Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/amjoto

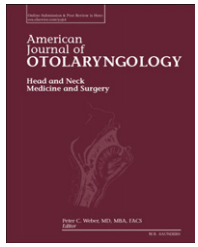

Image guided volumetric response during chemoradiotherapy for head and neck squamous cell carcinoma as a predictor of disease outcomes

Rajayogesh Davuluri, MD[a], *Jeff M. Krase, MD*[a], *Haiyan Cui, PhD*[b], *Uma D. Goyal, MD*[a], *Michael K. Cheung, MD*[a], *Charles C. Hsu, MD, PhD*[a], *Sun K. Yi, MD*[a,*]

[a] *University of Arizona Cancer Center, Department of Radiation Oncology*
[b] *University of Arizona Cancer Center, Department of Biostatistics*

ARTICLE INFO

Article history:
Received 16 December 2015

ABSTRACT

Purpose: The goal of this study was to correlate volumetric image guided disease response to clinical outcomes in patients receiving chemoradiation therapy (CRT) for locally advanced head and neck squamous cell carcinoma (HNSCC).

Materials and methods: Thirty four patients completing definitive CRT for locally advanced HNSCC with megavoltage computed tomography (MVCT) guided tomotherapy IMRT were retrospectively reviewed for volumetric response. Grossly identifiable primary tumor (PT) and nodal disease (ND) response was evaluated by weekly MVCT regression. Percent end-of-treatment (EOT) residual volumes and regression rates were correlated with risk of local failure (LF), progression free survival (PFS), and overall survival (OS).

Results: A total of 7 LFs were identified in 6 patients at a median follow-up of 8 months. The mean percent EOT residual volumes for PT and ND in patients with and without LF were 20% vs. 5% ($p = 0.005$) and 47% vs. 6% ($p = 0.0001$), respectively. The PT and ND volume regression rates for patients with and without LF were 12.7% per week vs. 15.9% per week ($p = 0.04$) and 3.4% per week vs. 10.5% per week ($p < 0.001$), respectively. Utilizing an EOT cut-off value of 25% residual volume, the relative risks of LF for PT and ND were 14.7 ($p = 0.03$) and 25 ($p = 0.001$), respectively. Patients found with PT and/or ND residual volumes <25% at EOT had longer 2 year OS of 100% vs. 67% ($p = 0.0023$) and PFS of 87% vs. 17% ($p < 0.001$) compared with patients with residual volumes >/= 25% at EOT.

Conclusion: Patients with locally advanced HNSCC who have significant MVCT volume reduction over the course of definitive CRT tend to have favorable clinical outcomes.

1. Introduction

Head and neck cancers account for more than 550,000 cancers annually worldwide and represent 3% of all diagnosed cancers annually in the United States [1]. Radiotherapy plays an integral role in the management of head and neck squamous cell carcinoma (HNSCC) either definitively or adjuvantly. Chemoradiation therapy (CRT) for locally advanced HNSCC provides organ-preservation and is now considered standard of care [2].

Improvements in radiation delivery with intensity modulated radiation therapy (IMRT) has allowed for safe dose escalation and reductions in treatment related toxicities [3]. With improved

* *Corresponding author at:* 1501 N. Campbell Ave. Tucson, AZ, 85724. Tel.: +1 520 694 7236.
E-mail address: sunkyi@email.arizona.edu (S.K. Yi).

http://dx.doi.org/10.1016/j.amjoto.2016.03.003
0196-0709/

conformity and faster dose fall-off with IMRT, daily set-up precision has become increasingly important to decrease the risk of marginal misses [4]. The routine use of image guided radiotherapy (IGRT) allows for improvements in daily set-up error [5–7] and is therefore commonly utilized when verifying patient positioning, particularly in complex areas such as the HN region.

In addition to positional verification, volumetric on-board imaging may allow for treating physicians to serially evaluate disease response over the course of therapy [8]. IGRT measured disease response has been found predictive of oncologic outcome for patients undergoing radiotherapy for lung cancers [9,10]. To our knowledge no such study has been performed with patients undergoing CRT for HNSCC. The clinical implications of on-board disease assessment may include the implementation of adaptive planning [11,12] and dose escalation to non-responding areas or early surgical intervention [13]. We therefore analyzed the volumetric reduction of both primary tumor (PT) and nodal disease (ND) in patients treated with CRT for HNSCC on weekly megavoltage computed tomography (MVCT) and correlated their response to clinical outcomes.

2. Materials and methods

2.1. Patient selection

This retrospective study was approved by our institutional review board. A total of 34 patients treated with definitive CRT between 2008 and 2014 for Stage III–IV HNSCC using IMRT on our tomotherapy linear accelerator (Madison, WI) were retrospectively reviewed. Patients were included only if they had radiographically identifiable disease at the start of therapy, defined as having measurable PT and/or ND measuring $\geq$2.5 cm^3 and $\geq$1 cm in short-axis diameter. We excluded patients if they had received neoadjuvant chemotherapy, had non-squamous cell histology, were diagnosed with multiple synchronous head and neck primary cancers, or suffered treatment breaks that lasted longer than two weeks during their therapy.

2.2. IMRT technique

All 34 patients underwent diagnostic PET/CT scan prior to treatment. CT simulation images were acquired with a Philips Brilliance Big Bore scanner (Andover, MA) in 3 mm contiguous slices from skull vertex to mid-thorax after 100 cm^3 of isoview contrast (Bracco Imaging, Monroe Township, NJ) was administered. IMRT planning was performed with simultaneous integrated boost utilizing 2–3 dose levels for each patient. Macroscopic gross disease with additional margin accounting for microscopic disease, internal motion, and daily set-up uncertainties (planned target volume [PTV 1]) was contoured and prescribed to 70 Gy in 33–35 fractions. High risk microscopic regions and nodal levels (PTV2) were prescribed a dose ranging from 59 to 63 Gy in 33–35 fractions. Low risk elective nodal regions (PTV3) were prescribed a dose ranging from 52 to 56 Gy in 33–35 fractions. All PTVs were prescribed to a minimum of 95% coverage. Thirty three patients underwent post-treatment PET/CT scan at a median time of 101 days (range: 62–444 days).

2.3. Volumetric analysis

All patients underwent daily image guidance with MVCT prior to each fraction of treatment. MVCT images were acquired utilizing the gantry mounted system with an energy of 1 MeV, dose rate of 266–283 cGy per min, slice thickness of 5 mm, and field-of-view extending the length of PTVs contoured. The estimated additional dose delivered to the patient ranged from 1 to 4 cGy per daily MVCT. A total of 7 weekly representative MVCT image sets were extracted per patient and were imported from tomotherapy dataserver into Pinnacle planning software (Philips Healthcare, Andover, MA). Week 0 MVCT represented images taken at the start of therapy and week 6 represented those taken at the end of therapy. Delineation of identifiable PT and/or ND was performed on each patient's image sets utilizing head and neck windowing. When contouring on week 0 MVCT imaging, disease was delineated with the assistance of pre-treatment hypermetabolic findings and enhancing portions from diagnostic PET/CTs and with contouring fused from the original treatment plan. For subsequent serial MVCTs, the window leveling which was utilized for week 0 for a given patient was fixed in effort to reduce interpreting variability. Given the poorer soft tissue contrast with MVCT versus kilovoltage CT, changes in more obvious asymmetric and exophytic components of disease served as a surrogate for contouring changes in contiguous but less obvious infiltrative and endophytic portions of disease.

PT was contoured only when an obvious asymmetric or exophytic component of $\geq$2.5 cm^3 and $\geq$1 cm in short axis was observable on week 0 MVCT. ND was contoured only when an asymmetric component of $\geq$2.5 cm^3 and $\geq$1 cm in short axis was seen when compared to the contralateral neck at that level. When the patient presented with multiple pathologic nodal involvement, only the largest node or nodal conglomerate was chosen for MVCT contouring. In 19 of 34 total patients, both the PT and ND volumes were identifiable and therefore contoured. In 6 patients, only the PT was contoured because nodes were not clearly visible on MVCT (n = 1) or the patient had node-negative disease (n = 5). In 9 patients, only the ND was contoured since the PT was not clearly visible on the MVCT. Contouring for each patient was performed while blinded to patient outcome to minimize bias. Given time constraints, a resident physician (RD) contoured in tandem with the head and neck radiation oncologist (SY) for averaging effects of potential interobserver variability.

2.4. Outcomes and variables analyzed

Patient characteristics that were analyzed included smoking status, p16 status, T stage, N stage, and whether the patient required a break from therapy. Disease related outcomes analyzed included percent residual disease volume, rate of disease regression, local failure (LF), progression-free survival (PFS), and overall survival (OS). LF was defined as persistent or recurrent disease within the specified contoured volume on serial MVCTs. Treatment failures were confirmed either as clinically and radiographically enlarging masses or by pathologic assessment.