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De-intensification for HPV positive oropharyngeal cancer: and yet it moves!
2019 in review

Pierluigi Bonomo [1,*], Lorenzo Livi

Radiation Oncology, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy

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ABSTRACT

In the last decade, the recognition of the strongly positive prognostic impact of human papilloma virus (HPV) infection on the natural history of squamous cell carcinoma of the oropharynx has reshaped the historical monolithic view of a "one-size-fits-all approach" for head and neck cancer. Unlike their HPV negative counterparts, patients affected by HPV positive oropharyngeal cancer are usually in their prime with a low burden of comorbidities: most importantly, they are less likely to die for their disease, for second primary tumors or for intercurrent mortality. On these grounds, the scientific community was confronted with a pragmatic question: can the morbidity induced by standard concurrent chemo-radiotherapy be reduced without compromising efficacy? Worldwide, several prospective studies were launched, with the common aim to look for alternative treatment paradigms in the frame of de-intensification. This mini-review focuses on three new important trials published in 2019 and discusses their potential implications for clinical practice in the management of patients with HPV positive oropharyngeal cancer.

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1. Discussion

Anticipated by presentations at international conferences and early online access in Fall 2018, the NRG Oncology RTOG 1016 [1] and De-ESCALaTE [2] trials were simultaneously published in the Lancet in January 2019. Their findings have been echoing at meetings all year long. After 12 months, the dust has settled. These two large phase 3 randomized studies were designed to explore the replacement of cisplatin with cetuximab in addition to radiotherapy (RT) as a de-intensified strategy for human papilloma virus (HPV) - positive oropharyngeal cancer (OPC). The assumption proved to be wrong in both trials.

In RTOG 1016, 849 patients were randomised to receive two cycles of cisplatin (100 mg/m^2 every 3 weeks) or cetuximab (400 mg/m^2 loading dose, then 250/m^2 weekly) on top of moderately accelerated IMRT, as per US standard (70 Gy in 35 fractions over 6 weeks). The primary endpoint was to demonstrate a non-inferior overall survival (OS) in the cetuximab arm, hypothesizing a 1-sided, upper boundary of hazard ratio (HR) inferior to 1.45. At a median follow-up of 4.5 years, 5-year OS was significantly better in patients who received cisplatin (84.6% vs 77.9%, p = 0.01; non-inferiority for cetuximab not shown with actual HR of 1.45, 95% upper CI 1.94). In De-ESCALaTE, 334 patients were randomly allocated to have 3 cycles of 3-weekly cisplatin or cetuximab (both at usual dosage) in combination with conventionally fractionated

* Corresponding author at: Radiation Oncology, Azienda Ospedaliero – Universitaria Careggi, University of Florence, largo Brambilla 3, 50134 Florence, Italy. Tel.: +39 055 7947261; fax: +39 055 7947363.
E-mail address: bonomop@aou-careggi.toscana.it (P. Bonomo).
[1] ORCID: 0000-0001-8999-5208.

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IMRT (70 Gy in 35 fractions in 7 weeks). The primary endpoint was to detect a reduction of more than 25% in the cumulative incidence of G3-G5 toxicities in the cetuximab arm. At a median follow-up of 25.9 months, no statistically significant difference could be demonstrated: the same mean number per patient of severe acute and late adverse events was reported (4.8; p = 0.98) in both arms, based on the TAME [3] method. The use of cetuximab was not associated with a benefit in terms of patient-reported quality of life either.

The quest for de-intensification in HPV positive OPC traces back to almost 10 years ago [4]. In the first pivotal publication of RTOG 0129 trial, Kian Ang and colleagues highlighted the strong, indipendent prognostic impact of immunohistochemical p16 positivity, as proxy for HPV infection. Compared to HPV-negative counterparts, a consistent 60% reduction in risks of death and disease progression was reported in a number of post-hoc analyses of phase 3 trials [5]. In view of the rising epidemiologic trend of HPV-related OPC [6] with a median age at diagnosis usually well below 65 years [7], the exquisite radiosensitivity observed in these patients [8] and the unquestionable burden of toxicity bound to concurrent cisplatin-based chemoradiotherapy [9], several strategies were envisaged with the aim to de-intensify treatment morbidity without compromising efficacy [10,11]. In this framework, substituting cetuximab for cisplatin in conjuction with RT was viewed as a rationale approach. In the pre-HPV era, the IMCL 9815 trial [12] showed that the addition of cetuximab to RT yielded a magnitude of benefit in survival much comparable to what obtained with chemotherapy, without an appreciable increase in toxicity. However, these results were ultimately biased by the everlasting absence of a direct comparison with concurrent cisplatin. In addition, the lack of predictive biomarkers for anti-EGFR blockade in head and neck squamous cell carcinoma (HNSCC) [13] and the suboptimal tolerability of cetuximab in clinical practice [14,15] limited its use to a large extent. Controversial data emerged on its specific efficacy for HPV positive patients, as well [16].

After 13 years from the publication of the IMCL 9815 trial, the negative results of NRG Oncology RTOG 1016 and De-ESCALaTE put an end to the supposed interchangeability of cetuximab and cisplatin as best radiosensitizing agent in HNSCC. Taking both trials together, bio-radiotherapy was significantly less effective than chemo-radiotherapy. The overall rate of $\geq$G3 toxicity was equivalent between the two combinations, with expected distinct profiles. In De-ESCALaTE, only the incidence of serious adverse events (SAEs) was lower (mean rate of events per patient: 0.6 vs 1, p < 0.0001) mainly due to more hospitalizations in the cisplatin arm. The pending results of TROG 12.01 [17] will provide the complete picture, by comparing cetuximab – RT with weekly cisplatin (40 mg/m^2) in terms of symptom severity assessed with MD Anderson Symptom Inventory Head and Neck Cancer (MDASI-HN) severity score. One-hundred eighty-nine patients were randomized in this trial until June 2018. In locally advanced HNSCC, the use of bio-radiotherapy remains confined as a possible option for patients unfit for cisplatin, albeit supported by limited prospective evidence [18] in this specific category. For the time being, concurrent three-weekly cisplatin based-chemoradiotherapy remains the standard non-surgical approach for all patients with HPV positive OPC suitable to this intensive regimen.

Some caution may be advised when extrapolating the described findings to current practice.

RTOG 1016 was an "all-comers" trial restricted to the HPV positive population: overall, about 15% among those who received cisplatin ultimately succumbed from their disease, and 20% experienced disease progression. The accrual of the trial was accomplished over just 3 years, probably reflecting a large inclusion of low disease burden cases (71% low risk per RTOG 0129 classification). Only 12% and 4% of patients enrolled had T4 and N3 disease, respectively, but roughly 40% of the whole sample were heavy smokers (>10 pack/years). The relatively mixed composition of study population somewhat hampers the interpretation of the efficacy data in light of the 3-staged prognostic stratification of non-metastatic HPV positive OPC outlined in TNM 8th edition. Clearly, it should also be born in mind that although the number of pack-years was established as a significant determinant of OS in the Ang classification, the smoking history is a very weak surrogate of complex underlying etiology [19] and represents an ambiguous factor for patients' selection. In addition, less than 15% of accrued patients were older than 65 in both RTOG 1016 and De-ESCALaTE. The epidemiologic trend of HPV positive OPC is rapidly evolving [20,21], with a projected increase of incidence in the elderly of 50% in the next decade. Very limited information obtained from the two trials is therefore applicable to their management.

In last 15 years, the recognition of a HPV epidemic in HNSCC was accompanied by a resurgence of interest in head and neck surgery for OPC through the introduction of transoral robotic surgery (TORS) [22]. The availability of optimized, less morbid surgical techniques for transoral resection and the intrinsically favorable biology of HPV driven OPC contributed to a renewed shift in the "swinging pendulum" [23] of disease management towards primary surgery. In the frame of de-intensification, 3 large randomized trials (ECOG 3311, ADEPT and PATHOS) were launched [24] to essentially test the efficacy and toxicity of a less intense sequence of treatment for resectable OPC, based on upfront minimimally invasive surgery followed by a risk-adapted adjuvant strategy. The results of these studies will not be available soon. Meanwhile, the steady refinement of surgical and radiation techniques inspired the design of prospective head-to-head comparisons for the management of early stage OPC [25,26]. Thus far, equivalent disease control was assumed mainly from cross comparisons of retrospective data [27]. No insight was possible in regards to equipoise of treatment-related morbidity. In this view, the recent publication of the randomized phase 2 ORATOR trial [26] was welcomed as the the first of its kind. Sixty-eight patients with T1-T2, N0-N2 (less than 4 cm) OPC (88% HPV positive) were randomized to IMRT (with concurrent CT in case of node positive disease) or TORS plus neck dissection (with adjuvant treatment on the basis of pathological report). The study was designed to test the superiority of TORS in terms of MD Anderson Dysphagia Index (MDADI) one year after treatment, hypothesizing a clinically meaningful difference (10 points) in swallowing-related quality of life in respect to the RT arm. In contrast to this assumption, mean MDADI score was significantly better in patients receving primary RT rather than being operated on with TORS (86.9 vs 80.1, p = 0.042) although this difference was below the prespecified threshold of clinical meaningfulness. A similar rate of grade 2 or worse adverse events was reported in both cohorts, with clearly distinct profiles. The supposed less morbidity associated with the use of minimally invasive surgery for early stage OPC was therefore not demonstrated. Whatever direction the pendulum is swinging, expertise [28] and quality of care [29] are of pivotal importance in ensuring the best chance of disease control.

Eagerly awaiting for what's yet to come, very relevant insights on HPV positive OPC management were presented in 2019 (Table 1). Overall, it is not the proper time for de-intensification for any HPV positive patient yet, outside of clinical trials. Still, undisputed progress in knowledge was made possible by formally negative trials such as NRG Oncology RTOG 1016, De-ESCALaTE and ORATOR. Cisplatin-based concurrent chemoradiotherapy is still the one-size-fits-all approach for locally advanced HNSCC, far from being a desirable strategy. Nothing has truly changed in the field of de-intensification and the monolythic view of head and neck cancer management has still not been replaced, but

Table 1
Main characteristics of 3 analyzed trials.

Trial (enrollment period)	Study design (no. of patients)	Clinical stage (TNM/ AJCC 7th edition)	Smoking history (pack/ years)	Median follow-up time (years)	Regimens	Primary outcome measure	Main message
NRG Oncology RTOG 1016 (06/2011-07/2014) [1]	Randomized, non-inferiority phase 3 trial (n = 987)	T1-T2, N2a-N3 or T3-T4, N0-N3	all	4.5	Cisplatin (100 mg/m^2) q3w × 2 + RT (70 Gy/35 fx in 6 weeks) ***vs*** Cetuximab 400 mg/m^2 then 250 mg/m^2 q1w × 7 + RT (70 Gy/ 35 fx in 6 weeks)	Overall survival (non-inferiority met if the upper boundary of the one-sided 95% CI for the HR was <1.45)	• Non-inferiority of Cetuximab-RT not shown (one-sided 95% CI upper boundary: 1.94) • 5-year OS 84.6% ***vs*** 77.9% (p=0.01)
De-ESCALaTe (11/2012-10/2016) [2]	Randomized phase 3 trial (n = 334)	T3-T4, N0 or T1-T4, N1-N3	< 10	2.1	Cisplatin (100 mg/m^2) q3w × 3 + RT (70 Gy/35 fx in 7 weeks) ***vs*** Cetuximab 400 mg/m^2 then 250 mg/m^2 q1w × 7 + RT (70 Gy/ 35 fx in 7 weeks)	Overall (acute and late) severe toxicity (G3-G5 according to CTCAE v.4 for a period of 24 months from the end of treatment)	• Same mean number of severe events per patient (TAME method) in both arms: 4.8 (95% CI 4.2–5.4; p=0.98) • All-grade toxicity: mean number of events per patient was 29.2 (95% CI 27.3–31) ***vs*** 30.1 (95% CI 28.3–31.9; p=0.49)
ORATOR (08/2012-06/2017) [26]	Randomized phase 2 trial (n = 68; 60/68 p16 positive)	T1–2, N0–2 (nodal size ≤4 cm)	all	2.2	RT (70 Gy/35 fx in 6 or 7 weeks) ±CT (#regimens) ***vs*** TORS + neck dissection ± adjuvant RT/CT based on pathologic findings)	Swallowing-related quality of life (MDADI total score at one year after treatment)	• Non-clinically significant higher mean MDADI total score in non-surgical arm: 86.9 (SD 11.4) ***vs*** 80.1 (SD 13) (p=0.042) • Similar incidence of ≥ G2 adverse events (CTCAE v.4): 91% ***vs*** 97%

RT: Radiotherapy; fx: fractions; CI: confidence intervals; HR: hazard ratio; OS: overall survival; CTCAE: Common Terminology Criteria for Adverse Events; MDADI: MD Anderson Dysphagia Inventory; CT: chemotherapy.

quoting physicist Galileo Galilei's repel of skepticism on Earth revolving around the Sun: and yet it moves [30]!

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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