

Scientific Article

# Elective nodal dose of 60 Gy or 50 Gy in head and neck cancers: A matched pair analysis of outcomes and toxicity

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## Abstract

**Purpose:** The main objective of this study was to evaluate appropriate doses for elective nodal irradiation (ENI) in head and neck squamous cell carcinoma (HNSCC) patients to optimize the therapeutic ratio.

**Methods and materials:** A matched pair analysis of 2 similar cohorts of HNSCC treated with intensity modulated radiation therapy with different dose prescriptions to the elective nodal regions was conducted. One group received 60 Gy, whereas the other received 50 Gy (ENI<sub>60</sub> and ENI<sub>50</sub> groups, respectively). Isolated regional recurrences (IRR) and locoregional control were evaluated. Doses received by the parotid and thyroid glands were compared among both groups and were clinically correlated with the trend of salivary function recovery and incidence of hypothyroidism.

**Results:** Of the 110 patients studied, 97 were eligible for analysis after matching based on propensity scores. The 3-year locoregional control rate was similar in ENI<sub>60</sub> and ENI<sub>50</sub> (78.7% and 77%, respectively;  $P = .93$ ). There were no IRR in ENI regions in either group. The mean ipsilateral parotid dose in ENI<sub>60</sub> was significantly higher compared with ENI<sub>50</sub> (42 vs 35.7 Gy,  $P = .03$ ). There was no significant difference in the mean contralateral parotid doses (32.5 vs 31.7 Gy,  $P = .6$ ). The mean thyroid doses were high in ENI<sub>60</sub> compared with ENI<sub>50</sub> (54.7 vs 43.3 Gy,  $P < .001$ ). A significant difference in ipsilateral parotid salivary excretory fraction ratio at 1 year ( $P = .03$ ) was observed with quicker recovery of salivary function. The salivary excretory fractions were poorer in the ENI<sub>60</sub> group with higher mean parotid doses ( $P = .009$ ). At 2 years, 26 patients (54%) in the ENI<sub>60</sub> group and 13 patients (26.5%) in the ENI<sub>50</sub> group developed biochemical hypothyroidism ( $P = .007$ ).

Conflicts of interest: None.

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**Conclusions:** Doses of 50 Gy equivalent are sufficient to sterilize the uninvolved nodal regions because the rates of IRR are extremely low. Using ENI<sub>50</sub> results in clinically meaningful reduction in salivary and thyroid toxicity in HNSCC.

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## Introduction

Standard radiation therapy (RT) dose for gross disease (primary and lymph node) is about 66 to 70 Gy. The prophylactic dose of the uninvolved lymphatics in the neck is about 45 to 60 Gy as used in practice and in clinical trials worldwide.<sup>1-3</sup> There is a lack of consensus on the appropriate prophylactic dose to the neck. In practice, there have been 2 schools of thought regarding the elective nodal dose. In 1 approach, 2 prophylactic dose levels are used (60 Gy equivalent to “high risk” and 50 Gy equivalent to “low risk” region), depending on the location of primary and the involved nodal levels. Here, the uninvolved lymph nodal region close to involved nodes is assumed to be at a higher risk of harboring micrometastatic disease and hence a higher dose to the first echelon beyond the involved nodes. In the second approach, all uninvolved neck regions are considered at equal risk of relapse and prescribed about 45 to 50 Gy.

Whether the use of 60 Gy in high risk prophylactic regions prevents more relapses compared with a lower dose is uncertain and the subject of this work. Although the higher dose approach may include a certain safety margin for the assumed higher burden of microscopic disease, there seems to be no definite radiobiological or clinical rationale for the same. This is especially true with the use of modern imaging. The higher prophylactic dose is quite likely to lead to higher toxicity, which is being evaluated in the present paper.

At our center, there has been a gradual shift in dose and volumes in elective nodal irradiation (ENI) using intensity modulated radiation therapy (IMRT) over the past decade. In the initial years, a 2 dose approach was used for ENI in practice as well as in clinical trials. Over time, we moved over to a single dose approach for all ENI with the availability of better imaging and routine use of positron emission tomography (PET)-computed tomography (CT) scanning for staging. In the absence of randomized trial data, we sought to address this issue by performing a matched pair analysis of 2 similar cohorts of patients treated in 3 prospective, ethics-approved institutional trials. The primary aim of this work was to identify the differences in the pattern of nodal relapse between the 2 approaches. We also sought to determine the dose to organs at risk (parotid and thyroid glands) and if the dose reduction in the 50 Gy approach leads to a clinically meaningful benefit.

## Methods and materials

Patients with head and neck squamous cell carcinoma (HNSCC) who were treated at our institute in 3 prospective studies between August 2005 and September 2013 with radical intent were evaluated for the inclusion in the present analysis. All patients were treated with IMRT technique, with the majority receiving concurrent chemotherapy. Two of the studies were identical prospective randomized controlled trials comparing IMRT with 3-dimensional conformal RT. Only patients in the IMRT arm were included in this analysis. The third study was a prospective phase 2 study with identical patient populations undergoing IMRT. The only real differentiating factor between the 2 groups was the dose received by the elective nodal regions. One hundred and ten patients were eligible for the study at baseline, of which 97 were analyzed after matching. In the randomized controlled trials (48 patients, 49.5%), the regions immediately adjacent to involved lymph nodes or those deemed at higher risk of metastasis based on the primary lesion were termed as high risk volumes and a dose of 60 Gy equivalent was delivered (ENI<sub>60</sub>).<sup>4</sup> In the phase 2 study (49 patients, 50.5%), all the uninvolved lymph nodal levels irrespective of their proximity to the involved lymph nodal levels were termed as low risk volumes and a dose of 50 Gy equivalent was delivered (ENI<sub>50</sub>). The grouping for this analysis was done based on the ENI dose delivered to these regions (ie, 60 ENI<sub>60</sub> or ENI<sub>50</sub>).

## Patient, tumor, and treatment details

Patients with previously untreated oropharyngeal, laryngeal, and hypopharyngeal cancers with T1-4a, N0-N2b, M0 (stages I-IVb; American Joint Committee on Cancer, 2002) were included except T1-2 laryngeal tumors. All patients underwent standard baseline investigations including an <sup>18</sup>F-fluorodeoxyglucose PET-CT scan. Baseline <sup>99m</sup>Tc-pertechnate salivary scintigraphy was done, and consent was obtained from all patients in the respective studies. All patients underwent simulation with a 4-clamp thermoplastic mask and a planning CT scan with intravenous contrast with a slice thickness of 2.5 to 3 mm was acquired, the details of which were published previously.<sup>5,6</sup>

## Segmentation, planning and dose prescription

The gross tumor volumes as defined clinically and radiologically were delineated in a similar manner in both

the groups. A 10- to 15-mm margin was grown around the gross tumor volume and edited from the skin, bone, and air cavity spaces to generate clinical target volume (CTV). A uniform expansion of 5 mm was done to generate the planning target volume (PTV). The PTVs to the gross disease were planned to receive 66 Gy in 30 fractions in both the groups.

The uninvolved lymph nodal levels were contoured as per consensus contouring guidelines<sup>7,8</sup> in both groups; the respective PTVs for the uninvolved neck were generated with a uniform 5 mm margin. In the ENI<sub>60</sub> cohort, high-risk CTV included 1 lymph node level above and below the involved lymph node regions. Levels in which the probability of spread was expected to be lower were termed low-risk CTVs. In the ENI<sub>50</sub> cohort, the uninvolved neck regions were considered low-risk CTVs and given a 50 Gy equivalent dose.

In the ENI<sub>60</sub> group, the PTVs generated for the high-risk CTVs (uninvolved neck) were planned for 60 Gy in 30 fractions; low-risk PTVs received 54 Gy in 30 fractions (50 Gy equivalent) as a simultaneous integrated boost (SIB). In the ENI<sub>50</sub> group, the entire ENI volume received 54 Gy in 30 fractions (50 Gy equivalent). There was no 60 Gy PTV in the ENI<sub>50</sub> cohort.

Planning for IMRT in ENI<sub>60</sub> group patients was done either in the Sunrise-Plato system (version 2.7.4) or Eclipse treatment planning system. The patients were treated with 6 MV photons with 7 to 9 coplanar fields using the step-and-shoot mode of IMRT. In the Plato system, optimization was done with gradient-search algorithm, whereas anisotropic analytical algorithm and pencil beam convolution algorithm was used in the Eclipse system. All the ENI<sub>50</sub> group patients were planned and treated on a tomotherapy system with 6 MV photons in dynamic mode using convolution-superposition algorithm with a width of 2.5 cm, pitch of 0.3, and modulation factor of 3 to 3.5.

Plan evaluation was done in accordance with the International Commission on Radiation Units & Measurements 62 guidelines. Dose coverage of 95% or higher of the prescription volumes were accepted. The doses to the organs at risk (OARs) were in tolerance as per QUANTEC guidelines. Highest priority was given to the spinal cord (maximum point dose of <45 Gy), followed by parotid glands with a mean of <26 Gy to each of the glands. The planning constraints were similar irrespective of the group or treatment planning system and have been published previously.<sup>5,6</sup>

## Chemotherapy

Chemotherapy was administered in 36 (75%) patients in the ENI<sub>60</sub> group and 37 (75.5%) patients in the ENI<sub>50</sub> group. Cisplatin 30 mg/m<sup>2</sup> was given in a once-weekly regimen as per institutional protocol. Patients in stages III and IV with adequate renal function parameters were given

cisplatin. In patients with mildly impaired renal functions, carboplatin (AUC-2) was given.

## Definition of regional recurrences

Isolated regional recurrence (IRR) was defined as recurrence in-field in the ENI regions (uninvolved high and low risk). Locoregional recurrence (LRR) was defined as the persistence of the primary or nodal disease or the re-appearance of disease at the primary or the involved lymph nodal regions after complete disappearance of disease.

## OAR doses and clinical correlation

The mean doses received by the ipsilateral and contralateral parotid glands were compared between the 2 groups. Dynamic salivary scintigraphy with 99mTc pertechnetate was done in all the patients at baseline and posttreatment at 6-month intervals. The clinical endpoint was evaluation of post-sialogogue salivary excretory fraction (SEF) and the rate of improvement over time in SEFs in both the groups. SEFs were evaluated at baseline and posttreatment at intervals of 3, 6, 12, 18, and 24 months. The SEF ratio was defined as ratio of SEF at a particular point to the baseline SEF and expressed as a percentage. The recovery pattern of salivary functions as defined by the SEF ratios of the ipsilateral and contralateral parotid glands were compared among both groups and correlated with the mean parotid doses received. Similarly, the mean thyroid doses were evaluated and the proportion of patients developing hypothyroidism was compared. Thyroid function test (thyroid-stimulating hormone [TSH], T4, and T3 levels) was done in all patients at baseline before starting RT and every 6 months thereafter. A TSH value >4.7  $\mu$ IU/mL with normal T4 level was defined as subclinical hypothyroidism, whereas a T4 level of <4.5  $\mu$ IU/mL was defined as biochemical hypothyroidism. Patients with TSH levels >10  $\mu$ IU/mL or presence of clinical symptoms were started on thyroxine replacement therapy.

## Follow-up and salvage

All patients were reviewed 6 to 8 weeks after completion of RT for response evaluation. A PET-CT scan was done in all patients at 10 to 12 weeks after RT. Three-month follow-up was advised for the first 2 years after RT, every 6 months thereafter for 5 years, and annually afterward. Patients were evaluated with a complete physical examination and, in clinical suspicion, underwent imaging and pathological confirmation. Depending on the extent of disease, patients either underwent surgery or chemotherapy.

## Statistical analysis

With the baseline division of patients into 2 groups, matched pair analysis was done to match the baseline

characteristics between the 2 groups. All imbalanced variables with a significance level of  $P > .05$  on  $\chi^2$  test between the 2 groups were included in the logistic regression to calculate the propensity score, modeling the probability of a patient receiving ENI<sub>60</sub> or ENI<sub>50</sub>. A 1:1 matching without replacement was performed by using nearest neighbor matching method. Variables considered for matching were: age ( $\leq 50$  vs  $> 50$ ), nodal status (N0 vs N+), T stage (T1+T2 vs T3), and site (hypopharynx/larynx vs oropharynx).

Categorical variables were expressed as percentage and compared using the  $\chi^2$  test; non-normal data were expressed as median and interquartile ratio and compared between the groups using the Mann-Whitney test. Comparison of mean parotid and thyroid doses between groups was done using the  $\chi^2$  test. Linear mixed-effect regression models were done with random intercepts to test the difference in the rate of change in the SEF ratio between the ENI<sub>60</sub> and ENI<sub>50</sub> groups. The IRR rates and LRR were evaluated with Kaplan Meier survival analysis and log rank test. Statistical analyses were undertaken using SPSS 21.0 software for Windows (SPSS Inc., Chicago, IL), and all tests were 2 sided with a significance level set at  $P < .05$ .

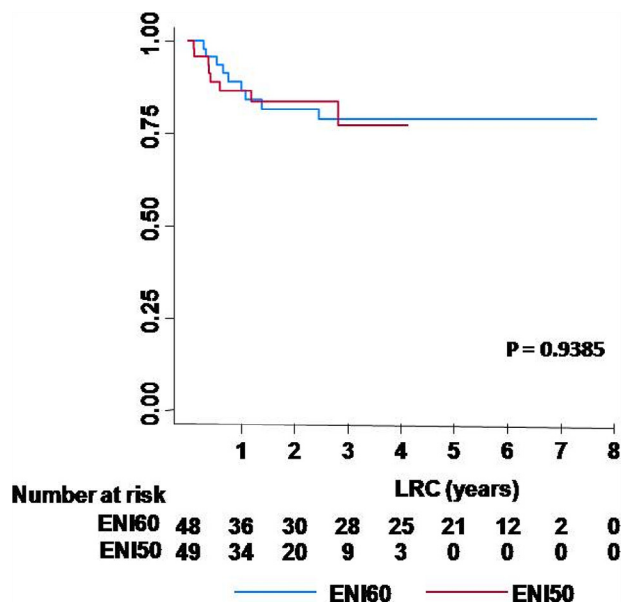
## Results

One hundred and ten patients were eligible for matching at baseline, of whom 97 were matched based on clinical characteristics as shown in Table 1.

**Table 1** Baseline characteristics of patients in ENI<sub>60</sub> group and ENI<sub>50</sub> group based on which matching was done

Characteristic	ENI <sub>60</sub>	ENI <sub>50</sub>	P value
No. of patients	48	49	.45
Mean age (range)	53.5 (31-65)	54 (32-68)	.63
Subsite			
Oropharynx	27	28	.30
Hypopharynx/larynx	21	21	
Sex			
Male	42	48	Not matched
Female	08	01	
T stage			
T1-2	23	24	.37
T3	25	25	
N stage			
N0-1	35	36	.23
N2	13	13	
Overall stage			
I	02	02	.29
II	13	10	
III	23	22	
IV	10	15	

ENI<sub>50</sub>, elective nodal irradiation receiving 50 Gy; ENI<sub>60</sub>, elective nodal irradiation receiving 60 Gy.



**Figure 1** Kaplan-Meier curve depicting locoregional control in both groups. ENI<sub>50</sub>, elective nodal irradiation receiving 50 Gy; ENI<sub>60</sub>, elective nodal irradiation receiving 60 Gy; LRC, locoregional control.

## Locoregional control and IRR rates

The 3-year locoregional control was 78.7% (95% confidence interval [CI], 63-88) and 77% (95% CI, 56-89) in the ENI<sub>60</sub> and ENI<sub>50</sub> groups, respectively ( $P = .93$ ), as depicted in Fig 1. There were no IRRs in the ENI regions of either group. Two patients had nodal recurrence, of which 1 had a persistent nonsalvageable node (ENI<sub>60</sub>). Three patients in the ENI<sub>60</sub> developed second primary cancer. The median follow-up of patients in ENI<sub>60</sub> was 51 months and 32 months in the ENI<sub>50</sub> group.

## Dosimetric results

The mean ipsilateral parotid dose in ENI<sub>60</sub> was significantly higher compared with ENI<sub>50</sub> (42 vs 35.7 Gy,  $P = .03$ ). There was no significant difference in the mean contralateral parotid dose between the groups (32.5 vs 31.7 Gy,  $P = .6$ ).

The mean thyroid doses were significantly higher in ENI<sub>60</sub> group compared with the ENI<sub>50</sub> group (54.7 vs 43.3 Gy,  $P < .001$ ).

## Scintigraphy results

There was a significant difference in the ipsilateral parotid SEF ratios at 1 year ( $P = .03$ ). The SEF ratios were lower in the ENI<sub>60</sub> group, which received a higher mean parotid dose ( $P = .009$ ). There was no difference in the mean SEF



**Table 2** Ipsilateral parotid SEF ratios at various time points among the groups

SEF ratio	ENI <sub>60</sub> group	ENI <sub>50</sub> group
Post-RT (2 mo)	52.1	60.5
6 mo	61.1	83.4
12 mo	64.9	86.9
18 mo	73.7	94.2
24 mo	93.4	92.7

RT, radiation therapy; SEF, salivary excretory fraction. Other abbreviations as in Table 1.

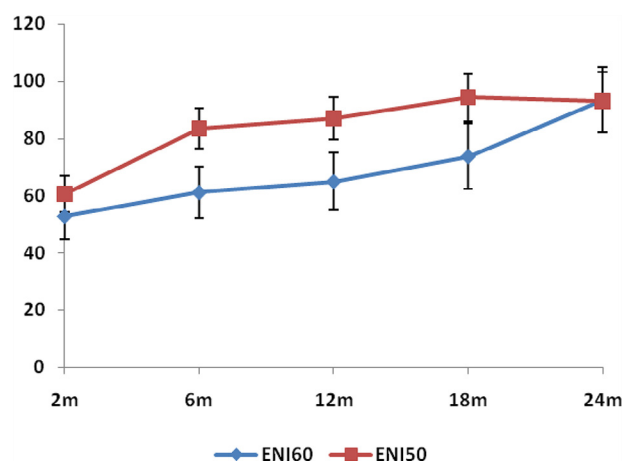
ratios of the contralateral parotid gland between the groups. The time taken for improvement in the SEF ratios was significantly shorter in ENI<sub>50</sub>, as shown in Table 2. At 12 months, the SEF had recovered to 86.9% of baseline in the ENI<sub>50</sub> group, whereas in the ENI<sub>60</sub> group, it reached only 65% of baseline. The time taken for improvement in the SEFs was significantly shorter in the ENI<sub>50</sub> group compared with the ENI<sub>60</sub> group, although the values equalized at 24 months, as shown in Fig 2.

## Hypothyroidism

At 2 years after RT, 26 patients (54%) in the ENI<sub>60</sub> group and 13 patients (26.5%) in the ENI<sub>50</sub> group developed biochemical hypothyroidism ( $P = .007$ ) needing thyroxine replacement therapy.

## Discussion

The goal of this work was to evaluate the IRR rates in electively irradiated nodal regions and to ascertain if a dose of 50 Gy to these regions is adequate instead of a higher dose, as has been common practice worldwide. We report



**Figure 2** Rapid recovery of salivary excretory fraction ratios in ENI<sub>50</sub> vs ENI<sub>60</sub>. See Fig 1 for abbreviations.

the absence of IRR in either group (ENI<sub>60</sub>, ENI<sub>50</sub>) with a statistically and clinically significant dose reduction in the ipsilateral parotid and thyroid gland in the ENI<sub>50</sub> group. The patterns of failure literature in HNSCC indicate that regional recurrences mainly occur in the initial involved nodal regions.<sup>1,9,10</sup> Although IMRT series have reported IRR rates in the range of 0% to 10%, most delivered 60 Gy for lymph nodal regions assumed to be at a higher risk of recurrence.<sup>9,10</sup> The present study highlights similar outcomes in patients treated with a 50 Gy prescription volume to all microscopic lymph nodal basins. The traditional use of 50 Gy to microscopic disease is mainly based on the historical series by Fletcher et al using conventional radiation therapy.<sup>11</sup> With the change in practice from conventional to conformal techniques, the dose volume of 60 to 64 Gy emerged as a prophylactic dose to certain high-risk areas, the rationale of which was not clear. The general assumption was that the levels above and below the involved nodal region harbors a larger microscopic disease burden requiring higher doses for sterilization.

In the present study, there were 2 regional-only events in the absence of primary recurrence (both the events in ENI<sub>60</sub> group); of these, 1 patient had persistent nodal disease that was nonsalvageable; another patient developed nodal recurrence in the initially involved region to which 66 Gy was delivered. These results emphasize the fact that LRR in the initially involved site is the most common pattern of failure in patients treated with radiation therapy. The IRR in the ENI regions is very low, irrespective of the dose received. In addition, definition and reporting of IRR differ in the reported literature, making interpretation and comparison difficult. Duprez et al reported no significant difference in IRR in patients treated with IMRT with elective nodal regions receiving a dose of 56 to 70 Gy or 56 Gy. The 2-year IRR in the higher dose volumes was 3%, compared with 0% in low-dose volumes ( $P = NS$ ).<sup>12</sup> This study, however, was retrospective with mixed inclusion criteria of postoperative and radically treated patients. Dandekar et al, in a retrospective review of 114 patients treated with IMRT with SIB technique, reported no IRR in the ENI regions receiving 59.4 or 54.4 Gy.<sup>13</sup> Bedi et al reported the results of a retrospective comparison in which equivalent control rates in patients treated with IMRT-SIB with either conventional dose fractionation (54 Gy/30 fractions) or reduced dose per fraction (50 Gy/35 fractions) to elective nodal levels was achieved. None of the patients in either group developed IRR at a median follow up of 31 months.<sup>14</sup> In our study, the median follow-up of the ENI<sub>50</sub> group was shorter than the ENI<sub>60</sub> group (32 vs 51 months). Because most locoregional events (>90%) occur in the first 2 years after treatment, the follow-up for the ENI<sub>50</sub> group (median, 32 months) was considered sufficient for the purpose of this study endpoint.<sup>1,9,12,15,16</sup>

With the reduction in volumes and doses in ENI<sub>50</sub>, a difference in the doses to the OARs was expected. It is

well established that the radiation dose is the most important predictive factor in the development of parotid dysfunction. The ipsilateral mean parotid doses were significantly less in the ENI<sub>50</sub> group compared with the ENI<sub>60</sub> group (35.7 vs 42 Gy,  $P = .03$ ). This dosimetric improvement was expected to have a clinical benefit in terms of salivary function recovery. Chao et al have reported a 5% exponential loss of function with every 1 Gy increase in dose to the parotid glands.<sup>17,18</sup> This was confirmed with the observation that the ENI<sub>50</sub> group had shorter time to recover salivary function compared with the ENI<sub>60</sub> group. In the ENI<sub>60</sub> group, there was recovery in the SEF ratio in the range of 65% at 1 year, which is similar to the reported parotid-sparing IMRT series.<sup>19,20</sup> The ENI<sub>50</sub> group had a significantly quicker improvement of 87% at 1 year, although the recovery tends to equalize at 2 years. The contralateral parotid doses did not differ because most patients in both groups received similar doses to contralateral level II lymph nodal region.

An incidence of 30% to 60% hypothyroidism in patients treated with IMRT has been reported in the literature.<sup>21-23</sup> In the present series, we report similar incidence in the ENI<sub>60</sub> (56%) at 2 years, whereas there is significant reduction in hypothyroidism in ENI<sub>50</sub> (26%). This may be explained by the lower mean thyroid doses in the ENI<sub>50</sub> cohort. Chyan et al reported that V45 is an important predictor of developing hypothyroidism.<sup>21</sup> In the meta-analysis by Vogeliuss et al, mean dose of 45 Gy was associated with a 50% risk of hypothyroidism.<sup>24</sup> The only randomized trial addressing the reduction of doses for ENI was recently reported by Nuyts et al.<sup>25</sup> In this study, the elective nodal volumes received either 50 or 40 Gy. Dosimetric analysis revealed significant decrease in OAR doses (spinal cord and pharyngeal constrictors); however, there was no difference in long term dysphagia rates. The regional relapse rates at 2 years were higher in the 40 Gy group (13%) compared with the 50 Gy group (5.5%). Further reduction of ENI doses were reported by Salama et al, in which elective nodal regions that received 36 Gy had poorer control compared with 50 Gy volumes.<sup>26</sup> Reduction of doses up to 50 Gy may be considered clinically safe, with regional events being similar to higher doses. Doses less than 45 to 50 Gy should not be recommended outside clinical trials.

The limitations of the present study include a relatively small sample size and the absence of patient-reported outcomes with respect to xerostomia and quality of life. The patients in the ENI<sub>50</sub> group were treated on helical tomotherapy which is expected to have better plan conformity and OAR sparing compared with step-and-shoot IMRT, although this difference is likely to be small because the OAR constraints used for both cohorts were identical. With an emphasis on dose deescalation in the era of human papilloma virus-related cancers, human papilloma virus status might have added value to the information presented.

## Conclusions

The rate of IRR in the initially uninvolved regions is low in HNSCC patients and a dose of 50 Gy (instead of 60 Gy) is sufficient to sterilize microscopic disease irrespective of the presence of nodes in the adjacent regions. This also leads to a reduction in doses to the parotid and thyroid glands, which leads to less toxicity. Although randomized data would be ideal, in the absence of such data, 50 Gy equivalent dose for ENI can be considered the appropriate dose for most patients with HNSCC.

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