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Original article

Local recurrences after curative IMRT for HNSCC: Effect of different GTV to high-dose CTV margins

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ABSTRACT

Introduction: The aim was to analyze position of CT-verified local recurrences (LR) and local control (LC) among three centers that used different GTV to CTV1 margins.

Materials and methods: In total, 1576 patients completing radical primary IMRT for larynx, pharynx, oral cavity HNSCC in three centers in Denmark between 2006 and 2012 were included. CT-verified LRs were analyzed as possible points of recurrence origin and compared between groups of small (0–2.5 mm), larger (>2.5 mm), and anatomical GTV-CTV1 margins. The recurrence point's position relative to the GTV and 95% prescription dose was evaluated. Overall local control rate was evaluated using Cox uni- and multi-variate analysis.

Results: After a median follow-up of 41 months, 272 patients had local failure. Median GTV-CTV1 margin in Center1, 2 and 3 was 0.0, 3.7 and 9.7 mm, respectively. 51% of local recurrences were inside the GTV. No difference in distribution of LRs in relation to GTV surface ($p = 0.4$) or the dose to LRs ($p = 0.2$) was detected between the groups. A difference in LC was found univariate between the centers ($p = 0.03$), but not in multivariate analysis ($p = 0.4$).

Conclusions: No relation was found between the recurrences' distributions as function of the margins used at three centers. In multivariate analysis, local control was not influenced by the centers.

Local and loco-regionally advanced head and neck squamous cell carcinomas (HNSCC) are primarily treated with curative radiotherapy (RT) in Denmark, which in the last decade mainly has been based on intensity modulated radiotherapy (IMRT) techniques.

IMRT in the head and neck region is very appealing because of the possibility to shape high doses to the target volumes while sparing organs at risk from excessive radiation dose [1]. An explicit definition of the treatment target, gross tumor volume (GTV), is an imperative primary step in the RT planning course [2–8]. However, definition of the high-dose CTV (CTV1), created around the GTV to account for extension of microscopic disease, remains a source of substantial uncertainty. The consensus of CTV1 delineation has only recently been proposed worldwide [9], but during the last decades, GTV-CTV1 margin did vary from zero to up to 20 mm, or included a whole organ or anatomical compartments [10–12]. According to the Danish Head and Neck Cancer Group (DAHANCA) IMRT guidelines from 2004, the CTV1 was loosely defined as 'at least GTV without margin', and as a consequence, it has varied in size between different centers in Denmark.

Finding the optimal GTV-CTV1 margin is highly important in the search for the optimal balance between a radical treatment goal and post-treatment morbidity, which may diverge depending on the size of margin. Although radioresistance, due to intrinsic and extrinsic factors, is believed to be primary reason of local treatment failure after RT, the treatment volume has a potential influence on failure pattern as well, with a possibility of geographical misses using highly conformal IMRT. Since the GTV-CTV1 margin may primarily have a direct influence on local tumor control (LC), only local treatment failures were evaluated in the present study. The evaluation of CT-verified recurrences after IMRT can be done by location of a possible point of recurrence's origin (PO) [12–15] relative to the treatment volumes, and this method was chosen in the current study.

The aim of this study was to analyze location of the CT-verified local recurrences, and local failure rates between three centers that used different GTV-CTV1 margins.

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Material and methods

Patient selection

All patients treated with curatively intended IMRT at three Danish cancer centers between 2006 and 2012 were included. Eligibility criteria were: stage I–IV biopsy-proven squamous cell carcinoma of the larynx, oropharynx, hypopharynx and oral cavity; completion of primary IMRT-based radiotherapy with curative intent, and follow-up of at least three years.

The study was approved by the Danish Data Protection Agency and National Health Data Protection Agency.

Treatment planning and delivery

Radiotherapy planning was performed using Pinnacle (Philips Healthcare Fitchburg, WI) or Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning systems. Patients were treated with step-and-shoot or sliding window IMRT, or Volumetric Modulated Arc Therapy (VMAT) using simultaneously integrated boost. The IMRT and VMAT dose plans were delivered by Elekta Synergy or Varian iX linear accelerators, all using 6 MV.

Tumor (GTV-T) was identified on the planning CT (pCT), guided by all accessible clinical and radiological modalities. Treatment was carried out in accordance with the guidelines from DAHANCA 2004 [16]. First, the GTVs were manually expanded to define the CTV1s. In Center1, CTV1 generally included GTV-T with a margin of zero mm. In Center2, CTV1 contained GTV-T with varying margins, predominately of five mm. In Center3, a margin of 10 mm was typically used. CTV1 volumes were completed in all centers by adapting the volume to the local anatomy (air cavities and bones). The elective CTV (CTV3) had additionally contained the regional elective nodal region(s) according to the DAHANCA guidelines [16]. The standard margin added to the CTVs in order to obtain the planning target volumes (PTVs) were 5 mm at all three centers.

The treatment consisted of radiotherapy with a prescription dose of 66–68 Gy given in five fractions per week (conventional fractionation), or 66–68 or 76–78 Gy in six or ten fractions per week (altered fractionation) to CTV1 and weekly concomitant platinum-based chemotherapy (if patient had N+ disease and compliance to receive chemotherapy) and daily hypoxic radiosensitizer nimorazole (in all cases, and if tolerated) [17].

Patients' assessment and follow-up

Patients were assessed two months after completion of treatment for the first clinical response evaluation. During follow-up, patients underwent a clinical examination every three months in the first two years and every six month in the next three years. One center used routine MRI of the neck at two month after treatment, and one center – ultrasound of the neck during the first two years. In all three centers imaging using CT, PET/CT, MRI, or combinations thereof, were performed based on clinical suspicion of recurrence.

Point of origin analysis of CT-verified local recurrences

For the descriptive analysis, two groups of patients with local recurrences were formed: one consisting of CT-verified local recurrences with successful deformable image registration (DIR), and another consisting of LRs verified by MRI, clinical examination and ultrasonography, or CT without successful DIR.

For all patients with CT verified LR, the recurrence volume (V_{rec}) was identified. The use of CT verification was in 49, 31, and 39 cases for Center1, 2 and 3, respectively. For the majority of patients in the analysis, the LRs were verified by biopsy (111 out of 119).

We have previously defined origin of a recurrence as the focal point [12]. The mathematically estimated PO of recurrences was chosen for the present study. This PO represents the maximum surface distance, expressed as the point within a recurrence volume with the largest distance to the recurrence surface [12].

Deformable image registration was used to co-register pCT and recurrence CT (rCT) using previously validated software for this specific purpose [18]. The 3 mm uncertainty of DIR was used to estimate the error in dose estimate, which did not change the results [12]. Since the intensity-based algorithm (Elastix) was validated on CT images, the MRI verified LRs were excluded from the analysis. For the point analysis, LRs were divided into two groups that were based on the size of the most frequent GTV-CTV1 margin used in the primary treatment planning, and the third group that consisted of the anatomical region as CTV1 (12 patients with larynx as anatomical margin, and two patients with oral cavity as anatomical margin). The patient-specific GTV-CTV1 margin was calculated as median surface distance from GTV to CTV1.

The POs positions were analyzed in relation to GTV surface based on the shortest distance between PO and GTV. The distance distribution between the margin groups where compared. Likewise, PO distance distribution relative to the 95% of prescription dose for the high-dose treatment level was evaluated.

Definition of local failures and analysis of local control

Data concerning treatment failures were obtained from the DAHANCA database and validated through examination of local treatment records for all patients. Patients were followed from date of entry at the center and failure status was tracked until the study cut-off date, January 13, 2016. A cut-off of three years after completing treatment was chosen to distinguish between recurrences and a second primary cancer [19]. For the current study only first-time local failures that occurred during the three years after treatment were included. Events were defined as local failure i.e. persistent disease (disease prior to two months after RT) or recurrences (as a tumor within the same region or in a nearby region). The event time was calculated from last day of RT to persistence or first local recurrence. Death prior to recurrence was censored within the survival analysis. Since the patient specific GTV-CTV1 margins were only available for the recurrences, the local control time analysis was divided in three groups based on treatment center being a proxy for margin size. Univariate and multivariate analysis using the Cox proportional hazard model were performed in order to analyze for factors influencing local control rate within the first three years after treatment.

Statistical analysis

All statistical analyses were performed using SPPS, version 24. Differences between patient and treatment characteristics were compared using Pearson Chi-square test. Median and interquartile range (IQR) were used to describe PO-GTV variation in the different margin groups. Kruskal–Wallis test was used to analyze the difference in distribution of recurrences between different margin groups. Differences were accepted to be statistical significant for p-values below 0.05. Log-rank test for trend was used to perform overall univariate local control comparison across the three centers.

Results

A total of 1576 patients were included. Fig. 1 shows all included patients.

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