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Regional Radiation Therapy for Oropharyngeal Cancer in the HPV Era

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Oropharyngeal carcinoma associated with the human papillomavirus is increasing in incidence and represents a unique head and neck disease with favorable treatment outcomes. This review evaluates the evolving role of radiotherapy in regional management with an overall goal of treatment de-escalation in the appropriate patient. Determining the optimal approach and selection factors for treatment de-escalation is under active investigation. Response to induction chemotherapy, refining adverse pathologic factors after a primary surgical approach, decreasing radiation dose with or without chemotherapy in the definitive or adjuvant settings as well as more selective nodal level irradiation all are current strategies for treatment de-escalation. This review details the likely changes in regional radiotherapy management for oropharyngeal carcinoma in the modern human papillomavirus era and discusses future approaches to patient selection with the goal of reducing toxicities while maintaining function preservation and quality of life in group of patients who are younger and healthier than traditional head and neck cancer patients.
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Introduction

The incidence of human papillomavirus (HPV)-associated oropharyngeal carcinoma (OPC) has more than doubled from 1988 to 2004 while conversely the incidence of HPV-negative cancers declined by 50%.[1] Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer. For instance, Ang et al. reported 3-year overall survival rates of 82% in HPV-positive OPC compared with 57% in HPV-negative OPC in a prospective study of nonmetastatic stage III-IV treated with concurrent chemoradiation (AJCC 7th edition).[2] Moreover, epidemiologic studies have shown that such patients are younger at diagnosis, are healthier and less likely to be heavy smokers.[3]

With better treatment outcomes for HPV + patients, the 7th edition AJCC staging system is inadequate to distinguish outcomes by stage regardless of treatment approach. Based on an analysis of a consortium of large institutional databases, a new staging system was developed and validated for HPV-positive OPC[4,5] with both a clinical system for those undergoing primary radiation and a pathologic system in patients undergoing definitive resection. These findings are currently represented in the latest AJCC 8th edition.[6] Major changes involve the nodal staging. For example, a patient undergoing primary radiation with multiple ipsilateral nodes is downstaged from N2b to N1 with a T1-T2 primary, the overall stage is downstaged from stage IV in the AJCC 7th edition to stage I in the current edition. However, a patient undergoing primary resection with multiple pathologic ipsilateral nodes can be staged as N1 or N2 depending on the number of nodes (ie 4 or fewer lymph nodes is pN1 and more than 4 lymph nodes is pN2).[6] These changes enhance outcomes stratification and improve clinical trial design. However, despite the recent introduction of the 8th edition, for the purposes of this review, all staging will be reported according to AJCC 7th edition unless otherwise specified.

Currently, the standard nonsurgical management of locally advanced oropharyngeal cancer is definitive radiotherapy with concurrent chemotherapy.[7,8] A recent consensus statement by American Society of Clinical Oncology and American Society for Radiation Oncology states that a definitive dose of 70 Gy over 7 weeks should be delivered to the gross primary and nodal disease in patients with stage III-IV (AJCC 7) OPC selected to receive standard, once-daily definitive radiotherapy.[9] The guidelines were released prior to AJCC 8th edition and do not vary treatment recommendations based on HPV status. Although such treatment is highly effective in eradicating disease in the HPV + population, such patients tolerate treatment more poorly than HPV- patients.[10]

Significant progress has been made to understand the dose tolerances of various head and neck structures to

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Table 1. Clinical Trials Evaluating Dose De-escalation in the Definitive Treatment Setting

Trial	Design	N	Eligibility	Treatment Arm(s)	Primary Endpoint/ Results
Chera et al.[19]	Phase II	43	T0-T3, N0-N2c	60 Gy IMRT with concurrent weekly cisplatin (30 mg/m^2) followed by primary biopsy and LN dissection	pCR 86%
Chera et al.[20]	Phase II	113	T0-T3, N0-N2c	60 Gy IMRT with concurrent weekly cisplatin (30 mg/m^2) (second choice cetuximab). T0-T2 N0-1 did not receive chemotherapy. Post-treatment PET to determine need for planned neck dissection	2-year PFS of 93%
NRG-HN002	Phase II (randomized)	295	T1-T2, N1-N2b or T0, N0-N2b;	60 Gy IMRT with concurrent weekly cisplatin (40 mg/m^2) vs accelerated IMRT 60 Gy alone (5 weeks with 6 fractions/week)	2-year PFS
Lineberger Comprehensive Cancer	Phase II	115	T0-T3, N0-N2c	60 Gy with weekly cisplatin (30-40 mg/m^2)	2-year PFS

decrease the risk of toxicities involving dysphagia, stricture, xerostomia, trismus, dentition, hearing and osteoradionecrosis.[11] For example, a steep dose-effect relationship between dose and swallowing complaints has been observed.[12] In fact, an increase in probability of dysphagia of 19% has been shown with every additional 10 Gy. Similarly, significant correlations have been observed between video fluoroscopy-based aspirations and the mean doses to the pharyngeal constrictors and the glottis and supraglottic larynx.[13] In general, such tolerances are significantly lower than the standard dosing of 50-70 Gy to address microscopic or gross disease often given with chemotherapy which also increases the risk of acute and chronic toxicities.[14]

Thus, there is significant interest in overall treatment de-escalation in this typically younger and healthier patient population. Clinical evidence from other HPV + driven tumor sites such as squamous cell cancers of the anus and cervix suggest that lower doses may be adequate in both the definitive treatment of gross disease and elective irradiation of nodal stations at risk utilizing doses as low as 54-60 Gy (for anal cancer) and 30 Gy-45 Gy (for anal and cervix cancer), respectively.[15-18] In this article, we will evaluate the rapidly evolving landscape of dose de-escalation in the neck management for HPV-positive oropharyngeal carcinoma.

Dose De-escalation in Definitive Treatment

Several phase II studies have evaluated definitive radiotherapy dose de-escalation for HPV-positive OPC given the favorable prognosis and excellent disease-free survival after chemoradiotherapy (Table 1). Chera et al. was the first to report on dose de-escalation in T0-T3, N0-2c HPV positive OPC with 60 Gy of intensity modulated radiotherapy (IMRT) with weekly low-dose cisplatin followed by planned surgical evaluation. In a study population of 43 patients, he reported a pathologic complete response (pCR) rate of 86%.[19]

A follow up study by Chera et al. reported preliminary results in a larger phase 2 study in T0-T3, N0-N2c, M0 with HPV or p16 positive and minimal and/or remote smoking history.[20] In this study, patients with T0-T2 N0-1 were treated with radiation alone with treatment de-escalation to 60 Gy. Patients had a 10- to 12-week post-treatment PET/CT to determine the need for planned neck dissection. Among the 113 patients enrolled there was a minimum follow up of 1 year in 82 patients. Post-treatment PET/CT complete response occurred at 97% at the primary site and 81% in the neck. Eight patients had planned neck dissection of whom 1 had pathologic residual disease. Two-year local control (LC), regional control (RC), distant metastasis-free survival (DMFS), and overall survival (OS) were excellent at 98%, 99%, 95%, and 95%, respectively.

Currently, several additional ongoing phase II trials evaluate definitive radiotherapy dose de-escalation. University of North Carolina' (UNC) Lineberger Comprehensive Cancer is performing a single-arm phase II study to evaluate the use of 60 Gy with low dose weekly cisplatin (30-40 mg/m^2) (NCT02281955). Eligibility includes HPV/p16 positive T0-3, N0-2c with ≤10 pack year smoking history or ≤30 pack years with ≥5 years abstinence from smoking. Patients with a positive PET/CT at week 10-16 after treatment will undergo surgical evaluation.

NRG Oncology has designed important trials assessing de-escalation strategies such as HN002 a randomized phase II trial evaluating concurrent chemoradiotherapy with 60 Gy in 6 weeks with 40 mg/m^2 weekly cisplatin vs accelerated radiotherapy alone (60 Gy in 5 weeks with 6 fractions/week) (NCT02254278). Eligibility includes p16 positive T1-T2, N1-N2b or T0, N0-N2b cancers with ≤10 pack year smoking history. Another example is the recently completed RTOG 1016 which showed inferior outcomes with cetuximab compared with standard of care cisplatin. More

Table 2. Clinical Trials Evaluating Dose De-escalation in the Induction Chemotherapy Setting

Trial	Design	N	Eligibility	Treatment Arm(s)	Primary Endpoint/Results
E1308[23]	Phase II	80	Stage III-IV	Induction chemotherapy with cisplatin, paclitaxel, and cetuximab Complete CR received IMRT 54 Gy with weekly cetuximab Less than CR received IMRT 69.3 Gy with weekly cetuximab	2-year PFS 80% in patients who received 54 Gy (95% in patients with <T4, <N2c, and ≤10 pack year smoking)
Chen et al.[24]	Phase II	45	Stage III-IV	All patients received two cycles of induction chemotherapy (paclitaxel and carboplatin) followed by IMRT with 30 mg/m^2 paclitaxel concomitantly Complete or partial responders to induction chemotherapy received 54 Gy in 27 fractions, and those with less than partial or no responses received 60 Gy in 30 fractions	2-year PFS 92%
OPTIMA[36]	Phase II	62	Low risk (≤T3, ≤N2B, and ≤10 year pack-year smoking history) High risk (T4 or ≥N2c, or >10 pack-year smoking history)	Low risk with ≥50% response received low dose radiotherapy alone to 50 Gy (RT50). Low risk with 30-50% response or high risk patients with ≥50% response received low-dose concurrent chemoradiotherapy to 45 Gy (CRT45). Remaining patients received regular dose chemoradiotherapy to 75 Gy. All patients underwent primary site biopsy and neck dissection after de-escalated treatment for pathologic confirmation.	2-year PFS 100% in low risk; 2-year PFS 91.6% in high risk
Quarterback	Phase III randomized	365	Stage III/IV	Induction chemotherapy with docetaxel, cisplatin, and 5-FU (TPF) Clinical CR or PR will be randomized to 56 Gy radiotherapy with weekly carboplatin vs standard 70 Gy with weekly carboplatin Remaining patients receive standard 70 Gy chemoradiotherapy	3-year PFS and LRC

information is needed on the results of this trial. However its results demand caution in using dose de-escalation in patient management decisions outside of a clinical trial and in the absence of high level data.

Induction Chemotherapy Response Approach to Radiotherapy Dose De-escalation

The use of induction chemotherapy to select favorable risk patients for treatment de-escalation has been reported by both single institution and cooperative groups (Table 2). This approach represents an extrapolation of the concept of use of induction chemotherapy to select for organ preservation in larynx cancer as in VA Larynx study and by University of Michigan.[21,22] The Eastern Cooperative Oncology Group (E1308) stratified patients after induction chemotherapy with cisplatin, paclitaxel, and cetuximab in stage III/IV oropharyngeal squamous cell carcinoma (OPSCC).[23] Patients with a complete clinical response received radiotherapy dose de-escalation (54 Gy) with weekly cetuximab and those with less than a complete response received 69.3 Gy with cetuximab. Among the 80 patients evaluated, 51 were de-escalated and for this subgroup, the investigators reported a 2 year progression-free survival and overall survival rates of 80% and 94%, respectively. In the 27 patients with favorable risk features (T1-3, N0-2b, <10pk-yr Tob) who were treated with ≤54 Gy 2-year PFS and OS were 96% and 96%, respectively.

Chen et al. *recently* reported results on a phase II study in which 45 patients with stage III or IV OPC received 2 cycles of induction chemotherapy (paclitaxel and carboplatin) followed by IMRT with 30 mg/m^2 paclitaxel concomitantly.[24] Complete or partial responders to induction chemotherapy received 54 Gy in 27 fractions, and those with less than

partial or no responses received 60 Gy in 30 fractions. In the study, 55% of patients had a complete or partial response and received 54 Gy IMRT and the remaining 45% patients received 60 Gy IMRT. The primary endpoint of 2-year PFS was 92%.

Similarly, an ongoing phase II trial evaluating response-adapted volume de-escalation at University of Chicago has reported preliminary results with dose de-escalation after induction chemotherapy with 3 cycles of carboplatin and nab-paclitaxel. Patients were defined as low risk (≤T3, ≤N2B, and ≤10 year pack-year smoking history) or high risk (T4 or ≥N2c, or >10 pack-year smoking history). Patients with low risk with ≥50% response received low dose radiotherapy alone to 50 Gy (RT50). Patients with low risk with 30%-50% response or high-risk patients with ≥50% response received low-dose concurrent chemoradiotherapy to 45 Gy (CRT45). All patients also received de-escalated radiotherapy volumes limited to the first echelon of uninvolved nodes. The rest of the patients (n = 12) received regular dose chemoradiotherapy to 75 Gy. All patients underwent primary site biopsy and neck dissection after de-escalated treatment for pathologic confirmation. They reported a pCR of 94.4% after RT50 and 92.3% after CRT45. At a median follow up of 1 year, the 2-year PFS and OS were 100% and 100%, respectively for low-risk patients and 91.6% and 97.0%, respectively for high-risk patients.

The Quarterback trial is an ongoing phase III trial evaluating chemoradiotherapy with 56 Gy or 70 Gy after induction chemotherapy with docetaxel, cisplatin, and 5-FU (TPF) (NCT01706939). Eligibility includes HPV positive by PCR or p16, stage 3 or 4 disease without distant metastasis, and cannot have had active smoking within the past 20 years with a cumulative pack year history of 20 pack-years or active smoking (defined as >1 cigarette per day) within the last 2 years. Patients with a clinical or radiographic CR or PR will be randomized 2:1 to 56 Gy or standard 70 Gy radiotherapy with weekly carboplatin. Patients not meeting response criteria will be treated with standard dose chemoradiotherapy.

Standard Regional Management

Clinical target volumes for lymph nodes in head and neck cancer are based on surgical data undergoing upfront elective and therapeutic neck dissection. Historic series were based on radical neck dissection with limited imaging workup. For example, Candela et al. reported a retrospective series from Memorial Sloan-Kettering Cancer Center in which the rate of neck involvement was evaluated in patients with oropharyngeal SCC who had undergone therapeutic radical neck dissection for a clinically positive neck from 1965 to 1986.[25] The pathological disease involvement of lymph nodes predominantly affects levels II and III whether patients treated electively or therapeutically. For clinically node negative patients, the incidence of involvement of levels I and V is less than 5% and the incidence of level IV involvement is less than 10%. In contrast, in node positive patients, the incidence of level IV involvement increases to 15%-31% while the risk of disease in level I and V is 15% and 9%, respectively. Using such surgical literature, Gregoire et al. reported guidelines for the selection of node levels to be irradiated for the major head and neck sites.[26] Thus, they recommended oropharyngeal carcinoma elective neck coverage include II, III, and IV (and retropharyngeal for posterior pharyngeal wall tumors) in stage N0-N1 and coverage of I-V and retropharyngeal nodes in stage N2b.

Sanguineti et al. reported on a more contemporary series incorporating HPV status and modern CT based imaging in a retrospective study from Johns Hopkins Hospital on the risk of ipsilateral subclinical neck nodal involvement.[27,28] For node positive oropharyngeal SCC with mostly HPV-positive disease (approximately ¾), the pathologic positivity rates were 9.5%, 91.3%, 40.8%, 18.0%, and 3.3% for levels IB, II, III, IV, and V, respectively. The risk of subclinical disease despite negative CT imaging (defined as LN diameter <1 cm) were 3.1%, 76.3%, 17.5%, 6.3%, and 1.0% for levels IB, II, III, IV, and V respectively. The risk of level IB subclinical involvement exceeds 5% when 2 + ipsilateral levels besides IB are involved. The risk of occult disease in level IV is reported to be <5% when level III is not involved compared with 34.3% when level III is involved. Therefore, the data supports the exclusion of elective nodal volume of level V and level IB (except when 2 + other levels are involved). Based on these data, Level IV might also be spared when level III is negative.

Recent series have reported on the feasibility of using such surgical literature to guide regional treatment with IMRT. Investigators at Memorial Sloan Kettering Cancer Center recently reported on their patterns of treatment failure among patients with locally advanced head and neck SCC after chemoradiotherapy using modern techniques with IMRT.[29] The authors reported that regional treatment failures were less common among patients with OPC positive for HPV or p16 than those who were negative for HPV or p16 with 2-year cumulative incidences 2.7% vs 6.2% (P = 0.06) for regional treatment failure. Furthermore, survival following local-regional failure was significantly longer for those patients positive for HPV or p16 compared with those negative for HPV or p16 (median OS 36.5 vs 13.6 months; P = 0.007). Thus, the overall local-regional treatment failure in patients with HPV-positive OPC is extremely low and survival after LRF appears favorable.

Reduction in Elective Nodal Station Coverage

Based on the growing surgical series with modern imaging that comprehensive nodal irradiation may not be necessary, several large institutions have reported retrospective results in which nodal levels (eg level IB and V) with a risk >5% were included in the clinical target volume while low-risk (<5%) nodal stations were spared. These single and multi-institutional studies reported on the local-regional control rates with selective nodal irradiation, and some of the studies also evaluated quality of life outcomes.

Robin et al. reported multi-institutional data on sparing the contralateral IB lymph node level, which potentially preserves function of the contralateral submandibular gland and thus may decrease patient reported xerostomia.[30] In another study, *Tam* et al. reported on a large single-institution analysis of patients with sparing of bilateral level IB lymph nodes.[31] Level IB was not spared with disease extension into the oral cavity or ipsilateral IB nodal involvement. The spared cohort had an excellent 2-year LRC of 97.5% and experienced significant benefits in patient-reported xerostomia scores ($P = 0.021$) and observer-rated xerostomia scores ($P = 0.006$). In addition, there were significant dosimetric advantages to the contralateral submandibular gland (45.0 vs 56.2 Gy; $P < 0.0001$), oral cavity (35.9 Gy vs 45.2 Gy, $P < 0.001$), and contralateral parotid gland (20.0 vs 24.4 Gy; $P < 0.001$).

Moreover, Spencer et al. reported on predominantly OPC tumors that sparing the contralateral retrostyloid level II and retropharyngeal lymph nodes in a contralateral node negative neck improves patient reported quality of life without increasing regional failure.[32] Similarly, Leeman et al. reported no failures in the treated ipsilateral retropharyngeal nodes or the spared contralateral high retropharyngeal nodes in a cohort of 102 patients.[33] The same group also reported that elective treatment of bilateral cervical lymph node V can be safely omitted in a cohort of mostly node positive (98%) and all stage III-IV disease oropharyngeal carcinoma.[34] The authors reported no level V failures and a cumulative rate of regional failure of 2.2%. The authors propose omitting elective treatment of bilateral IB, high contralateral retropharyngeal, level IB, and bilateral level V.

Investigators from University of Montreal in Quebec, Canada are currently evaluating the omission of contralateral level 4 lymph nodes in a single institution phase I/II study.[35] Eligibility includes stage III-IVa-b OPC patients. De-intensified IMRT consisted of omission of contralateral retropharyngeal and lymph node level 4 and reduction of dose to low lymph node levels to 43.2 Gy in 24 fractions. Six patients underwent planned neck dissection, and 2 had residual disease on pathology. Preliminary results demonstrated excellent disease control with 2- and 5-year LRC of 100% and 100%, respectively.

Investigators at the University of Chicago are evaluating response-adapted volume de-escalation in locally advanced head and neck cancer after induction chemotherapy. Induction chemotherapy is used to address areas that are typically treated electively with radiation and focus post-chemotherapy radiation volumes to initially involved nodal areas and the next draining echelon.[36] In this study, elective radiotherapy volumes were limited to the first echelon of at risk nodes in HPV positive oropharyngeal cancer patients who receive induction chemotherapy. Patients were also eligible for radiotherapy dose de-escalation to 45 Gy-50 Gy if they were low risk or high risk with a favorable response to induction chemotherapy (see section on Induction Chemotherapy Approach to Radiotherapy Dose De-escalation for more details). Primary site biopsy and neck dissection were performed only after de-escalated treatment (RT50 and CRT45) for pathologic confirmation. Despite the radiotherapy volume and dose reduction, the study reported high regional control. Among the patients receiving de-escalated doses to GTV, they reported a pCR rate of 94.4% after 50 Gy radiotherapy and a pCR rate of 92.3% after 45 Gy radiotherapy with concurrent chemotherapy. The 2-year PFS and OS were both 100% for low-risk patients and 91.6% and 97.0% for high-risk patients.

Ipsilateral Neck Radiotherapy

Although HPV + disease often presents with bulky nodal disease associated with small tonsil primaries, the risk of contralateral disease is not increased.[37] Thus another approach to de-escalation has been to expand the use of unilateral radiation in patients with lateralized T-stage tonsillar carcinoma with multiple ipsilateral nodes. Traditionally unilateral radiotherapy has been confined T1-T2 N0-N1 tonsillar cancer with minimal involvement of the tongue base or soft palate.[9,38,39]

However, multiple institutions have demonstrated low rates of contralateral neck failure after unilateral treatment in

Table 3. Definitive Unilateral Treatment of Oropharyngeal Cancer

Author	#pts	Site	Definition of Laterality	%N2/3	%T3/4	%CLF in N2/3
2D/3D						
O'Sullivan[38]	228	1	A,B	17% (n = 39)	16% (n = 37)	0%
Jackson[62]	178	1	NS	17% (n = 30)	35% (n = 62)	NR
Liu[63]	58	1	B	33% (n = 19)	31% (n = 18)	0%
Murthy[64]	32	1	NS	31% (n = 10)	47% (n = 15)	10%
Kagei[65]	32	1,2	D	16% (n = 5)	43% (n = 14)	0%
IMRT	(%IMRT)					
Al Mamgani[42]	185 (100%)	1,2,3	B	27% (n = 50)	7%	2%
Chronowski[41]	102 (67%)	1	C	42% (n = 43)	NS	0%
Cramer[66]	23 (100%)	1	NS	96% (n = 22)	0%	0%
Present series	45 (71%)	1,4	B	60% (n = 27)	11%	0%

A = > 1 cm from midline if soft palate involved or <1 cm involvement of tongue base B = >1 cm from midline, C = <1 cm of soft palate involvement
D = did not cross midline NS = not stated.
1 = tonsil, 2 = soft palate 3 = pharyngeal wall 4 = oral cavity.
(From Hu et al.[40], with permission from John Wiley and Sons).

more advanced nodal disease and tonsil tumors >1 cm from midline [40](Table 3). Several studies have since included a larger percentage of N2/N3 disease with no reported failures in the contralateral neck. For instance, Chronowski et al. evaluated a retrospective series of 102 patients (67% with N2/N3 disease) who received IMRT to the unilateral neck and reported a 0% risk of contralateral neck failure.[41] Al-Mamgani et al. reported a large retrospective series of 185 patients with tumors >1 cm from midline who received unilateral neck IMRT and reported 5-year regional control of 96% with a 1.1% rate of contralateral neck failure.[42] In a prospective study using unilateral radiation in a prospective study using PET/CT and definition of lateralization of tonsil cancer >1 cm from midline, Hu et al. reported excellent outcomes using unilateral radiation.[40] In this study, the investigators evaluated 37 patients, including 21 patients with N2b disease, and reported 3-year local-regional control, contralateral regional failure, distant metastasis-free survival, and disease-free survival rates of 96%, 0%, 7%, and 93%, respectively.[40] Therefore, the recent guidelines suggest that unilateral radiotherapy may be considered in patients with lateralized (>1 cm from midline without base of tongue involvement).[9,39,40]

Unilateral neck radiotherapy results in significant dosimetric advantages which can impact acute toxicity and long-term functional outcomes. Hu et al. reported doses to contralateral organs and midline organs that were reduced to below tolerance levels, which included median mean doses to the contralateral submandibular gland of 18.0 Gy, contralateral parotid gland of 10.0 Gy, middle constrictor muscles 42.0 Gy, cervical esophagus 24.4 Gy, larynx 31.9 Gy, and oral cavity 38.2 Gy. In the unilateral studies, a feeding tube rate was 9%-17%.[41-43] Additionally, patients receiving unilateral treatment experienced lower rates of hospitalization (17% vs 67%, $P < 0.01$) and had a decreased mean weight loss (6.3% vs 8.4%, $P = 0.08$).

Elective Nodal Dose Reduction

Standard elective dosing involves the biologically equivalent dose of approximately 50 Gy in 2-Gy fractions for clinically and radiographically negative regions at risk for microscopic spread of tumor.[9,44] The role of elective nodal irradiation (ENI) is supported by older single institutional retrospective studies demonstrating a reduced risk of relapse in head and neck cancers.[44,45] In some of the earliest studies using 2D technique without modern imaging, the risk of neck failure was 1.9% with ENI compared with 18% without ENI.[45] Patients receiving doses below 50 Gy had a regional failure rate of 9%-10.5% compared with 0% at a dose of 50 Gy in 5 weeks.[44] However, modern prospective studies suggest that elective regional doses below 50 Gy may be adequate.

A recent multi-center randomized controlled trial in Belgium reported that a reduction of the dose to the elective nodal sites in head and neck cancer is feasible.[46] With 200 analyzable patients with squamous cell carcinoma of the oropharynx (n = 83), hypopharynx, larynx, or cervical lymph node metastasis with unknown primary, the standard arm received 50 Gy in 2 Gy fractions and the experimental arm received 40 Gy in 2 Gy fractions. Among those with oropharyngeal tumor, 20.5% had HPV positive tumor. When comparing the 40 Gy vs the 50 Gy arm, there were no significant differences in the regional failure rate (13.0% vs 15.5%), local failure rate (14.1% vs 14.4%), disease-free survival (57.9% vs 65.3%), and overall survival (72.0% vs 73.2%). Furthermore, the investigators reported a significant reduction in salivary gland toxicity at 6 and 18 months with the 40 Gy arm. Limitations include a relatively high overall regional failure rate of 13%-15% which may be attributed to the heterogeneous head and neck primaries which were predominantly HPV-negative and 63 patients did not receive concurrent systemic therapy

Another phase II trial of locally advanced head and neck cancer reported on the feasibility of elective nodal dose reduction.[47] All patients received definitive chemoradiotherapy with 70 Gy to gross tumor at the primary site and involved nodes concurrent with cisplatin 35 mg/m^2. Among the 54 patients enrolled, 57% had HPV-positive disease. Patients received dose de-escalation to 36 Gy to the low-risk which was defined as clinically uninvolved, elective neck nodal regions bilaterally at risk of harboring microscopic disease. No additional dose levels and no differentiation between first vs higher echelon nodes were described. With a median follow up of 36 months, there were no elective nodal failures. The 3-year OS for the HPV-positive group was 96%. Therefore, elective neck radiotherapy doses of 36 Gy to 40 Gy may be effective in disease control and reducing toxicity.

Postoperative Dose Reduction

In the setting of postoperative radiotherapy, the most recent clinical practice guideline by American Society of Clinical Oncology/American Society for Radiation Oncology states that total doses of 60-66 Gy should be used for microscopic positive margins and extracapsular nodal extension (ECE).[9] In the absence of positive margins or ECE, total radiation doses of 56-60 Gy are recommended. Similar to the definitive setting, there is significant interest in treatment de-escalation in the post-operative setting by reducing radiotherapy dose.

Modern retrospective data with HPV-positive OPC suggests that ECE may not require standard postoperative chemoradiotherapy.[48,49] In one retrospective analysis of 210 patients with p16 positive oropharyngeal cancer, ECS was determined not to be prognostic and adjuvant chemoradiotherapy provided no additional benefit to adjuvant radiotherapy alone.[48] Similarly, another retrospective analysis of 347 patients with oropharyngeal carcinoma found that ECS was not associated with worse disease-free survival, regardless of HPV status.[49] Additional studies suggest the extent of extranodal extension (ENE) may be important to consider and that a greater extent of ENE may be associated with worse prognosis.[50]

A prospective study based on favorable risk HPV + patient is being conducted by ECOG [ECOG 3311 (NCT01898494)] (Table 4). The study evaluates whether low-risk patients can be spared radiation and intermediate-risk patients can be dose

Table 4. Clinical Trials Evaluating Dose De-escalation in the Postoperative Setting

Trial	Design	N	Eligibility	Treatment Arm(s)	Primary Endpoint/ Results
E3311	Phase II (randomized)	511	Stage III-IVB (N1-N2B minimum)	Low risk receive no radiotherapy. Intermediate risk (negative margins with 2-4 positive lymph nodes or minimal ENE (≤1 mm) or PNI/LVI) are randomized to 50 Gy vs 60 Gy radiotherapy. High risk with >1 mm (extensive) ENE will receive post-operative chemoradiotherapy.	3-year PFS and LRC
MC1273[51]	Phase II	80	Cohort A:≥T3, ≥N2, LVI, or PNI; Cohort B + ECE	Cohort A: 30 Gy delivered 1.5 Gy BID over 12 days with concurrent weekly docetaxel Cohort B: Same treatment plus a simultaneous integrated boost to nodal levels with ECE to 36 Gy delivered 1.8 Gy BID	2-year LRC 95%
PATHOS	Phase II/III (randomized)	242	T1-T3, N0-N2b	Low-risk (no adverse pathological features) - no adjuvant treatment Intermediate-risk pathology group with T3 tumors (or T1-T2 with additional risk factors), N2a-N2b, PNI and/or vascular invasion, or close margins (1-5 mm) randomized to postoperative radiotherapy with 60 Gy or 50 Gy. High-risk pathology group with positive margins (<1 mm) and/or ECE randomized to chemoradiotherapy with 60 Gy or radiotherapy alone with 60 Gy.	1-year patient reported swallowing outcome (MD Anderson Dysphagia Inventory)
ADEPT	Phase II (randomized)	41	T1-4a, N + with pathologic ECE	Randomized to chemoradiotherapy with 60 Gy vs radiotherapy alone with 60 Gy	2-year DFS

reduced. ENE is subgrouped into minimal (≤1 mm) or extensive. Patients with intermediate risk (negative margins with 2-4 positive lymph nodes or minimal ENE or perineural invasion/lymphovascular invasion (PNI/LVI)) are randomized to 50 Gy vs 60 Gy radiotherapy. Patients with >1 mm (extensive) ENE will receive standard post-operative chemoradiotherapy.

Mayo Clinic reported preliminary results of a single-arm phase II study (MC1273) using aggressively deescalated radiotherapy in HPV-positive OPC undergoing initial resection.[51] All patients had p16 + OPC with ≤10 pack-year smoking history and underwent margin-clearing surgery and simultaneous neck dissection. Cohort A included patients with ≥T3, ≥N2, lymphovascular invasion, or perineural invasion who received 30 Gy delivered 1.5 Gy BID over 12 days with concurrent weekly docetaxel. Patients who were positive for ECE formed Cohort B and received the same treatment plus a simultaneous integrated boost to nodal levels with ECE to 36 Gy delivered 1.8 Gy BID. With a median follow up of 24 months, the investigators reported excellent outcomes with a local-regional control rate of 95%, distant control of 94%, and disease-free survival of 89%.

PATHOS is an ongoing multicenter phase II/III randomized controlled trial that is evaluating reduced intensity adjuvant treatment in patients undergoing transoral surgery for HPV positive OPC (NCT02215265).[52] Patients in the low-risk (no adverse pathological features) pathology group will receive no adjuvant treatment which is consistent with standard of care. Patients in the intermediate-risk pathology group with T3 tumors (or T1-T2 with additional risk factors), N2a-N2b, PNI and/or vascular invasion, or close margins (1-5 mm) will be randomized to receive either standard dose postoperative radiotherapy with 60 Gy or reduced dose radiotherapy with 50 Gy. Finally, patients in the high-risk pathology group with positive margins (<1 mm) and/or ECE will be randomized to receive either standard postoperative chemoradiotherapy with 60 Gy or radiotherapy alone with 60 Gy.

Currently, the ADEPT trial is a postoperative de-intensification randomized controlled trial for HPV-associated OPC (NCT 01687413). Patients will either receive standard chemoradiotherapy with 60 Gy or radiotherapy alone with 60 Gy (experimental arm). Eligibility includes T1-4a, N + OPC that is p16 positive after undergoing TORS with pathologic finding of ECE.

Biomarkers and Radiomics

Biomarkers and radiomics may help identify patients who are suitable for treatment de-escalation. For example, radiomic analysis in HPV-positive OPC on the probability of local

Table 5. Clinical Trials Evaluating Dose De-escalation With the Use of Biomarkers and Radiomics

Trial	Design	N	Eligibility	Treatment Arm(s)	Primary Endpoint/ Results
Lee et al.[56]	Prospective/ Pilot	33	III-IVB	Pretreatment hypoxia or with resolution of hypoxia on intratreatment scan at 1 week into chemoradiotherapy received a 10-Gy dose reduction (final dose of 60 Gy) Otherwise, standard 70 Gy chemoradiotherapy	2-year LRC 100%
Riaz et al.[57]	Prospective/ Pilot	19	T1-T3; N1-N2b	30 Gy radiotherapy with concurrent chemotherapy (high dose cisplatin or carboplatin/5-FU) if without hypoxia at baseline or 5-10 days after initiation of chemoradiotherapy Otherwise, standard 70 Gy chemoradiotherapy	Accuracy of hypoxia imaging for head and neck cancers
NYU	Phase II	54	T1-T2 N1-N2b or T3, N1-N2b	60 Gy IMRT with weekly cisplatin (40 mg/m^2) if mid-treatment CT assessment shows >40% response in involved nodes	2-year PFS

failure may be useful in identifying a subgroup of patients with the lowest risk of disease recurrence after therapy who would be candidates for de-intensification. Preliminary efforts in the use of CT radiomics for the prediction of HPV status and the probability of local failure have been reported.[53-55] In particular, texture analysis appears to be promising in discriminating HPV phenotype and to identify patients who will develop a local recurrence.[55]

Hypoxia

Lee et al. recently reported in a single institution study, the use of (18)F-FMISO PET to evaluate for hypoxia in selecting patients with HPV positive OPC to undergo radiotherapy dose de-escalation (Table 5).[56] Patients without pretreatment hypoxia or with resolution of hypoxia on intra-treatment scan at 1 week into chemoradiotherapy received a 10-Gy dose reduction to metastatic lymph nodes. All 33 enrolled patients showed pretreatment hypoxia. Of these, 30% met criteria with resolution of pretreatment hypoxia to qualify for a 10-Gy reduction to the nodal gross disease for a final dose of 60 Gy. They reported excellent outcomes with 2-year LRC of 100%, DMFS of 97%, and OS of 100%.

Recently, *Riaz* et al. reported preliminary results with the use of reduced radiotherapy dose 30 Gy (over 3 weeks) with chemotherapy in patients without hypoxia at baseline or 5-10 days after initiation of chemoradiotherapy (NCT00606294).[57] Patients with persistent hypoxia received standard dose of 70 Gy over 7 weeks with chemotherapy. On pretreatment hypoxia evaluation with (18)F-FMISO PET found 13 patients to have hypoxia and 6 were negative for hypoxia. Of the 12 with pre-treatment hypoxia (1 not done due to intermittent illness, this patient received 70 Gy), 3 were positive for persistent hypoxia and received 70 Gy. All patients who received dose de-escalation [n = 9] underwent neck dissection at 4 months post chemoradiotherapy with a complete pathologic response observed in 8 out of 9 patients. The single case without a complete pathological response had only received 1 cycle of cisplatin. At the time of reporting, 18 of the 19 patients remained disease-free.

Adaptive Dose De-escalation Without Induction Chemotherapy

Another approach is to adaptively de-escalate radiation dose based on mid-treatment response. In patients with node positive oropharynx cancer who underwent standard chemoradiation treatment and monitored with daily cone-beam CT, 2 reports demonstrate that percent nodal shrinkage at week 4 predicts for improved regional control.[58,59]

Hu et al. evaluated 44 patients and demonstrated that rapid nodal shrinkage by mid-treatment predicted improved locoregional control and disease-free survival.[59] Evaluating tumor shrinkage at weeks 2, 4, and 7, the investigators found that week 4 response offered the greatest predictive information. Patients with nodal volume shrinkage of >40% at week 4 had improved 2 year locoregional control (100% vs 78%, $P = 0.031$) compared to those with less responsive tumors. Among the subset of p16 + patients which comprised 71% of the patients, locoregional control at 2 years was 100% vs 78% ($P = 0.05$) in those with nodal shrinkage >40% at week 4. Multivariate analysis showed that nodal response at day 20 was independent of smoking status in predicting locoregional control ($P = 0.039$).

Latifi et al. reported similar results in 49 head and neck cancer patients with predominantly oropharyngeal carcinoma (n = 47) who received definitive radiotherapy and nodal volumes were delineated on pre-treatment CT simulation, as well as on weekly CBCTs or CT on rails.[58] Response at week 4 was the earliest time point with the best correlation with outcome and patients with nodal response greater than 32% at week 4 had a 1 year LRC rate of 100% compared

with 75.4% for patients with a <32% response ($P = 0.013$). Similarly, patients with a nodal response >32% had a 1-year DFS rate of 100% vs 62.7% for <32% response ($P = 0.002$). Greater nodal response was observed in p16 positive patients compared to p16 negative (30% vs 22%, $P = 0.08$).

Based on such studies, investigators at New York University School of Medicine is conducting a phase II trial to evaluate chemoradiotherapy with radiotherapy dose de-escalation using 60 Gy in patients who experience early tumor shrinkage mid-treatment (NCT03215719). Mid-treatment CT scan at 4 weeks is used to assess for a good response defined as >40% nodal shrinkage to stratify patients into receiving a dose de-escalation (60 Gy) or standard dose (70 Gy).

Radiation Sensitivity Assays

The proliferation sensitivity index (PSI) represents another potential image-based tool in identifying patients for treatment de-escalation.[60] PSI is defined as the ratio of tumor volume to the host-influenced tumor carrying capacity which is a conceptual measure of the maximum volume that can be supported by the current tumor environment including oxygen and nutrient availability, immune surveillance, and acidity. PSI is estimated from routine radiological images using CT scans. Preliminary data showed that a patient-specific pretreatment PSI is sufficient to fit individual patient response data ($R^2 = 0.98$) when tumor doubling time and radiosensitivity is assume constant across patients. PSI varied greatly between patients (coefficient of variation >128%) and correlates inversely with radiotherapy response. PSI may serve as a predictor for radiation response and provides a potential new paradigm and rationale to select personalized RT dose-fractionation.

Finally, genome-based models may also provide a framework to individualize radiotherapy dose to tumor radiosensitivity.[61] In a recent study, investigators used the gene-expression-based radiation-sensitivity index and the linear quadratic model to derive the genomic-adjusted radiation dose (GARD). The authors found a wide range of GARD values (range, 1.66-172.4) across the patients despite assignment of uniform radiotherapy doses within disease types. Median GARD values were lowest for gliomas and sarcomas and highest for cervical cancer and oropharyngeal head and neck cancer. The wide range of dose sensitivities and ability to predict clinical outcome present an opportunity to study individualized dose prescription based on GARD tumor analysis.

Conclusion

Oropharyngeal carcinoma in the HPV era represents a unique head and neck disease with favorable treatment outcomes. Multiple treatment paradigms with a focus on treatment de-intensification have been reported and are being developed for HPV-associated oropharyngeal carcinoma. Ongoing clinical trials include the use of induction chemotherapy to select for treatment de-escalation, upfront radiotherapy dose de-escalation with reductions in elective nodal volumes as well as upfront surgical management with dose reduction based on pathologic findings. Aside from TNM staging, further studies are underway to best select patients for de-escalation and those that require treatment intensification. Functional and quality of life outcomes will guide patients and healthcare providers in tailoring treatment for the individual.

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