doi: 10.1002/cncr.20181. PMID: 15112257.
5. Mendenhall WM, Amdur RJ, Morris CG, Hinerman RW. T1–T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. *J Clin Oncol*. 2001 Oct 15;19(20):4029–36. doi: 10.1200/JCO.2001.19.20.4029. PMID: 11600604.
6. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys*. 2006 Jan 1;64(1):77–82. doi: 10.1016/j.ijrobp.2005.06.014. Epub 2005 Sep 19. PMID: 16169681.
7. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995 Mar 30;31(5):1341–6. doi: 10.1016/0360–3016(95)00060–C. PMID: 7713792.
8. Mendenhall WM, Parsons JT, Million RR, Fletcher GH. T1–T2 squamous cell carcinoma of the glottic larynx treated with radiation therapy: relationship of dose–fractionation factors to local control and complications. *Int J Radiat Oncol Biol Phys*. 1988 Dec;15(6):1267–73. doi: 10.1016/0360–3016(88)90220–9. PMID: 3143690.
9. Lohynska R, Slavicek A, Bahanan A, Novakova P. Predictors of local failure in early laryngeal cancer. *Neoplasma*. 2005;52(6):483–8. PMID: 16284693.
10. Yiotakis J, Stavroulaki P, Nikolopoulos T, Manolopoulos L, Kandiloros D, Ferekidis E, Adamopoulos G. Partial laryngectomy after irradiation failure. *Otolaryngol Head Neck Surg*. 2003 Feb;128(2):200–9. doi: 10.1067/mhn.2003.63. PMID: 12601315.
11. Ermiş E, Teo M, Dyker KE, Fosker C, Sen M, Prestwich RJ. Definitive hypofractionated radiotherapy for early glottic carcinoma: experience of 55Gy in 20 fractions. *Radiat Oncol*. 2015 Sep 23;10:203. doi: 10.1186/s13014–015–0505–6. PMID: 26395876; PMCID: PMC4580345.
12. Lim YJ, Wu HG, Kwon TK, Hah JH, Sung MW, Kim KH, Park CI. Long–term outcome of definitive radiotherapy for early glottic cancer: prognostic factors and patterns of local failure. *Cancer Res Treat*. 2015 Oct;47(4):862–70. doi: 10.4143/crt.2014.203. Epub 2015 Feb 13. PMID: 25687859; PMCID: PMC4614182.
13. Benson R, Prashanth G, Mallick S. Moderate hypofractionation for early laryngeal cancer improves local control: a systematic review and meta–analysis. *Eur Arch Otorhinolaryngol*. 2020 Nov;277(11):3149–3154. doi: 10.1007/s00405–020–06012–9. Epub 2020 May 6. PMID: 32377855.
14. Salas–Salas BG, Domínguez–Nuez DJ, Cabrera R, Ferrera–Alayón L, Lloret M, Lara PC. Hypofractionation vs. conventional radiotherapy fractionation in the conservative treatment of T1 glottic cancer: a prospective cohort study. *Clin Transl Oncol*. 2020 Jan;22(1):151–157. doi: 10.1007/s12094–019–02118–7. Epub 2019 Jun 1. PMID: 31152306.
15. Kumar S, Moorthy R, Dhanasekar G, Thompson S, Griffiths H. The incidence of thyroid dysfunction following radiotherapy for early stage carcinoma of the larynx. *Eur Arch Otorhinolaryngol*. 2011 Oct;268(10):1519–22. doi: 10.1007/s00405–011–1504–3. Epub 2011 Feb 16. PMID: 21328003.
16. Kim ES, Yeo SG. Volumetric modulated arc radiotherapy sparing the thyroid gland for early–stage glottic cancer: A dosimetrical analysis. *Oncol Lett*. 2014 Jun;7(6):1987–1991. doi: 10.3892/ol.2014.2039. Epub 2014 Apr 4. PMID: 24932276; PMCID: PMC4049699.
17. Mackie TR. From model–based dose computation to tomotherapy. *Med Phys*. 2023;50(Suppl 1):70–73. doi: 10.1002/mp.17301.

18. Katano A, Yamashita H. Clinical outcomes of curative intent radiotherapy by helical tomotherapy for laryngeal squamous cell carcinoma: A retrospective analysis in a tertiary referral center. *World J Oncol*. 2024;15(1):136–142. doi: 10.14740/wjon1638.

19. Chatterjee S, Mallick I, Chakraborty S, Prasath S, Arunsingh M, Achari RB, Arun B, et al. Helical radiotherapy in early laryngeal cancers could lead to excess local recurrence: lessons from a phase II prospective study. *Clin Oncol (R Coll Radiol)*. 2020;32(2):e67–e75. doi: 10.1016/j.clon.2019.11.004.

20. Bolukbas MK, Turna M, Karaca S, Basaran H. Results of radiotherapy in squamous cell laryngeal cancer: A tomotherapy center experience. *Indian J Cancer*. 2022;59(3):330–336. doi: 10.4103/ijc.IJC_682_21