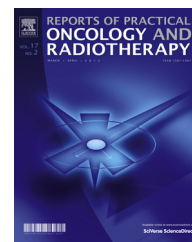


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## Review

# 3D conformal hypofractionated radical radiotherapy in early glottic cancer



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## ABSTRACT

**Aim:** The purpose of this study was to evaluate acute and late toxicity and the locoregional control in patients treated with hypofractionated radical radiotherapy 2.25 Gy/fraction/day for early glottic carcinoma.

**Materials and methods:** A retrospective analysis was performed of 27 patients, stage T1–T2 N0 glottic squamous cell carcinoma, that underwent radical RT from April 2008 to October 2011. The mean age was 64.6 years (range 36–81). Seventeen patients were staged T1a, 3 patients T1b and 7 patients T2. All patients were 3D planned and treated in a 6 MV LINAC, 2.25 Gy/fraction/5 days per week, to a total dose between 63 Gy and 67.5 Gy. Biological Effective Dose (BED ( $\alpha/\beta = 10$ )) ranged from 77.18 Gy to 82.69 Gy and EQD2 from 64.31 Gy to 68.91 Gy. Patients were evaluated in periodic follow-up. Toxicity was evaluated according to RTOG Toxicities Scales.

**Results:** With a median follow-time of 24.7 months (range 3.6–44.2 months), no evidence of locoregional recurrence was observed. The treatment was well tolerated and no unscheduled interruptions in treatments for toxicity were documented, with the median overall treatment time of 41 days (range 38–48). Only grades 1 and 2 acute toxicity were observed and no evidence of severe late toxicity.

**Conclusion:** The authors believe that this moderately hypofractionated scheme can provide a good locoregional control for T1–T2 glottic carcinomas with no increase of toxicity. As the limitation of this work is the reduced number of patients and the lack of long term follow-up, the authors hope to update this retrospective study in the future in order to improve the power of the results.

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## 1. Background

Larynx cancer is the most common cancer of the head and neck with the exception of the skin and it accounts for 2% of

all cancer diagnoses.<sup>1,2</sup> Glottic cancer is a larynx malignancy that involves the true vocal cords and/or anterior and/or posterior commissures. It is the most common laryngeal cancer and it has the most favorable prognosis, mainly if diagnosed early.

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Persistent hoarseness is the usual presenting symptom of glottic carcinoma present even in small lesions, which brings patients (pts) to medical attention and allows a sooner diagnosis, as the lesions are easily visible by laryngoscopy and reached for a biopsy. About 70% of all cases have localized disease at diagnosis.<sup>2,3</sup>

Tobacco has a major role in the development of the disease, with alcohol consumption and occupational exposure (diesel fumes, sulfuric acid, coal dust and machining fluids) being other main risk factors.

Squamous cell carcinoma (SCC) is the most common histological type of glottic cancer, usually being well differentiated. In early lesions lymph node involvement is rare (<3%) due to the lack of lymphatic drainage of the glottis.<sup>1,2</sup>

The goal of the conservative treatment in early glottic cancer (EGC) is the control of the disease while maintaining a good quality of the essential laryngeal functions: phonation and swallowing. Ideally, EGC (T1–T2 N0) should be managed with a single modality either microsurgery or definitive Radiotherapy (RT). RT is considered gold standard in some Institutions and in northern European countries,<sup>4–8</sup> reserving surgery for salvage of failures. The local control rate with definitive radiotherapy is approximately 83–95% for T1 and 70–80% for T2 lesions.<sup>2,9,23</sup>

There is no consensus for the best fractionation schedules for definitive RT in EGC. Fractionation policy for early laryngeal cancer differs between reporting institutions, varying largely from very hypofractionated schedules like 50–52.5 Gy/16 fractions over 21 days currently employed in the UK<sup>6</sup> to conventional fractionated schemes.

Since there is level 1 evidence that 2.25 Gy/fraction is better than conventional fractionation, the aim of our analysis was to evaluate the acute (AT) and late toxicity (LT) as well as LRC in the pts treated for EGC in our Institution.

A recent Japanese prospective trial randomized pts with T1 N0 SCC of the glottis to definitive RT at 2 Gy/fraction or 2.25 Gy/fraction. The 5-year local control rates were 77% with 2 Gy/fraction vs. 92% with 2.25 Gy/fraction ( $p < 0.004$ ) and no difference in either AT or LT.<sup>11</sup>

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## 2. Materials and methods

A retrospective analysis was performed of twenty-seven pts, stage T1–T2 N0 glottic SCC, that underwent radical RT from April 2008 to October 2011 in the Department of Radiation Oncology of Hospital de Santa Maria – CHLN. None of these patients received elective nodal treatment or chemotherapy. The mean age was 64.6 years (range 36–81); 22 males and 5 females. All pts had SCC proven histology; 17 pts with T1a stage, 3 pts T1b and 7 pts T2 Stage; 19 pts (70%) were heavy smokers. All pts were 3D planned, in a supine position with hyperextended neck and immobilized with a head and shoulders thermoplastic mask and were treated with a 2 or 3 field technique in a 6 MV LINAC, 2.25 Gy/fraction, 5 days per week, to a total dose between 63 Gy and 67.5 Gy. Biological Effective Dose (BED ( $\alpha/\beta = 10$ )) ranged from 77.18 Gy to 82.69 Gy and EQD2 from 64.31 Gy to 68.91 Gy. T1 lesions were treated to a total dose of 63 Gy and T2 lesions to 65.25 Gy; just one T1 patient was treated with 67.5 Gy to compensate a treatment interruption due to a LINAC scheduled maintenance and 2 banking

holidays. The clinical target volume (CTV) included all the larynx mucosa with the fields limits superiorly up to the top of the thyroid cartilage and caudally at the bottom of the cricoids, cartilage anteriorly and laterally, and posteriorly the posterior mucosa or the anterior edge of the vertebral body, No GTV was delineated and the margin to the PTV was 5 mm isotropically. The OARs delineated were the spinal cord – maximum dose 45 Gy and esophagus – maximum dose 105% of prescribed dose and median <35 Gy, both absolute doses as equivalent doses for 2 Gy/fraction.

Pts were evaluated in periodic follow-up that included a disease specific history with neck examination to detect enlarged nodes, panendoscopy and, if clinically indicated, cervical computed tomography to confirm LRC. Toxicity, acute and late, was evaluated according to RTOG Toxicities Scales.

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## 3. Results

With a median follow-time of 24.7 months (range 3.6–44.2 months) no evidence of loco-regional recurrence was observed. Two pts died 2.5 and 17 months after the end of the treatment, both for other causes than glottic cancer (post-operative complication for other head and neck cancer and chronic obstructive lung disease, respectively) and one patient developed a synchronous cancer (oropharynx) at 2.5 months of follow-up. No other second primaries detected. All other patients had at least 5 months of follow-up.

The treatment was well tolerated and no unscheduled interruptions were documented, with the median overall treatment time (OTT) of 41 days (range 38–48), with 92.6% of the pts (25 pts) with OTT  $\leq$  43 days. Grades 1 and 2 acute dysphagia were observed in 3 (11%) and 19 pts (70%), respectively; grades 1 and 2 acute radiodermatitis in 11 pts (41%); acute odynophagia grade 2 in 16 pts (59%). No AT grade 3 were observed. No evidence of severe LT: 6 pts (22%) with grade 1 hoarseness, 3 pts (11%) with grade 1 dysphagia and 1 pt (4%) with xerostomia.

No evidence of distant metastases was observed during the follow-up time and there was no need for surgery, tracheostomy or gastrostomy in any pts of this study.

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## 4. Discussion

In general, EGC (T1–T2 N0) are managed with a single modality, but there are no randomized trials comparing surgery to RT to laser resection. However, in spite of having similar local control, survival and preservation of the larynx functions, it seems that RT or laser resection are better in voice quality preservation than partial laryngectomy. For larger T2 lesions or impaired cord mobility, laser does not present so good results in voice preserving as RT, also having a high rate of recurrences; so RT becomes the best modality in non-selected EGC pts.<sup>9</sup>

The shorter overall treatment time and larger fraction size could be advantageous in radiobiology of well differentiated tumors. There are many studies which demonstrate that external beam RT schedules using a fraction size greater than 2 Gy, in EGC, result in equivalent or even better local control and disease-free survival than longer schedules and no

difference in AT and LT.<sup>8,10–13</sup> When external beam RT is used as the primary treatment modality in pts with EGC, hypofractionated regimens should be used, without chemotherapy or prophylactic treatment of the neck nodes, but many schemes of hypofractionation are described in the literature.

According to the University of Florida – San Francisco,<sup>9</sup> in our Department, we began to use 2.25 Gy/fraction instead of conventional scheme in EGC, in order to shorten OTT trying to avoid repopulation of cells. This fraction size was also proved to be more effective than conventional one in a Japanese randomized trial – Yamazaki et al.<sup>11</sup>

The small volumes irradiated allowed the use of hypofractionation without the concern of severe toxicities, as it diminished the normal tissues of the irradiation field. Some authors correlated dosimetry parameters, such as mean laryngeal dose of V50 Gy with late laryngeal toxicity.<sup>24,25</sup> The aim of our study was not to assess such parameters since our late toxicities were only grade 1.

Our results are very similar to those published in the literature, showing that hypofractionation have excellent results and cures a high percentage of pts with EGC. For T2 lesions our results tend to be better in local control than those reported in the literature, although we still have a short follow-up time. In 92.6% of pts (25 pts) we accomplished the OTT  $\leq$  43 days, that is the cut-off for no influence on the local control in T2 lesions in a published trial by University of California,<sup>8</sup> using the same fractionation scheme as ours. Short OTT brings benefit in EGC local control, as already proved in many trials,<sup>8,14–19</sup> which can be explained by the fact of almost all cases being well differentiated SCC, having a faster doubling time and a rapid capacity of repopulation, which was documented in CHART and DAHANCA studies.<sup>6,19–22</sup>

Regular follow-up is needed after a potentially curative treatment to ensure that local control is achieved for a long time. Almost all local recurrences will occur in the first four years, mainly in the first year, but continuously follow-up is required, especially in pts who maintain their smoking and drinking habits.

The fact of no documented local failure within the follow-up time, and no need for surgery, tracheostomy or gastrostomy tube could be related with the reduced number of pts and the lack of long term follow-up, which are the main limitations of this work.

## 5. Conclusions

The authors believe that for T1–T2 glottic carcinomas, definitive RT with 2.25 Gy/fraction can provide a good term local control and survival with the preservation of the normal structure and function of the larynx.

An important limitation of this study relates to its retrospective nature with its inherent biases, to the few pts involved and the lack of long term follow-up. Due to the good results in terms of LRC and toxicity and a shorter OTT, this fractionation scheme became a standard treatment in our Institution. We hope to update this retrospective study in the future in order to improve the power of our results.

## Conflict of interest

None declared.

## Financial disclosure

None declared.

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