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Standard of care vs reduced-dose chemoradiation after induction chemotherapy in HPV+ oropharyngeal carcinoma patients: The Quarterback trial

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ABSTRACT

Background: Human Papillomavirus oropharyngeal carcinoma (HPVOPC) has better progression free (PFS) and overall survival (OS) than non-HPVOPC. Standard-dose chemoradiotherapy (sdCRT) results in significant acute toxicity and late morbidity. We hypothesized that after induction chemotherapy (IC), reduced dose chemoradiation (rdCRT) would result in equivalent PFS and OS compared to sdCRT plus IC in HPVOPC and would reduce toxicity.

Methods: Patients with p16+, previously untreated, locally advanced HPVOPC and ≤20 pack years smoking history received 3 cycles of IC with docetaxel, cisplatin and fluorouracil (TPF). Clinical responders who were HPV positive by type-specific PCR were randomized 1:2 to sdCRT (7000 cGy) or rdCRT (5600 cGy) with weekly carboplatin. The endpoints of the study were 3 year PFS and OS.

Results: 23 patients were enrolled, 22 were evaluable for TPF toxicity and 20 were randomized, 8 to sdCRT and 12 to rdCRT. Sixteen (80%) were HPV 16+ and 4 (20%) were other high risk (HR) variants. Fourteen (70%) had high risk features: T4, N2c, or N3. Median follow up was 56 months (range 42–70). Three-year PFS/OS for sdCRT and rdCRT are 87.5% vs 83.3% (log-rank test p = 0.85), respectively. All 3 failures are locoregional within 4 months of completion of CRT; 2 were in HR variants (50%).

Conclusions: rdCRT after IC resulted in similar PFS/OS compared sdCRT. These data support Phase 3 clinical trials of radiation dose reduction after IC as a treatment strategy in HPVOPC. Molecular HPV with variant testing and smoking history are necessary for de-escalation trials.

Introduction

There has been a significant increase in the incidence of oropharynx cancer (OPC) in the United States and Europe over the last two decades [1,2] due to Human Papillomavirus (HPV) infection. Among High Risk (HR) variants, HPV16 accounts for almost 85% of OPC cases [1]. Multiple studies have established that patients with HPVOPC have a better prognosis than HPV-negative patients [3,4]. Current therapeutic standards derive from trials that did not stratify by HPV status and most likely subject HPVOPC patients to excessive treatment-induced toxicity. Chronic side effects such as swallowing dysfunction, feeding tube dependence, aspiration, xerostomia, osteoradionecrosis, dental failure and increased mortality occur in a radiation dose dependent fashion; progressive swallowing dysfunction can be observed with each 1000 cGy above 5500 cGy given to pharyngeal constrictors [5]. Addition of chemotherapy to radiation increases toxicity and increases late non-cancer

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mortality, however, the primary alterable causes of treatment toxicity are radiation dose and field size [6]. Numerous clinical trials of different treatment strategies to maintain high cure rates while minimizing long-term morbidity in HPVOPC are underway.

Defining appropriate inclusion criteria for de-escalation trials is essential to establishing valid outcomes. Smoking status and accurate HPV testing are arguably the most relevant and impactful [7]. The negative impact of smoking on the prognosis of HPV-positive patients results in increased risk for both local recurrence and distant metastases [8]. Further, using p16 as the sole marker of HPVOPC can be significantly inaccurate. p16 overexpression can occur independently of HPV infection and neither p16 alone nor p16 in combination with HPV in situ hybridization (ISH), an insensitive assay, serve as accurate biomarkers of HPVOPC [4,9]. In de-escalation clinical trials, where validity of the HPV determination is critical for reliable data and safe outcomes, p16 in conjunction with high-accuracy molecular HPV testing should be a necessary standard [10]. In this study, we randomized only patients who were p16 and HR HPV positive by PCR, and tracked HR HPV types other than HPV16.

Induction chemotherapy (IC) improves local regional control, reduces distant metastases and improves functional outcome when delivered sequentially [6]. IC also provides prognostic data based on response. IC may play a role in de-intensification of treatment by reducing the dose of chemoradiotherapy (CRT) necessary to achieve locoregional sterilization while reducing distant metastases [11]. This strategy was incorporated in E1308, a Phase II de-escalation study. In E1308 77 operable p16+ OPC patients received 3 cycles of IC followed by CRT with cetuximab [12]. Responding patients received reduced dose CRT (rdCRT) with 5400 cGy. Two-year progression free survival (PFS) in the low dose patients was 80% and the majority of treatment failures were in subjects with > 20py smoking histories.

For the Quarterback Trial, HPVOPC patients were given IC with TPF, and responders randomized to rdCRT or standard dose CRT (sdCRT) [13]. We hypothesized that a dose of 5600 cGy, compared to the standard 6900–7200 cGy of definitive radiotherapy, would be reasonably expected to be as effective and provide a proportional decrease in radiation toxicity. Both groups received weekly carboplatin as a radiation sensitizer as per the TAX 324 trial (13).

Methods

Study design

The Quarterback Trial (NCT 01706939) was approved by the IRB of the Icahn School of Medicine at Mount Sinai (ISMMS). Patients were enrolled on the study after they signed an IRB approved consent form. The study is a phase III clinical trial of patients with previously untreated, HPVOPC. To enter the study and initiate sequential therapy patients had to meet all eligibility criteria except HPV PCR testing of tissue or cytology. Eligibility included p16+ by immunohistochemistry (ICH), American Joint Commission on Cancer (AJCC) 7th edition stage 3 or stage 4 without distant metastases (DM). Patients may have had a locally advanced unknown primary, or a primary tumor of the supraglottic larynx, hypopharynx, nasopharynx and oropharynx, adequate organ function, PS 0 or 1, and no prior chemotherapy, radiation therapy or definitive head and neck cancer surgery (other than tonsillectomy or biopsy). Patients could not be active cigarette smokers, defined as 1 cigarette or equivalent per day in the last 5 years, or have a > 20 pack year smoking history. Patients with HIV, Hepatitis C, or other significant illness were excluded. Prior to and after IC patients were staged based on clinical exam and imaging. Patients could be started on IC based on p16 positivity prior to PCR confirmation. Pretherapy tissue or cell block confirmation of HR HPV by PCR at the ISMMS and at least a partial response clinically and radiographically after 3 cycles of IC was required for randomization prior to initiating chemoradiotherapy. Eligible responders were randomized 1:2 to carboplatin based CRT with 70 Gy (sdCRT) or 56 Gy (rdCRT) of radiotherapy. Patients who were not randomized were followed for survival and IC related toxicity.

Sample collection and PCR for HPV

All patients' tumor samples were tested for type specific HPV by PCR and p16 by IHC in the Icahn School of Medicine at Mount Sinai (ISMMS) molecular pathology laboratory. HR HPV subtypes were required for randomization. For p16 ascertainment, a section of tumor or cell block was subjected to immunohistochemical stain with a p16 specific antibody. Nuclear staining of tumor cells was counted and strong nuclear stain in > 75% tumor cells was considered as positive. All tumors were tested for HPV HR variants by PCR testing (see supplement for PCR methodology).

Response evaluation

Initial tumor assessment for staging and pre and post IC were done by clinical examination and radiographic evaluation with PET/CT scans and Contrast Enhanced CT or MRI. Tumors were measured and classified as: complete or partial response (CR, PR) stable disease (SD), or progressive disease (PD) according to RECIST 1.1 Criteria. Primary-site clinical CR was defined as complete disappearance of the primary lesion on physical inspection. Nodal CR was defined as complete resolution of palpable adenopathy. A radiographic CR was defined as disappearance of all measurable target lesions. Clinical and radiographic responses at primary and nodal areas were determined separately. The primary site and nodal clinical or radiographic PR or CR was required for randomization. Radiographic response was determined based on PET or CT scan using the RECIST 1.1 criteria and correlated with clinical response assessment.

Sequential chemoradiotherapy

Three cycles of of modified TPF were delivered to each patient. TPF, was given every 21 days, as docetaxel 75 mg/M2 and cisplatin 100 mg/M2 on day 1, and 5-Fluorouracil 750 mg/M2 × 4 days by continuous infusion. All patients received prophylactic antibiotics on days 5–15 and were not allowed to receive growth factors. Patients with a clinical or radiological PR or CR after IC and HPV positive by PCR were randomized to sdCRT or rdCRT in a 1:2 ratio, respectively. All others were given standard of care CRT of 7000 cGy. CRT started 4–6 weeks after cycle 3, day 1 of TPF induction chemotherapy. Patients received either 7000 cGy (sdCRT) or 5600 cG (rdCRT) with weekly carboplatin at AUC 1.5 or, in the first 4 patients entered, additional cetuximab at 400 mg/m2 loading dose followed by 250 mg/m2 weekly to the end of radiotherapy. Due to increased mucositis seen in first 4 patients, the protocol was amended and carboplatin alone at AUC 1.5 was given after regulatory approval. Patients were evaluated every 3–4 months for 2 years and at longer intervals thereafter. Adverse events were assessed after each cycle of IC and weekly during CRT, and graded according to Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Radiotherapy

All patients were treated with daily intensity modulated radiotherapy (IMRT). Goals of IMRT plans were to keep the mean dose to the parotids < 2600 cGy and the mean dose to the pharyngeal constrictors to < 5000 cGy, when possible. Image-guided radiotherapy (IGRT) with either daily kV or cone-beam CT imaging was used for each fraction to ensure set-up accuracy. Patients were treated 5 days/week with 200 cGy fractions via a simultaneous integrated boost (SIB) technique. There were 2 dose levels for each patient. Patients in the sdCRT arm received 7000 cGy to gross disease and 5600 cGy to the elective neck in 35 fractions. Patients in the rdCRT arm received 5600 cGy to gross

disease and 5040 cGy to the elective neck in 28 fractions. The GTV was based on pre-IC imaging, endoscopy, and physical exam. The gross tumor volume (GTV) was expanded by 5 mm to create a clinical target volume (CTV) to account for microscopic disease. The CTV excluded air and bone. The CTV was expanded by 5 mm to generate a planning target volume (PTV) to account for set-up error. All radiation treatment plans were reviewed by a 2nd radiation oncologist.

Statistics

The primary objectives of the study are a non-inferior rate of progression free survival (PFS) and locoregional control (LRC) of the experimental (rdCRT) arm compared to sdCRT at 3 years. Secondary endpoints included non-inferior overall survival (OS) at 3 and 5 years and non-inferior PFS and LRC at 5 years, comparative acute toxicity and quality of life (QOL) during the first year of therapy, and comparative long term toxicity and QOL at 2,3, and 5 years. The study was planned as a multicenter trial and initial targeted accrual was 365 patients with 240 in the experimental arm. This minimal sample size of 240 would provide power of 74% and 78.5% to detect a differences of 10% between the two therapy groups in the PFS or LRC rates, respectively, at 3-years following treatment using a one-sided Type I error rate of 10%. These calculations were based on a 3.5-year accrual period with 3 more years of follow-up. The historic PFS for 3 years, based on TPF, is 81% and on RTOG 0129 is 74%, hence the predicted PFS for the control arm should be 77% (average of two aggressive therapies with standard CRT) for the purposes of calculation (3,4). Based on PFS, LRC recurrences in TPF representing approximately 80% of PFS failure, the LRC rate should be 82% for the purposes of sample size determination. Power was calculated based on the log-rank test at 3-years post-therapy in all patients. The original statistical plan was revised because of poor accrual. The trial terminated after 20 evaluable patients were randomized and treated. October 1, 2018 was the cutoff date for data analysis.

Results

Patient characteristics

The CONSORT diagram showing the treatment disposition of all consented patients is shown in Fig. 1; patient characteristics are listed in Table 1. A total of 23 patients met initial enrollment criteria and 20 were randomized; 8 patients to sdCRT and 12 to rdCRT. Three patients were not randomized; 2 were p16 positive and HPV negative by PCR and 1 patient was HPV18 positive and withdrew after 2 cycles of IC. One of the HPV negative patients developed a lymphoma during the first cycle, was deemed ineligible and was excluded from toxicity and response analysis.

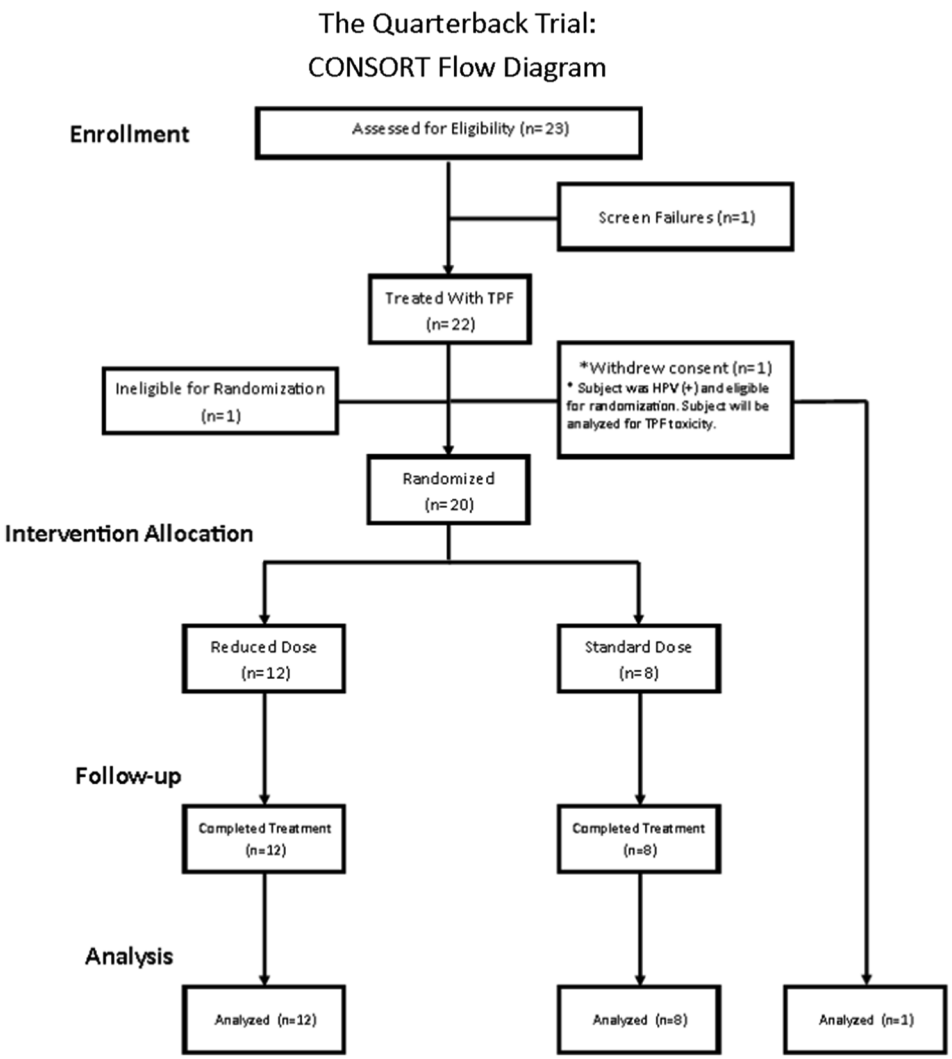

Fig. 1. Consort Flow Diagram.

Table 1
Randomized Subject Demographics.

	Number (%)	Standard Dose CRT	Reduced Dose CRT
Total Subjects	23		
Randomized	20 (87%)	8	12
Off Study*	3 (13%)	NR	NR
Age in Years (Median)	57.5 (range 36–78)	57	55
ECOG			
0	13 (65%)	5	8
1	7 (35%)	3	4
Smoking Hx			
Never	12 (60%)	3	9
< 10 pack yrs	5 (25%)	2	3
10–20 pack yrs	3 (15%)	3	0
Primary Site			
BOT	10 (50%)	5	5
Tonsil	10 (50%)	3	7
HPV Type			
HPV16	16 (80%)	6	10
Non-HPV16	4** (20%)	2	2
Race			
Caucasian	14 (70%)	6	8
African-American	6 (30%)	2	4
Ethnicity			
Hispanic	2 (10%)	1	1
Non-Hispanic	18 (90%)	11	7

* Not randomized: 2 HPV negative on final pathology and 1 subject who completed 2/3 TPF cycles and withdrew due to toxicity.

** Non-HPV 16 subtypes: 2 HPV 33, 1 HPV 18, 1 HPV 35, 1 additional non-randomized subject had HPV 18.

Among randomized patients, median age was 56.5 yrs (range 36–78); 6 (30%) were African-American, 2 (10%) Hispanic, 1 (5%) female; 16 (80%) were HPV 16+ and 4 (20%) were other high risk (HR) variants; 12 (60%) never smoked, and 8 (40%) had ≤20 pack year2; 14 (70%) had high risk features: T4, N2c, or N3 (Table 2), and 6 (30%) would have required mutilating surgery and were eligible for organ preservation.

Treatment delivery and toxicity

Two subjects who were not randomized and 3 who were randomized experienced an SAE during IC. One non-randomized HPV 18 positive patient had neutropenia and cholangitis with hospitalization during cycle 2 and refused further protocol therapy. One p16+/HPV negative patient had mucositis which prompted hospitalization. Three randomized subjects experienced SAEs, one for mucositis, neutropenic fever twice in a single patient, and 1 for urinary retention. There were dose reductions in 3 randomized patients or neutropenia and mucositis. One patient had carboplatin substituted for cisplatin for acute hearing loss.

All 20 patients who were eligible and completed IC were randomized in 1:2 ratio, 8 to sdCRT and 12 to rdCRT. All 8 patients in sdCRT arm completed the preplanned radiation dose. In the rdCRT arm 2 patients received a lower dose; 5000 cGy was given to 1 patient after a hospitalization due to dehydration when the patient refused further therapy. 5200 cGy was given to a 2nd patient due to thrombocytopenia and refusal for further therapy. Chemotherapy during XRT was held in 1 patient for 1 week at week 4, the patient then continued with reduced dose carboplatin.

Table 2
Patient Staging*.

	N0	N1-N2	N2c-N3	Total
T1-T2	0	2	2	4
	0	2	5	7
T3	0	1	1	2
	0	1	4	5
T4	1	0	1	2
	0	0	0	0
Total	1	3	4	8
	0	3	9	12

*Based on AJCC Seventh Edition Staging

Standard Chemoradiotherapy (sdCRT)
Reduced Dose Chemoradiotherapy (rdCRT)

* Based on AJCC Seventh Edition Staging.

Table 3
Post Induction Chemotherapy Response.

n = 20	Primary Site Clinical Response sdCRT/rdCRT	Radiographic CT	PET	Nodal Clinical Response sdCRT/rdCRT	Radiographic CT	PET
CR	6/10	13	15	7/9	11	12
PR	2/2	6	5	1/2	6	8
UE	0	1	0	0/1	3	0

CR, complete response; PR, partial response; SD, stable disease; UE, unevaluable.

Table 4
Overall Response to CRT.

n = 20	Primary, No. (%) rdCRT	sdCRT	Nodal, No.(%) rdCRT	sdCRT
CR	12 (100%)	8 (100%)	11 (91%)	8 (100%)
PR	0	0	1 (9%)	0
SD	0	0	0	0
UE	0	0	0	0

CR, complete response; PR, partial response; SD, stable disease; UE, unevaluable, rdCRT reduced chemoradiation, standard chemoradiation.

There were a total of 5 hospitalizations in 4 of 20 subjects during CRT. Two patients (25%) in sdCRT arm were hospitalized a total of 3 times, once each for syncope and dehydration in one patient and mucositis in a second. In rdCRT arm, 2 hospitalizations were reported during CRT: 1 for opioid overdose and 1 for mucositis and pain control. As noted above, one patient in rdCRT when getting weekly carboplatin and cetuximab and XRT developed grade 2 thrombocytopenia after 3 cycles and continued with radiotherapy alone. After enrolling first 4/12 patients in rdCRT arm, due to higher than expected mucositis and PEG placement in 2 patients the protocol was amended. The remaining 8 of 12 patients in rdCRT arm received carboplatin only as a radiosensitizer. A total of 6 randomized patients required PEG placement for dysphagia and mucositis; 4 (33%) in the rdCRT including 2 of 4 receiving concurrent cetuximab and carboplatin (50%) and 2 of 8 (25%) receiving concurrent carboplatin only, and 2 (25%) in the sdCRT arm.

Response evaluation

Clinical and radiographic responses were assessed after IC completion (Table 3). Among the 20 HPV+ patients who completed all 3 cycles of IC, 16 had a CR and 4 had a PR in the primary site. A CR was seen in 16 in nodal sites, a PR in 3, and 1 was invaluable in nodal sites. Thus, a significant response was seen in all 20 patients.

All patients had CR in the primary site after CRT (Table 4). Nodal CR was reported in 19/20 patients. One patient in rdCRT had partial response in his neck and salvage neck dissection was recommended as per standard of care after CRT.

Non-Randomized Subjects:

Of the eligible patients consented but not randomized, one received 3 cycles without an SAE and is alive and well after sdCRT at 3+ years and one was HPV18+ and refused further treatment and randomization after cholangitis during cycle 2 of IC. He also refused further CRT after 5200 cGy. He is alive without disease at 60+ months.

Progression free and overall survival

PFS and OS were analyzed after a median follow-up of 56 months (range 42–70). Living patients were followed for a minimum of 42 months. The PFS and OS have been stable after 3 years and is 87.5% for sdCRT (7/8) and 83.3% for rdCRT (10/12 patients) for both endpoints at 3 years. The hazard ratios for sdCRT and rdCRT for 3 year PFS and OS are non-signficant (Fig. 2A and 2B). There is a −5% difference in PFS between rdCRT and sdCRT with 95% confidence intervals of −36% to +26%. These estimates overlap our lower margin estimate of −10% for non-inferiority. Thus, as would be expected with such small numbers, we cannot demonstrate non-inferiority of rdCRT in this trial.

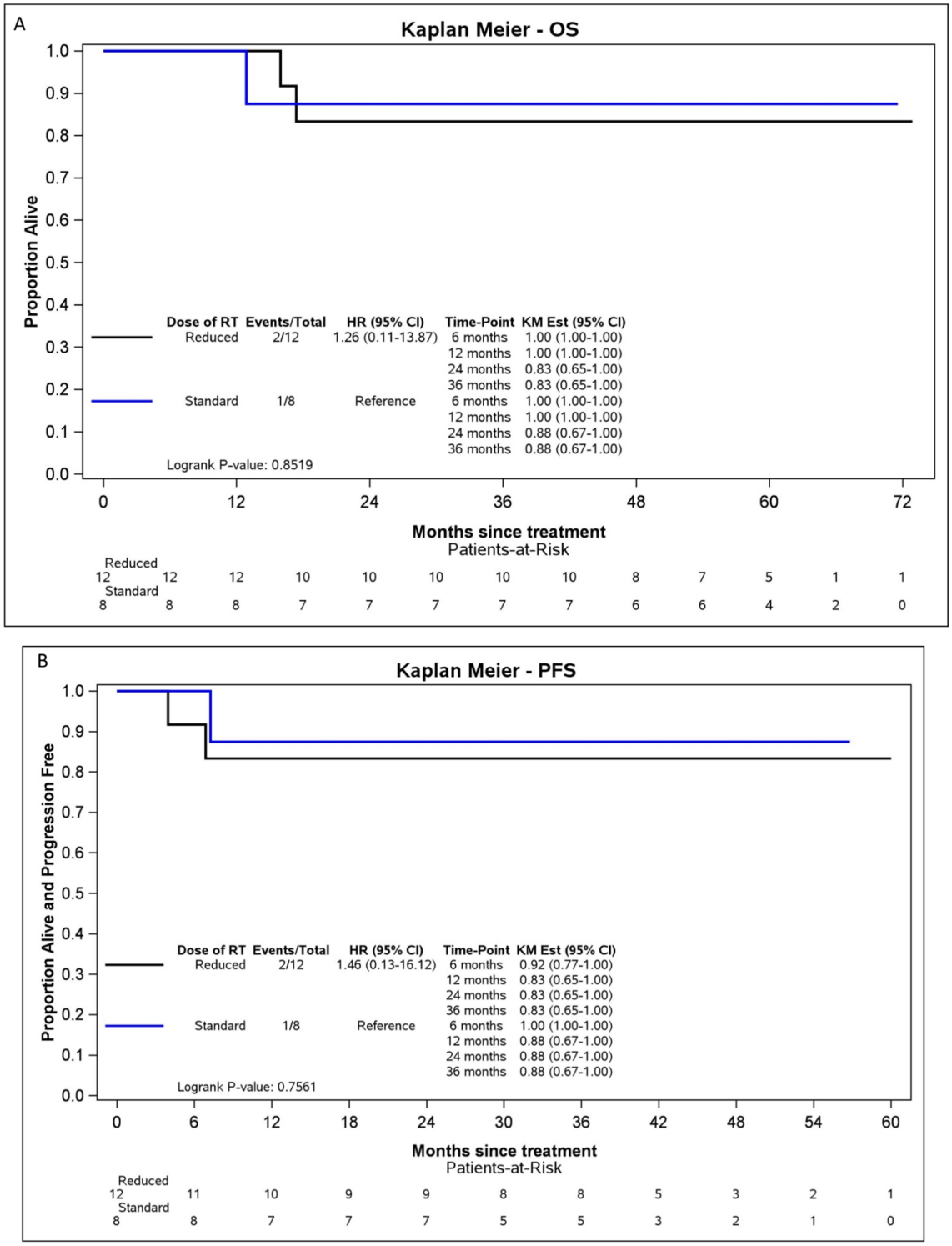

Fig. 2. (A) Kaplan Meir Plot of Overall Survival (B) Kaplan Meir Plot of Progression Free Survival.

Pattern of failure

All 3 failures occurred in the first 4 months after completion of therapy and were local or regional. Two of 12 patients in rdCRT experienced a treatment failure; one was HPV16 positive and the other was HPV35 positive. One patient refused recommended salvage neck dissection. This patient subsequently became inoperable and died of disease. The 1 patient with progression in the sdCRT had an unresectable local recurrence of an HPV18 positive tumor. All 3 patients with treatment failure subsequently died of disease. Non-HPV16 HR variants accounted for 66% of the failures and occurred in 50% of the randomized patients with HR variants. Only 1 of 16 (6%) HPV+ tumors progressed. No further local or regional failures, no distant metastases, deaths or second malignancies of the head and neck have been observed in follow up as of October 1, 2018.

Discussion

This is a prospective randomized study of radiation dose de-intensification in patients with advanced stage HPVOPC SCCHN. The study was terminated as a randomized trial early due to lack of financial support for infrastructure to expand to multiple sites and competing, subsequently a single institution Phase 2 was initiated. The small sample size limits the interpretation of the outcomes and the subset analyses; however the study provides valuable data and support for performing Phase 3 trials utilizing IC to reduce chemoradiotherapy dose in patients with locally advanced HPVOPC.

Three cycles of IC with TPF resulted in an excellent clinical and radiographic responses of 100% at both primary site and lymph nodes [13]. IC treatment was tolerated with expected toxicities. Both clinical and radiographic responses in this study were slightly higher than seen in E1308 de-escalation study. The majority of patients in this study were inoperable as opposed to E1308 which was limited to operable cases. In E1308 IC consisted of docetaxel, cisplatin and cetuximab [12]. The response results, 77% CR at the primary site and 75% in lymph nodes, were similar to the results in the Quarterback Trial in more advanced cases. Additionally, we randomized patients for whom a CR was not obtained at the primary site which differed from E1308. As in E1308, we also hypothesized that IC response would identify responders appropriate for reduced dose CRT and consequently reduce chronic toxicity as well as enhance quality of life. QOL assessment is reported in a separate manuscript.

Recently reported de-escalation clinical trials did not exclude cases with significant tobacco consumption. In the original analysis of RTOG 0129, a history of smoking above and below 20 pack years correlated to meaningfully different outcomes [4,7]. Different from E1308, in our study current smokers as well as patients with significant smoking history, defined as > 20py, were not allowed. In addition, the E1308 trial included only operable patients while the current trial included predominantly inoperable, relatively poor prognosis patients. Both the E1308 trial and the current trial take the position that radiation dose, radiation field size, and choice of chemotherapy agents for chemoradiotherapy determine acute and long-term toxicity. As noted, a recently reported NRG trial demonstrated an inferior PFS and survival outcome with sdCRT with cetuximab compared to cisplatin in p+ patients [14]. That trial did not address the fact that radiation dose is the principal driver of CRT toxicity. The 5 year PFS, OS and LRC were 78%, 85%, and 90%, respectively, for the high dose cisplatin arm. Similar results were seen with a trial comparing cetuximab and cisplatin CRT presented by a European group at ESMO 2018 [15]. These trials validate platinum sensitization with radiation because the cetuximab arms fared worse and thus one can expect radiation alone to be worse as well. Platinum sensitization or another equivalent sensitizer are indicated for "de-escalation" trials rather than radiotherapy de-esclation alone in advanced HPV oropharynx cancer.

In this study, the 3-year PFS and OS are 87.5% vs 83.3% (log-rank test, p = 0.85) for sdCRT and rdCRT, respectively. The E1308 study reported a failure rate of 80% in predominantly smokers [12,16]. All failures occurred in the present study occurred within 4 months of completion of therapy. No additional failures have been seen with median follow up 56+ months (range 42–70). All 3 treatment failures were local or regional; 2 occurred in non HPV16 HR variants. Two out of total of 4 patients with non-canonical HPV subtypes are still alive with no evidence of disease; both were HPV 33 positive. One non-randomized patient, with HPV18, stopped his CRT against medical advice at 5200 cGy is still alive and free of disease. The clinical and biological implications of non-HPV16 high risk subtypes on response and durability of remission are unknown [17]. Potentially more aggressive biology or early relapse with de-intensified therapy may be explained in part by differences in the transcriptional regulation of the viral proteins in different variants, different biologic activities of the Early Antigen (EA) proteins encoded by different HPV subtypes, or differences in HPV EA viral epitopes and the host immunological response to them [18,19].

Classification of HPVOPC based on p16 immunostaining results in false positive results in 5%-20% cases [20,21]. Patients misclassified because they are p16 positive and HPV DNA negative have worse prognosis than p16/HPV DNA positive patients. Inclusion may place study results and data integrity into question [10,22]. In the RTOG 0129 study only a fraction of tumors were evaluated for HPV-16 DNA by ISH and HR data was not reported [4]. This is the first prospective trial to use high quality PCR testing to identify non-HPV16 subtypes and report on their outcome. Two of 23 patients, or 9%, were p16 positive but HPV negative by PCR and 5 of 21 HPV positive patients, or 24%, were other HR variants with a potentially poorer prognosis [17,19]. PCR identified 7 of 23 or 30% of patients in this study with important confounding factors.

In conclusion, this study supports the potential clinical benefit of radiation dose reduction after IC as a treatment strategy with comparable survival to the sdCRT despite the small sample size. IC was safe and effective in this setting. QOL was noted to be significantly improved in the rdCRT arm as presented in an accompanying report. In order to establish a new treatment paradigm for HPVOPC large randomized phase III trials comparing rdCRT to sdCRT alone or with IC are warranted and are supported by this and numerous other studies including E1308, the reduced dose CRT/surgery trials reported by Chera et al and Ma et al in low risk subjects and the mixed risk definitive therapy OPTIMA trial [23–26]. Molecular HPV testing and careful patient selection for de-intensification trials based on risk factors related to TNM staging and smoking history, and HPV variants testing are warranted.

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Declaration of Competing Interest

The authors have no conflicts of interest to report.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.06.021.

References

[1] Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United. J Clin Oncol 2011;29:4294–301. https://doi.org/10.1200/JCO.2011.36.4596.

[2] Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in human papillomavirus-associated cancers - United States, 1999-2015. MMWR Morb Mortal Wkly Rep 2018;67:918–24. https://doi.org/10.15585/mmwr.mm6733a2. LID.

[3] Posner MR, Lorch JH, Goloubeva O, Tan M, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset. Ann Oncol 2011;22:1071–7. 10.93/annonc/mdr006 LID.

[4] Ang KK, Harris J, Wheeler R, Weber R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35. https://doi.org/10.1056/NEJMoa0912217. LID.

[5] Eisbruch A, Schwartz M, Rasch C, Vineberg K, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which. Int J Radiat Oncol Biol Phys 2004;60:1425–39.

[6] Forastiere AA, Zhang Q, Weber RS, Maor MH, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment. J Clin Oncol 2013;31:845–52. https://doi.org/10.1200/JCO.2012.43.6097.

[7] Kelly JR, Husain ZA, Burtness B. Treatment de-intensification strategies for head and neck cancer. Eur J Cancer 2016;68:125-33 LID - S0959-8049(16)32427-3 [pii] LID - 10.1016/j.ejca.2016.09.006 [doi].

[8] Gillison ML, Zhang Q, Jordan R, Xiao W, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol 2012;30:2102–11. https://doi.org/10.1200/JCO.2011.38.4099. LID.

[9] Misiukiewicz K, Bonomi M, Demicco E, Posner M. Controversies and role of HPV16 in recurrent/metastatic squamous cell cancers of the head and neck. Ann Oncol 2014;25:1667–8. https://doi.org/10.093/annonc/mdu194. LID FAU - Misiukiewicz, K.

[10] Seiwert TY. Ties that bind: p16 as a prognostic biomarker and the need for high-accuracy. J Clin Oncol 2014;32:3914–6. https://doi.org/10.1200/JCO.2014.57.9268. LID FAU - Seiwert, Tanguy Y.

[11] Worden FP, Kumar B, Lee JS, Wolf GT, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. J Clin Oncol 2008;26:3138–46. https://doi.org/10.1200/JCO.2007.12.7597. LID.

[12] Marur S, Li S, Cmelak AJ, et al. E1308: phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx—ECOG-ACRIN Cancer Research Group. J Clin Oncol 2017;35:490–7. https://doi.org/10.1200/JCO.2016.68.3300. LID.

[13] Posner MR, Hershock DM, Blajman CR, Mickiewicz E, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–15.

[14] Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet 2019;393:40–50. https://doi.org/10.1016/S0140-6736(18)32779-X. LID - S0140-6736(18)32779-X [pii] LID - 10.1016/S0140-6736(18)-X [doi].

[15] Mehanna HKA, Hartley A, Mistry P, Dalby M, Fulton-Lieuw T, Robinson M, Gray A, Foran B, Sen M, O'Toole L, Dyker K, Al Booz H, Moleron R, Brennan R, Aynsley E, Chan A, Srinivasan D, Buter J, Dunn J. Cetuximab versus cisplatin in patients with HPV-positive, low risk oropharyngeal cancer, receiving radical radiotherapy. Ann Oncol 2018;29(Supplement 8). October 2018.

[16] Rainey H, Roy E, Selkridge I, et al. Standard of care vs reduced-dose chemoradiation after induction chemotherapy in HPV + oropharyngeal carcinoma patients. J Clin Oncol 2017;35:6069-.

[17] Mazul AL, Rodriguez-Ormaza N, Taylor JM, et al. Prognostic significance of non-HPV16 genotypes in oropharyngeal squamous cell carcinoma. Oral Oncol 2016;61:98-103 LID - 10.1016/j.oraloncology.2016.08.019 [doi] LID - S1368-8375(16)30147-6 [pii].

[18] Nulton TJ, Kim NK, DiNardo LJ, Morgan IM, Windle B. Patients with integrated HPV16 in head and neck cancer show poor survival. Oral Oncol 2018;80:52-5 LID - S1368-8375(18)30117-9 [pii] LID - 10.1016/j.oraloncology.2018.03.015 [doi].

[19] Mesplède T, Gagnon D, Bergeron-Labrecque F, Azar I, et al. p53 degradation activity, expression, and subcellular localization of E6 proteins from 29 human papillomavirus genotypes. J Virol 2012;86:94–107. https://doi.org/10.1128/JVI.00751-11. LID.

[20] Nauta IH, Rietbergen MM, van Bokhoven A, et al. Evaluation of the eighth TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands and the importance of additional HPV DNA testing. Ann Oncol 2018;29:1273–9. https://doi.org/10.093/annonc/mdy060. LID.

[21] Wasylyk B, Abecassis J Fau - Jung AC, Jung AC. Identification of clinically relevant HPV-related HNSCC: in p16 should we trust? Oral Oncol 2013;49:e33-7 LID - 10.1016/j.oraloncology.2013.07.014 [doi] LID - S1368-8375(13)00658-1 [pii] FAU - Wasylyk, Bohdan.

[22] Rietbergen MM, Brakenhoff RH, Bloemena E, Witte BI, et al. Human papillomavirus detection and comorbidity: critical issues in selection of patients with oropharyngeal cancer for treatment De-escalation trials. Ann Oncol 2013;24:2740–5. https://doi.org/10.1093/annonc/mdt319. LID.

[23] Chen AM, Felix C, Wang PC, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. Lancet Oncol 2017;18:803–11. https://doi.org/10.1016/S1470-2045(17)-2. LID - S1470-2045(17)30246-2 [pii] LID.

[24] Chera BS, Amdur RJ, Tepper JE, et al. Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2018;124:2347–54. https://doi.org/10.1002/cncr.31338. LID.

[25] Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Lancet 2019;393(51–60):pp. https://doi.org/10.1016/S0140-6736(18)-1. [doi] LID - S0140-6736(18)32752-1 [pii] LID -.

[26] Ma DJ, Price KA, Moore EJ, et al. Phase II evaluation of aggressive dose de-escalation for adjuvant chemoradiotherapy in human papillomavirus–associated oropharynx squamous cell carcinoma. J Clin Oncol 2019:JCO1900463. https://doi.org/10.1200/JCO.19.00463. LID.