Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

The importance of actual tumor growth rate on disease free survival and overall survival in laryngeal squamous cell carcinoma

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ARTICLE INFO

Article history:
Received 11 July 2012
Received in revised form 30 May 2014
Accepted 2 June 2014
Available online xxxx

Keywords:
Growth rate
Doubling time
Laryngeal carcinoma
Outcome
DFS
OS

ABSTRACT

Background and purpose: Evaluation of the variation in tumor growth rate and the influence of tumor growth rate on disease free survival (DFS) and overall survival (OS) in laryngeal squamous cell carcinoma (LSCC).

Material and methods: We delineated tumor volume on a diagnostic and planning CT scan in 131 patients with laryngeal squamous cell carcinoma and calculated the tumor growth rate. Primary endpoint was DFS. Follow up data were collected retrospectively.

Results: A large variation in tumor growth rate was seen. When dichotomized with a cut-off point of −0.3 ln(cc/day), we found a significant association between high growth rate and worse DFS ($p = 0.008$) and OS ($p = 0.013$). After stepwise adjustment for potential confounders (age, differentiation and tumor volume) this significant association persisted. However, after adjustment of N-stage association disappeared. Exploratory analyses suggested a strong association between N-stage and tumor growth rate.

Conclusions: In laryngeal squamous cell carcinoma, there is a large variation in tumor growth rate. This tumor growth rate seems to be an important factor in disease free survival and OS. This tumor growth rate is independent of age, differentiation and tumor volume associated with DFS, but N-stage seems to be a more important risk factor.

The incidence rate of laryngeal cancer in Europe is almost 40,000 patients (International agency for research on cancer, EUCAN, website). There are several prognostic factors for outcome in patients with laryngeal carcinoma. For instance, it is commonly known that prognosis declines with more advanced tumor stage (T-stage) [1–5]. When treatment is delayed, tumors may grow and proceed to a more advanced stage with formation of metastatic clones [5]. In the Netherlands, the preferred time between diagnosis and start of treatment is 30 days or less, as stated by the Dutch Cooperative Head and Neck Group. Although recent years have shown some improvement, these 30 days are often not achieved. As seen in other countries, the unacceptable treatment delay is due to an increasing number of patients and lack of capacity in the past [6,7].

Whether a tumor will proceed to a higher stage or a larger volume will depend on the tumor growth rate and the waiting time. To determine this growth rate, a potential doubling time (Tpot), based on a BrdU-labeling index and the duration of the S-phase, has been used in previous studies. One study showed an association between Tpot and outcome [8]. However, several other studies could not find a correlation between Tpot and locoregional control or survival in head and neck cancers [2–4].

In two different retrospective studies concerning head and neck squamous cell carcinoma (SCC), growth rate was based on the increase in tumor volume between a diagnostic and a planning CT-scan. Within these studies, a wide variation in tumor growth rate and a loss in tumor control probability, due to treatment delay, were found [9–11].

Based on this knowledge, we wanted to investigate if the same variation in tumor growth rate is present in a homogeneous group of patients with laryngeal carcinoma. Therefore, the aim of the study was to evaluate the variation in tumor growth rate and the

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http://dx.doi.org/10.1016/j.radonc.2014.06.004
0167-8140/

influence of tumor growth rate on disease free survival (DFS) and overall survival (OS) in laryngeal SCC.

Methods and materials

Patients

Between 1996 and 2009, ~700 patients were treated for laryngeal SCC at the Radiation Oncology department of our hospital. For this study, we included patients with laryngeal SCC and who were primarily treated with radiotherapy. Also a diagnostic (dCT) and planning CT-scan (pCT) had to be available. Patients with a medical history of previous radiotherapy treatment in the head and neck area were excluded. These criteria were met in 159 patients. During analysis, 28 patients were excluded, because the tumor was not visible on the CT-scan, partly due to artifacts. Therefore, 131 patients were included in the final analysis. While the patients were treated with different treatment schedules, most patients received an accelerated radiotherapy schedule (92.4%).

Measurements: volume

Visible primary tumor mass (lymfnode volume excluded) was delineated manually on the axial slices of the contrast-enhanced dCT and pCT. In the majority of the CT-scans, a single-slice technique was used. Most dCT scans had a slice thickness of 1.5–2 mm and most pCT scans a slice thickness of 2–3 mm (range 1–5 mm). CT-scans that showed severe motion artifacts at the level of the larynx were excluded. Delineation was performed by the first author and consensus was reached with an experienced radiation-oncologist (CHJT). In difficult cases, an experienced head and neck radiologist (FAP) was consulted. Criteria for tumor involvement were: abnormal contrast enhancement, soft tissue thickening, presence of a mass lesion, infiltration of fatty tissue, or a combination of these. Delineation on both scans was performed using 3-D delineation software (in-house developed). This software package (VolumeTool) includes image quantification tools such as volumetry and 3D visualization. The delineation package is based on a combined Java/C+ library and includes a (in-house developed) DICOM server for storing image data-sets as well as delineated structures sets [12].

Growth and growth rate

The interval (in days) between the two CT scans was recorded. Tumor growth was based on the volume difference between the diagnostic and planning CT-scans. Exponential growth was assumed.

$$\text{Tumor growth rate(TGR)} = \ln(\text{Vplan} - \text{Vdiagn})/T$$

$$(\text{Vdiagn} = \text{tumor volume on dCT};\ \text{Vplan} = \text{tumor volume on pCT};\ T = \text{days between dCT and pCT})$$

Outcome

The primary objective in this study was disease free survival (DFS). We chose DFS as our primary endpoint since we hypothesized that fast growing tumors will not only result in a larger volume locally but also metastasize earlier to regional and distant locations. Follow-up data were collected retrospectively by chart control. If the patients were lost to follow-up in the Radiation Oncology department, follow-up data were retrieved from other hospitals, general practitioners or municipal databases, up until the time of analysis. DFS was measured from the start of treatment until an event occurred. Events were defined as a local or regional recurrence or a distant metastasis.

Statistical analysis

Descriptive statistics were used to characterize the study population and to describe growth rate.

Cox proportional hazard regression analysis was used to evaluate the influence of tumor growth rate on DFS. We evaluated tumor growth rate as both a continuous and a dichotomous parameter, with a threshold of −0.3 ln(cc/day) between fast and slow growth. The considered factors for further analysis on DFS were: age, sex, smoking, alcohol, location, differentiation, volume on diagnostic CT scan, mobility of the vocal cord, T-stage and N-stage. Age and volume were analyzed as continuous variables. To obtain sufficient data in the categories for the analyses, we combined poor, undifferentiated and basaloid differentiation in one category and we also combined micro-invasive and unknown differentiation in one category. Four categories were used for N-stage: 0, 1, 2a–b, 2c–3. The T-stage parameter includes both stages T2a and T2b. This is because two studies have shown that, for stage T2 laryngeal SCC, the presence of impaired vocal cord mobility was associated with worse ultimate local control (LC), when treated with a conventional radiotherapy schedule. The studies suggested a division of stage T2 into stage T2a, with normal vocal cord mobility and stage T2b, with impaired vocal cord mobility. Since LC of stage T2a laryngeal carcinoma showed a comparable LC to stage T1 laryngeal SCC, these two stages were combined in our analysis [13,14]. Furthermore, we investigated the primary location of the laryngeal tumors, supraglottic, glottic or subglottic.

In multivariate Cox regression analysis, we adjusted stepwise for potential confounding and intermediate factors. The parameters volume, mobility and T-stage are highly correlated. Therefore, we only adjusted for one of these parameters in the multivariate Cox regression analyses. First, the hazard ratio (HR) of tumor growth rate was adjusted for age (continuous). Next, differentiation (four categories) was added to the model. After this, volume (continuous) was added. Finally, HR's were adjusted for N-stage (four categories).

To explore the association between tumor growth rate and N-stage, we used cross-tabulation. The statistical software SPSS 16 was used for the analysis.

Results

Sixty-four glottic, sixty-six supraglottic and 1 subglottic laryngeal squamous cell carcinoma were analyzed. Table 1 gives an outline of the patient characteristics for these 131 patients. There was a significant difference between fast and slow growing tumors in location ($\chi^2 = 10.5$ $p = 0.005$) and N-stage ($\chi^2 = 19.4$ $p = 0.002$). Location and N-stage are significantly associated ($\chi^2 = 20.7$ $p = 0.024$).

The follow-up time ranged from 1 to 149 months with a mean follow-up of 50 months. These data were retrospectively and partly prospectively collected.

The mean time between the dCT- and pCTscans was 25.7 days (SD 11.6). The mean tumor growth rate was −0.3 ln(cc/day) and, therefore, this was used as cut-off point (Fig. 1).

For 39 of the patients, 48 events took place. Of these 27 were local recurrences, 5 were regional recurrences and 16 were distant metastases.

In crude Cox regression analysis (Table 2), no significant association between tumor growth rate as a continuous parameter and LC, DFS and overall survival (OS) could be found. However, when

Please cite this article in press as: van Bockel LW et al. The importance of actual tumor growth rate on disease free survival and overall survival in laryngeal squamous cell carcinoma. Radiother Oncol (2014), http://dx.doi.org/10.1016/j.radonc.2014.06.004