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Radiotherapy in the Management of Glottic Squamous Cell Carcinoma

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Abstract

Introduction: Our purpose is to review the role radiotherapy (RT) in the treatment of glottic squamous cell carcinoma (SCC).

Methods: A concise review of the pertinent literature.

Results: RT cure rates are: Tis- T1N0, 90%-95%; T2N0, 70%-80%; low volume T3-T4a, 65-70%. Concomitant cisplatin is given for T3-T4a SCCs. Severe complications occur in 1%-2% for Tis-T2N0 and 10% for T3-T4a SCCs. Patients with high volume T3-T4 SCCs undergo total laryngectomy, neck dissection and postoperative RT. Those with positive margins and/or extranodal extension (ENE) receive concomitant cisplatin. The likelihood of local-regional control at 5 years is 85%-90%. Severe complications occur in 5%-10%.

Conclusion: RT is a good treatment option for patients with Tis-T2N0 and low volume T3–T4a glottic SCCs. Patients with higher volume T3-T4 cancers are best treated with surgery and postoperative RT.

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Introduction

Squamous cell carcinoma (SCC) of the glottic larynx is treated with surgery, radiotherapy (RT), or a combination of the two modalities depending on the extent of the disease and the condition and wishes of the patient.[1-6] Concomitant cisplatin is often given with definitive RT for those with T3-T4 cancers as well as in the postoperative setting for patients with positive margins and/or extranodal extension (ENE).[7-12] Following is a concise discussion of the role of RT in the treatment of patients with glottic SCC that reflects the philosophy of the authors and not solely the institutional policies of the first author. Patients were staged according to the recommendations of the American Joint Commission on Cancer (AJCC) staging system.[13, 14] Patients with T1 tumors were stratified into those with SCC involving one (T1a) versus both (T1b) vocal cords. Patients with T2 SCCs were stratified into those with normal mobility (T2a) and those with impaired mobility (T2b). T3 denotes vocal cord fixation; a recent modification of the AJCC staging system upstages T2 lesions to T3 based solely on paraglottic space invasion which, in our estimation, results in stage migration.[13-15]

Carcinoma in situ (Tis)

The preferred treatment for patients with glottic Tis is transoral CO2 laser excision of the lesion provided that the lesion is suitable for complete resection with such a procedure.[16] Patients with Tis of both vocal cords plus the anterior commissure may not be candidates for transoral surgery and are treated with RT using fields encompassing only the larynx with parallel opposed fields or intensity modulated

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radiotherapy (IMRT).[17, 18] The National Comprehensive Cancer Network (NCCN) guidelines include 60.75 Gy at 2.25 Gy per fraction or 66 Gy at 2 Gy per fraction. An alternative would be to use the same dose fractionation schedule used for T1N0 SCCs which is 63 Gy at 2.25 Gy per once daily fraction. The field borders for parallel opposed fields are mid thyroid notch superiorly, the bottom of the cricoid cartilage inferiorly, falling off anteriorly, and 1 cm posterior to the thyroid ala posteriorly (**Figure 1**). The fields are weighted 3:2 towards the side of the lesion if it is lateralized. Most Tis and T1 cancers are in the anterior 1/3rd of the cord. The standard technique is using lateral wedges, typically 30 degrees, to achieve homogeneous dose distribution across the glottis. However, shifting the hot spot anteriorly by under-wedging or even omitting the wedges may be beneficial, increasing the tumor dose and decreasing the dose to the posterior non-involved cord and arytenoids.

Alternatively, the gross tumor volume (GTV)-clinical target volume (CTV)-planning target volume (PTV) concept, according to the International Commission on Radiation Units recommendation and recently reached international consensus,[19, 20] can be followed and patients can be treated with more sophisticated RT techniques, i.e. IMRT or volumetric arc therapy to reduce the dose to the carotid arteries and lower the likelihood of accelerating atherosclerosis.[21-23] There are data suggesting that if IMRT is employed that the image-guidance protocols should match to laryngeal tissue rather than bone.[17, 18] The potential disadvantages include an increased risk of a marginal miss if the target volume is too tight and increased dose heterogeneity which could increase the risk of a complication. Also, the utility of this approach is unknown, taking into account the relatively short length of the irradiated artery in glottic cancer. For example, the Madison group[24] found no differences in vascular events

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between elderly early glottic cancer patients who received standard RT or surgery. On the other hand, treating single cord in T1 glottic cancer using image-guided radiotherapy (IGRT) has a potential to reduce edema and improve voice quality. The Erasmus Cancer Center in Rotterdam conducted a careful study of laryngeal movement during respiration and designed single-cord RT plans using each patient's glottic movements based on cone-beam CT to define margins around the treated cord.[25] Using hypofractionation (to reduce the logistic complexity of the treatment), they reported good results and no complications in 30 patients.[26] However, the complexity of this treatment, the high biological equivalent dose, and the generally excellent outcome of standard RT makes this approach questionable. It should not be considered outside of a careful clinical study. Patients with recurrent Tis after one or more prior excisions are treated with RT because additional excisions are likely to cause additional deterioration of voice quality.

Sengupta et al reported on 37 patients treated at the University of Florida (UF) between 1967 and 2005; 23 of 37 (62%) had one or more prior vocal cord strippings.[5] All patients were treated with once daily fractionation to a median dose of 60 Gy (range, 56.25 to 66.5 Gy) at a median dose per fraction of 2.25 Gy (range, 2.2 to 2.6 Gy). Mean follow-up for all patients was 9.5 years (range, 8 months to 25 years) and mean follow-up for survivors was 8.6 years (range, 2.5 to 25 years).

Four patients developed a local recurrence at 6 months, 12 months, 48 months, and 13 years. The 5-year local control rate after RT was 91%. It is possible and, perhaps likely, that the "recurrence" at 13 years was a second primary cancer. One patient was salvaged with transoral CO2 laser resection and 2

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patients were salvaged with a total laryngectomy. The patient who developed a recurrence at 13 years declined salvage. No patient developed a regional or distant recurrence. The 5-year overall and cause specific survival rates were 83% and 100%, respectively. No patient developed a severe complication. The outcomes from 6 additional institutions are outlined in Table 1. Ultimate local control is defined as successful surgical salvage after a local recurrence. The local control rates are essentially the same as what one would expect after RT for T1N0 glottic SCC.

T1-T2N0 SCC

The treatment of T1-T2N0 glottic SCCs is either transoral laser excision or RT.[27] The treatment of choice varies with the extent of the lesion, the philosophy and expertise of the treating physicians, and the desires of the patient. In general, the more extensive the lesion, the more likely that RT will be selected. Patients with T1 SCCs were stratified into those involving one cord (T1a) and two cords (T1b). Patients with T2 cancers are those with extension off of the vocal cords and/or impaired vocal cord mobility. Although not part of the American Joint Committee on Cancer (AJCC) staging system, some stratify T2 lesions into those with normal (T2a) and impaired (T2b) vocal cord mobility.[28] The reason for this stratification is because those with impaired vocal cord mobility are more likely to recur locally after RT and may benefit from more aggressive treatment.

The RT treatment volume includes the primary site; the likelihood of regional lymph node metastases is low and elective neck irradiation is not employed.[6, 29] The treatment technique for T1N0 SCCs is the same as described above for Tis lesions. The treatment volumes for T2N0 SCCs are modified depending

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on the extent of the lesions. As previously discussed, IMRT may considered to reduce the dose to the carotid arteries.[6, 21] As previously noted, if partial laryngeal IMRT is employed, it is important match to the soft tissues rather than the cervical spine for precise targeting because the larynx moves relative to the bone and because spinal cord dose is low and away from the high dose target so that adjusting to vocal cord position would be unlikely to result in vocal cord overdose.[18] The NCCN guidelines for T1N0 SCCs include 63 Gy at 2.25 Gy per fraction (preferred), 66 Gy at 2 Gy per fraction, 50 Gy at 3.12 Gy per fraction, or 52 Gy at at 3.28 Gy per fraction. There are data suggesting that this 66 Gy at 2 Gy per fraction yields inferior outcomes compared moderately hypofractionated schedules.[30] NCCN guidelines for T2N0 SCCs include 65.25 Gy at 2 Gy per fraction and 70 Gy at 2 Gy per fraction. There are data from the Christie Hospital suggesting that 52 Gy at 3.28 Gy per fraction is another reasonable alternative.[31] The DAHANCA 6 randomized trial comparing 5 vs 6 fractions per week to 62 to 68 Gy at 2 Gy per fraction showed significantly improved local-regional control for the accelerated arm.[32]

Chera et al reported on 585 patients treated with definitive RT at UF between 1964 and 2006 for T1-T2N0 glottic SCCs.[6] Stage distribution was: T1a, 253 patients; T1b, 72 patients; T2a, 165 patients; and T2b, 95 patients. All patients had a minimum potential follow-up of 2 years. Patients were excluded if they had synchronous primaries or received adjuvant chemotherapy which was essentially not recommended during this time period. No patient received elective neck irradiation. The median and mean follow-up for living patients were 12.3 years and 14.3 years, respectively. Fourteen patients were lost to follow-up. Three patients were lost to follow-up less than 3 years from RT and were coded as

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dead with disease. The remaining 11 patients lost to follow-up had been followed for at least 5 years and were continuously disease-free.

The local control rates after RT and the ultimate local control rates including patients successfully salvaged after a local recurrence are depicted in **Figures 2 and 3**. The 5-year neck control rates for patients who remained continuously disease-free at the primary site were: T1a, 100%; T1b, 100%; T2a, 98%; and T2b, 94%. The 5-year rates of distant metastases-free survival were: T1a, 99%; T1b, 99%; T2a, 99%; and T2b, 94%. The 5-year cause specific survival rates were: T1a, 97%; T1b, 99%; T2a, 94%; and T2b, 90%. The 5-year overall survival rates were: T1a, 82%; T1b, 83%; T2a, 76%; and T2b, 78%. Ten patients (1.7%) experienced severe or fatal complications. One patient was hospitalized briefly during twice daily RT for severe mucositis. Two patients underwent a total laryngectomy for suspected local recurrence and no tumor was found in the specimen. Three patients with T2 tumors developed severe laryngeal edema necessitating a permanent tracheostomy. One patient who developed a local recurrence and underwent a salvage total laryngectomy experienced a pharyngo-cutaneous fistula. Two patients required permanent gastrostomies. One patient developed a fatal carotid artery angiosarcoma.

Robert et al reported on patients with T1-T2N0 SCCs treated with RT between 1987 and 2015 at 4 institutions in western France.[33] The 5-year outcomes were: local control, 87%; cause-specific survival, 95%; and laryngectomy-free survival, 88%. Two patients (0.8%) required a tracheostomy for tracheal stenosis. Cho et al reported on 160 patients with T1N0 SCCs treated between 2005 and 2016 with IMRT (23 patients) or 3 dimensional conformal RT (3DCRT) (137 patients) at the Memorial Sloan Kettering

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Cancer Center and observed the following 3-year local control rates: IMRT, 94%; 3DCRT, 91%; and overall, 91%.[22] Trotti et al reported on the Radiation Therapy Oncology Group (RTOG) 9512 trial where 239 patients with T2 glottic SCCs were stratified by substage (T2a vs T2b) and randomized to receive hyperfractionated RT (HFX) 79.2 Gy at 1.2 Gy twice daily or standard fractionation (SFX) 70 Gy in 35 once daily fractions.[34] Median follow-up was 7.9 years. The 5-year local control rates were 78% after HFX and 70% after SFX (p=0.14). Late effects were similar.

Rock et al reported on 139 patients with T2N0 SCCs treated between 2006 and 2013 with hypofractionated IMRT 60 Gy in 25 fractions over 5 weeks or moderately accelerated IMRT 66-70 Gy in 33-35 fractions over 5.5-6 weeks since 2010.[18] The image guided RT (IGRT) surrogate changed from cervical bone to laryngeal soft tissue in 2008. The 3 year local control rates for 3 sequential cohorts were: hypo fractionated RT matched to bone, 70%; hypofractionated RT matched to larynx, 80%; and accelerated RT matched to larynx, 89% (P = 0.02).

Bhateja et al reported on 84 patients treated for T2-T3 glottic SCCs.[35] Patients with T2a-T2b lesions received RT alone while those with T2b-3N0-2 SCCs received chemoradiation (CRT). The 3-year local control rates were: T2aN0, 95%; T2bN0, 73% after RT alone; and CRT, 92%. There are limited data pertaining to stereotactic ablative body radiosurgery (SABR) which appears no better, depending on the fractionation schedule, than conventionally fractionated RT.[36, 37] The outcomes after RT from 7 additional institutions are depicted in Table 2.

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T3-T4 SCC

The treatment of T3-T4 glottic SCCs are either surgery, which usually consists of a total laryngectomy and neck dissection, followed by postoperative RT or definitive RT and concomitant cisplatin (chemoRT).[1-4, 11, 12, 38] Patients with T3 SCCs are those with vocal cord fixation and almost all have subglottic extension and are at risk for level 6 lymph node metastases which are not routinely resected as part of a laryngectomy. Although some patients with low volume tumors may be suitable for a partial laryngectomy, these patients are also good candidates for chemoRT and, because some patients undergoing a partial laryngectomy would likely require postoperative RT, the functional outcome after successful chemoRT would probably be better. Patients who are suitable for chemoRT are those with unilateral cord involvement, low volume (3.5 cc or less calculated diagnostic contrast enhanced computed tomography), and a good airway.[39] Patients with more advanced T3-T4 SCCs are best treated with total laryngectomy and neck dissection followed by postoperative RT/chemoRT.[2] However, those without destruction of cartilage framework, significant base of tongue involvement, and no baseline laryngeal dysfunction can also be candidates for organ preservation treatment provided that the tumor shrinks significantly and/or mobility of the larynx restores after a few cycles of induction chemotherapy, confirming its sensitivity to chemotherapeutics and also radiotherapy. In case of insufficient response to chemotherapy, such patients must be treated with total laryngectomy.[40, 41] Patients with a clinically negative neck who will require postoperative RT may have the neck dissection omitted because the neck (levels 2-4) will be irradiated as well as the primary site (base of tongue and neopharynx) and level 6 nodes with a high likelihood of local-regional control and less facial edema.[42] NCCN guidelines for postoperative RT are 60 to 66 Gy at 2 Gy per fraction to high risk areas and 44 to 50 Gy at 2 Gy per

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fraction or 53 to 63 Gy at 1.6 to 1.8 Gy per fraction to low to intermediate risk areas. Alternatively , postoperative RT doses employed by some are 60 Gy for negative margins, 64-66 Gy for close (< 5mm) or positive margins and areas of ENE, and 70 Gy for gross residual disease at 2 Gy per once daily fraction. Patients with pathologically positive nodes receive RT to the retropharyngeal nodes on the involved side(s). IMRT may employed to reduce the dose to the swallowing muscles and lower the likelihood of long term swallowing problems.[42] Patients with extranodal spread, 4 or more positive nodes, and/or positive margins receive concomitant cisplatin with postoperative RT.[9, 43]

NCCN guidelines for definitive RT include 66 to 70 Gy at 2 Gy per fraction, concomitant boost to 72 Gy in 42 fractions over 30 treatment days, and hyperfractionation to 79.2 to 81.6 Gy at 1.2 Gy per twice daily fraction. NCCN guidelines recommend 70 Gy at 2 Gy per fraction if concomitant chemotherapy is employed likely based, at least in part, on the outcomes of the Radiation Therapy Oncology Group 0129 trial where patients with stage III and IV SCCs of the oral cavity, oropharynx, hypopharynx or larynx were randomized to receive 70 Gy in 35 fractions over 7 weeks or 72 Gy in 42 fractions over 6 weeks with 2 or 3 cycles of cisplatin 100 mg /M2 every 3 weeks.[44] When combined with cisplatin, there was no improvement in outcome with the accelerated concomitant boost RT compared with standard fractionation. That said, other altered fractionation schedules may be considered.[7, 8] Two schedules often preferred are hyperfractionation 74.4 Gy at 1.2 Gy per twice daily fraction in 31 treatment days and 70 Gy at 2 Gy per fraction in 30 treatment days giving two twice daily fractions once weekly as employed in a DAHANCA trial. The fields are reduced once at approximately 45 to 50 Gy and again at 60 Gy. An alternative with the DAHANCA schedule is to employ simultaneous integrated boost (SIB) to

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deliver 70 Gy to the gross disease, 63 Gy to the intermediate risk volume for high risk subclinical disease, and 56 Gy to the standard risk subclinical disease. The M.D. Anderson concomitant boost schedule of 72 Gy in 42 fractions over 30 treatment days with twice daily fractions of 1.8 Gy and 1.5 Gy given during the last 12 treatment days is included as an option in the NCCN guidelines. Although the local-regional control rates with the latter schedule are equivalent to those observed after hyperfractionation, the risk of late complications is increased.[45, 46] Additionally, patients treated with hyperfractionation had improved overall survival compared with those treated with standard fractionation. Patients treated with accelerated concomitant boost had no improvement in overall survival. Therefore, hyperfractionation is preferred by some with the DAHANCA schedule as a second choice if the former is not feasible. Regardless of the schedule chosen, the RT is delivered in a continuous course. Patients receive concomitant cisplatin 30 to 40 mg/m^2 per week or 100 mg/m^2 every 3 weeks. The former is likely better tolerated and is preferred by many clinicians.[8] As the risk of subclinical disease in clinically uninvolved nodes is 15% to 20% and levels 2-4 and 6 are electively irradiated bilaterally.

Percutaneous gastrostomy (PEG) placement is placed only if needed to maintain weight and hydration during RT because it has been shown to be associated with worse long-term swallowing. Dentulous patients are evaluated by a dentist prior to initiating RT; teeth that are likely to require future extraction are removed and fluoride trays are fashioned for use with fluoride gel following RT to reduce the risk of dental caries. Prophylactic extraction of healthy teeth prior to RT does not reduce the risk of osteoradionecrosis (ORN) and is not recommended.[39, 47] This is usually not an issue for patients with laryngeal cancer because the oral cavity is usually not irradiated.

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Hinerman et al reported on 109 patients with previously untreated T3 (87 patients) and T4 (22 patients) managed with definitive RT (99 patients) or RT combined with chemotherapy at UF between 1966 and 2002.[3] These patients were selected with low volume disease and do not include patients with advanced, high volume T3-T4 SCCs. The neck was clinically negative in 85 patients (77%). All living patients had a 2-year minimum follow-up. Median follow-up for all patients was 5.7 years and 10.6 years for living patients. The local control rates at 5 years were 81% for T4 SCCs and 63% for T3 lesions. The ultimate 5-year local control rate for T3-T4 cancers, including those successfully salvaged after a local recurrence, was approximately 87%. The 5-year local-regional control rates were 78% for stage IVa and 62% for stage III. The 5-year distant metastases-free survival rates were 100% for stage IVa and 97% for those with stage III cancers. The 5-year cause specific survival rates were 87% for stage IVa patients and 83% for stage III patients. The 5-year overall survival rates were 67% for patients with stage IVa SCCs and 52% for those with stage III cancers. Severe complications occurred in 13 patients (12%) and included cartilage necrosis (7 patients), permanent PEG (2 patients), edema requiring a tracheotomy (2 patients), stricture and dysphagia (1 patient), and aspiration/cardiac arrest (1 patient). Two complications were fatal.

The experiences reported from 3 additional institutions are depicted in Table 3. All of these patients were staged during a time period when T3 was defined as vocal cord fixation. Harwood et al reported on 39 patients treated with RT at the Princess Margaret Cancer Center for T4 glottic SCCs.[48] Local control after RT was obtained in 22 patients (56%). Similarly, Karim et al reported local control after RT at Free

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University between 1974 and 1984 for patients with T4 glottic SCCs in 24 of 38 patients (63%).[49] The local control rates after RT alone or combined with chemotherapy for patients with T4 SCCs from 5 additional institutions are depicted in Table 4.

Hinerman et al reported on 295 patients with previously untreated SCC of the larynx (199 patients), hypopharynx (80 patients), and oropharynx (16 patients) treated with surgery and postoperative RT at UF between 1964 and 2001.[2] Patients were treated before the era of transoral robotic surgery (TORS). Patients were staged pathologically according the AJCC staging system. All living patients had a 2-year minimum follow-up. Four patients were lost follow-up at 2.2, 3.1, 8.3, and 13.7 years, respectively. The mean and median follow-up times were 5.3 and 3.6 years, respectively. The primary site was glottic larynx in 95 patients. For patients with laryngeal cancer, margins were positive 13 patients (6.5%) and close/equivocal in 32 patients (16%). Four or more positive nodes were present in 33 patients (16.5%) with laryngeal cancer. For patients with laryngeal cancer, the presence of ENE was as follows: present, 39 patients (20%); absent, 22 patients (11%); and no data, 138 patients (69%). The 5-year local-regional control rates were 89% for stage III larynx and 85% for stage IVa larynx (P=0.33). The 5-year distant metastases-free survival rates for laryngeal cancer patients were: stage III, 90%; and stage IVa, 74% (P=0.03). The 5-year cause specific survival rates for laryngeal cancer patients were: stage III, 84%; and stage IVa, 66% (P=0.043). The 5-year overall survival rates for patients with laryngeal cancer were: stage III, 57%; and stage IVa, 44% (P=0.70). For the entire group, 23 patients (7.7%) experienced a severe post RT complication including: fistula, 11 patients; permanent PEG, 5 patients; ORN, 3 patients; wound dehiscence, 1 patient; stricture, 1 patient; stomal necrosis, 1 patient; and soft tissue necrosis, 1 patient.

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Rosenthal et al reported on 221 patients with T4 laryngeal SCC treated at the M.D. Anderson Cancer Center between 1983 and 2011.[50] The primary site distribution was: glottis, 43 patients (19%); subglottis, 3 patients (1%); supraglottis, 125 patients (57%); and transglottic, 30 patients (33%). Positive nodes were present in 147 patients (67%). Total laryngectomy (TL), neck dissection and postoperative RT or chemoRT was performed in 161 patients (73%) and larynx preservation (LP) with RT or chemoRT was performed in 60 patients (27%). Median follow-up was 47 months. Median overall survival for both groups of patients was 64 months (p=0.7). The 5-year local-regional control rate after initial treatment was 84% after TL and 63% after LP (p<0.007). However, taking into account the successful surgical salvage of local-regional recurrences after LP, the ultimate 5 local-regional control rate was 80% which was not significantly different from that observed after TL. The 5-year disease specific survival rate was 60% after TL and 48% after LP (p=0.1). During follow-up, 45% of the LP group had a tracheostomy, at some point in time, and 23% had aspiration.

Mendenhall et al reported on 173 patients who underwent a total laryngectomy with or without a partial or total pharyngectomy followed by postoperative RT at UF between 1983 and 1998.[51] Data pertaining to voice rehabilitation were available at 2-3 years and longer for 118 patients and for 5 years and longer for 69 patients. The methods of voice rehabilitation at 2-3 years and longer and 5 years and longer were: tracheoesophageal, 27% and 19%; artificial larynx, 50% and 57%; esophageal, 1% and 3%; non vocal, 17% and 14%; and no data, 5% and 7%, respectively.

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Conclusion

Patients with early and moderately advanced laryngeal SCC have a relatively high chance of cure with larynx preservation after RT or chemoRT that is related to extent of disease. Patients with more advanced cancers are best treated with surgery and postoperative RT alone or combined with concomitant chemotherapy. Although many patients undergoing total laryngectomy may be rehabilitated with tracheoesophageal speech, the majority are rehabilitated with an artificial larynx.

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Figures Legends:

Figure 1: Schematic diagram of a typical lateral field. (Reprinted from Million RR, Cassisi NJ, Mancuso AAL: Larynx, in Million RR, Cassisi NJ (eds): Management of head and neck: A multidisciplinary approach (ed 2). Philadelphia: Lippioncott, 1994; p.431-497).

Figure 2: Local control after radiation at 5 and 10 years (*N*=number of patients). (Reprinted from Chera BS, Amdur RJ, Morris CG, Kirwan JM, Mendenhall WM. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys 2010;78(2):461-6).

Figure 3: Ultimate local control with larynx preservation at 5 and 10 years (*N*=number of patients). (Reprinted from Chera BS, Amdur RJ, Morris CG, Kirwan JM, Mendenhall WM. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys 2010;78(2):461-6).

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Table 1: Carcinoma in-situ Outcomes after Radiotherapy				
Series	**Study Years**	**Number of Patients**	**5yr local control**	**5yr ultimate local control**
Spayne et al. 2001[52]	1980-1994	67	98%	100%
Le et al. 2000[53]	1958-1998	54	79%	100%
Smitt and Goffinet 1994[54]	1958-1990	29	92%	97%
Kalter et al. 1987[55]	1963-1981	62	100%	100%
Pene and Fletcher 1976[56]	1952-1973	79	86%	99%
Smee et al. 2009[57]	1967-2006	24	75%	88%

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Table 2: T_1-T_2 SCC: 5-year Local Control Rates							
Series	**Study Years**	**Follow-up**	**N**	**T_{1a}**	**T_{1b}**	**T_{2a}**	**T_{2b}**
Chera et al. 2010[6]	1964-2006	Median 12y	585	94%	93%	80%	70%
Groome et al. 2006[58]	1982-1995	Median 5.9y	704	82%	82%	63%	63%
Cellai et al. 2005,[59] Frata et al. 2005[60]	1970-1999	Median 9.3y	831	84%	81%	ND	ND
Warde et al. 1994[61]	1981-1989	Median 6.8y	735	91%	82%	69%	69%
Le et al. 1997[62]	1970-1998	Median 9.7y	398	85%	85%	70%	70%
Garden et al. 2003[63]	1970-1998	Median 6.8y	230	ND	ND	74%	70%
Smee et al. 2009[57]	1967-2006	Median 7.6y	498	83%	83%	72%	72%
N=number of patients; y=years							

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Table 3: T3 SCC – Local Control after Radiotherapy					
Series	**Study Years**	**Number of Patients**	**Minimum Follow-up**	**Local Control**	**Ultimate Local Control**
Harwood et al. 1980[64]	1963-1977	112	3y	51%	77%
Wang et al. 1997[65]	1970-1994	65	NS	57%	ND
Stewart et al. 1975[66]	1955-1965	67	10y	57%	67%
NS=not started; ND=no data; y=years					

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Table 4: T4 Laryngeal Carcinoma treated under definitive RT or ChemoRT				
Series	**Number of Patients**	**Cohort Years**	**Present Glottic**	**Local Control**
Knab et al. 2008[67]	32	1996-2002	9%	71%* (4y)
Parsons et al. 1998[68]	43	1964-1994	26%	52% (5y)
Vengalil et al. 2016[69]	65	2003-2010	40%	63% (3y)
Wick et al. 2017[70]	24	1998-2012	50%	75%* (ND)
Worden et al. 2009[71]	27**	ND	33%	45% (10y)
*Local-regional control **27 of 36 patients who received induction chemotherapy ND=no data; y=years				

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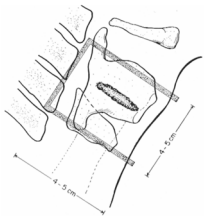

HED_26419_Figure 1.TIF

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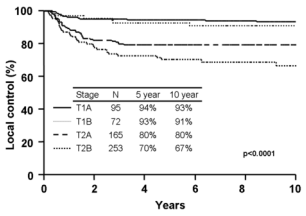

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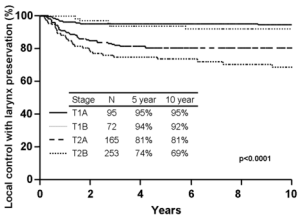

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