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Analysis of loco-regional failures in head and neck cancer after radical radiation therapy

Francesca De Felice [a,b], Christopher Thomas [c], Sally Barrington [d], Angela Pathmanathan [a], Mary Lei [a], Teresa Guerrero Urbano [a,*]

[a] Department of Clinical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[b] Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy
[c] Department of Medical Physics, Guy's and St Thomas' NHS Foundation Trust, London, UK
[d] PET Imaging Centre, St Thomas' Hospital, Division of Imaging Sciences and Biomedical Engineering, King's College London, King's Health Partners, London, UK

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SUMMARY

Objectives: To investigate the anatomical distribution of loco-regional treatment failures (LRF) in patients with head and neck squamous cell carcinoma (HNSCC) in relation to clinical target volume (CTV) delineation.

Materials and methods: 56 patients with LRF were retrospectively identified. Patients were previously treated with radical intensity modulated radiotherapy (IMRT) +/− chemotherapy. Target volumes include gross tumour volume (GTV), its volumetric expansion of 10 mm (GTV-HD), CTV high dose (CTV-HD) delineated by anatomic expansion from GTV and CTV low dose (CTV-LD) defined to receive a prophylactic dose. LRF were evaluated by PET-CT or CT scan.

Materials and methods: We analysed the association between sites of LRF and target volumes and dosimetry, using image co-registration. Based on percentage of volume that received 95% of prescribed dose, LRF were classified as in-field, marginal or out-field.

Results: Median interval time from end of treatment to LRF was 186 days. 65 (95.6%) LRF were classified as in-field. Considering primary target volumes, 40 (58.8%) LRF occurred inside GTV, 13 (19.1%) in GTV-HD and 7 (10.3%) in CTV-HD. The overall 1-year and 2-year post-failure survival (PFS) was 45.8% and 24.2%, respectively. Post radiation LRF managed with salvage surgery had a significantly higher median PFS when compared with palliative treatments ($p = 0.003$).

Conclusions: The majority of LRF occurred within GTV/GTV-HD, suggesting it is safe to reduce the CTV to a volumetric expansion. Given the low incidence of geographical misses, future studies should be directed towards dose escalation of high-risk volumes. Potential reduction of RT-related toxicity with volumetric expansion could facilitate salvage surgery.

Introduction

Patients with head and neck squamous cell carcinoma (HNSCC) can be cured by surgery and/or radiotherapy (RT) with or without chemotherapy (CHT), depending on the primary tumour site and clinical stage [1]. Loco-regional failure (LRF) however remains a significant cause of mortality and morbidity despite significant progress in therapeutic modalities [2,3]. Approximately 30% of patients develop LRF within 5-years from the end of treatment, and prognosis following LRF is often described as worst event, with 85% of deaths attributable to disease progression [2,3].

Primary RT, with or without CHT or target therapy, is increasingly administered in the primary setting to improve loco-regional outcomes, and different altered fractionated RT and CHT regimens have been tested [4,5]. These intensified schedules have shown improvements in survival benefit at the cost of increased toxicity.

The head and neck region is anatomically complex and the risk of radiation-induced toxicities is significant due to the proximity to organs at risk. The volume of normal tissues exposed to a specific dose is essential to predict normal tissue complications, and a reduction of the organ volume exposed to high radiation doses is known to have an impact in reducing toxicity [6].

Target volume definition techniques, both anatomical and volumetric, have been advocated, but which is the optimal expansion

* Corresponding author. Tel.: +44 02071884219; fax: +44 02079289968.
E-mail address: Teresa.GuerreroUrbano@gstt.nhs.uk (T.G. Urbano).

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approach is still a matter of debate [3]. Intensity modulated radiation therapy (IMRT) has a distinct advantage over 3D-conformal RT in that it can reduce high doses of RT to normal tissues whilst delivering a radical dose to the target volume. Therefore, it is crucial to identify the optimal target volumes to ensure good outcomes in terms both of cure and toxicity.

The aim of this study was to map loco-regional recurrences to their original IMRT plans to determine the relationship of the failures to the irradiated volume.

Methods and materials

Patient population

Data for 798 consecutive patients with histological proven HNSCC, treated between January 2009 and April 2014, were reviewed in this retrospective study. Patients who received either palliative RT ($n = 124$) or re-irradiation treatment ($n = 13$), as well as those who did not receive the complete prescribed dose ($n = 8$) were excluded from the analysis. Among 653 patients treated with curative intent, 106 patients (16.2%) were identified as having persistent or recurrent loco-regional disease. All cases were discussed in a multidisciplinary team meeting that included clinical oncologists, surgeons, radiologists, and pathologists. The sixth American Joint Committee on Cancer Staging System (AJCC) [7] was used for the TNM classification. Considering the potential confounding factor related to different treatment modalities, recurrences in patients treated with primary surgery ($n = 34$) were excluded, as well as those treated using 3D-conformal RT ($n = 7$). In order to minimize the possible effect of natural history on the patterns of failure due to different tumour histology ($n = 9$), the final analysis was restricted to those 56 patients with HNSCC who received primary (CHT) IMRT.

Radiation therapy and target volume delineation

RT was delivered using a "forward planned" IMRT solution that used a 5–7 beam arrangement and several segments per field optimised to achieve conformity and OAR sparing similar to that achieved with inverse planned IMRT until May 2011. After the above date, inverse planned IMRT was used. Target volume definition protocols were the same for both techniques. The gross tumour volume (GTV) consisted of the primary tumour and involved lymph nodes based on the disease extension on diagnostic imaging exams and clinical examination. Lymph nodes were considered involved if they measured more than 10 mm in diameter (7 mm in the case of retropharyngeal nodes), with extracapsular extension or increased uptake on staging 18fluorodeoxyglucose positron emission tomography (18FDG-PET). A volumetric expansion of 10 mm was used for both primary tumour and nodes GTV to delineate a high dose region (GTV-HD). An anatomic expansion was then adopted to create the CTV high dose (CTV-HD), which included the entire organ where the tumour arose.

CTV-HD was also edited to include structures at risk for microscopic tumour spread, and modified to exclude natural barriers, such as air and/or bone. CTV low dose (CTV-LD) was defined to receive a prophylactic dose and delineated according to the European Organization for Research and Treatment of Cancer (EORTC) consensus guidelines [8–10]. A planning target volume (PTV) was created adding a margin of 4 mm to each CTV.

Patients were treated supine and were immobilized in a thermoplastic shell, with three fixation points and shoulder depressors. CT scan was performed with 2 mm slices obtained from base of skull to the top of the carina.

For both forward-planned and inverse-planned IMRT treatments a simultaneously integrated boost (SIB) technique was used. The prescription dose was 65 Gy in 2.17 Gy/fraction to CTV-HD, concurrently with 54 Gy in 1.8 Gy/fraction to CTV-LD.

Chemotherapy

Concurrent chemotherapy was recommended in stage III and IV disease. Type of systemic drug was individualized based on patient's comorbidities. Usually carboplatin (AUC 5) or cetuximab (weekly 250 mg/m^2, loading dose of 400 mg/m^2) was used when cisplatin (100 mg/m^2 day 1–29) was contraindicated.

Induction chemotherapy was used in patients with bulky disease. It mostly consisted of two cycles of cisplatin (80–100 mg/m^2 day 1) plus 5-FU (1000 mg/m^2 days 1–4).

Follow-up

Patients were followed according to internal protocol weekly on treatment and up to 6 weeks post-(CHT)IMRT. After treatment, patients were monitored at 6 weeks intervals for the first year, at 3–4 monthly intervals for the additional 2 years, and every six months for subsequent years. Patients were followed up closely to detect persistent or recurrent disease by clinical exam and fiberoptic examination. Imaging, PET/CT or CT scan, was performed 12 weeks after the end of RT to assess disease response.

Failures: detection and analysis

Failures were defined as local (T) if they were within the area of the primary tumour, and as regional (N) if they occurred in the neck region. Persistent disease was defined as the presence of tumour within 6 months after RT completion. Cancer recurrence was defined as the re-emergence of disease following a minimum 6 month period of complete remission [11].

In all cases of suspected clinical loco-regional failure, patients underwent a diagnostic imaging exam, FDG PET-CT and/or CT with contrast.

Contouring of regions of failure was performed on the basis of evaluation of these exams in collaboration with a nuclear medicine physician.

Original treatment planning scans and radiologic imaging of failures were co-registered in order to transfer relapse volume contours to the planning CT scan.

Dose-volume histogram analysis was performed to evaluate the dose of radiation received by those failure volumes. Based on the percentage volume that received 95% of the prescribed dose, failures were classified as in-field (>95%), marginal ($\geqslant$20% $\leqslant$95%) or out-field (<20%) [12]. Then the volumetric and anatomic expansion of the original GTV that would have been required to include the area of failure was considered.

Statistical analysis

Statistical analysis was performed using RStudio-0.98.1091 software. Standard descriptive statistics were used to evaluate the distribution of each potential factor. Dose volume histograms (DVHs) were evaluated for ability to meet the desired target coverage. Post-failure survival (PFS) was calculated in months from the date of failure detection to the date of the last follow-up or death. Failures outcome was estimated according to Kaplan–Meier method [13].