Editorial

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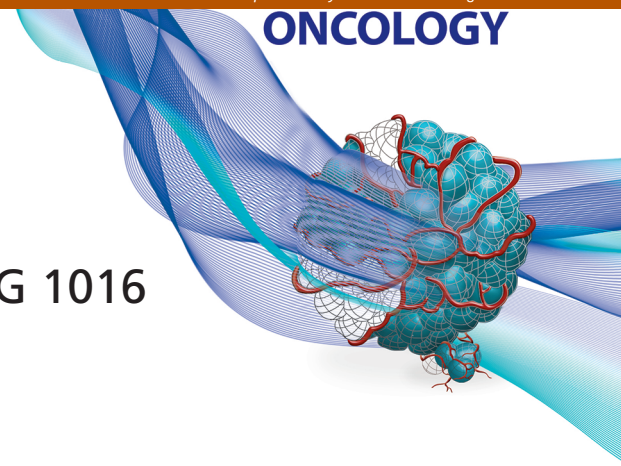

The day after De-ESCALaTE and RTOG 1016 trials results

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"How will the results of the De-ESCALaTE and the RTOG 1016 trials influence clinical research? Given their landmark results, we feel that the deintensification concepts of the three remaining different strategies currently under evaluation, namely deintensification with induction chemotherapy, deintensification with reduced intensity-modulated radiotherapy and deintensification with mininvasive surgery, should be challenged."

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Human papilloma virus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) is now considered a distinct disease entity from HPV-negative head and neck cancer, with a superior clinical outcome with current standard treatment approaches [1]. HPV-positive OPSCCs mostly occur in young individuals compared with their HPV-negative counterparts; thus, they can live longer with treatment-related morbidity and toxicity. In particular, full-dose cisplatinum-based chemoradiotherapy is associated with considerable toxicity [2] with potential life-threatening consequences, and increases long-term sequelae, such as xerostomia and dysphagia [3,4]. Therefore, young patients with HPV-positive OPSCC may experience life-changing side effects of the treatment affecting quality of life for several decades.

However, it is still unclear which subset of HPV-related tumors shows a better prognosis. Lower-risk subgroups within high-stage disease for which deintensified treatment may be safely considered have been clinically identified: namely, subjects with low nodal category and smoking history inferior to 10–20 pack-years.

In this scenario, de-escalation (reduction of toxicity while preserving antitumor efficacy) for favorable HPV-positive OPSCC represents a rational strategy and, indeed, it has been pursued by conducting prospective research [5].

One proposed strategy replaces cisplatin with cetuximab as the radiosensitizer. Indeed, radiotherapy can induce EGFR expression in head and neck cancers, thus contributing to acquired resistance [6]. By inhibition of EGFR, cetuximab might help overcome this resistance and induce antibody-dependent cell-mediated cytotoxicity, with a more favorable safety profile than cisplatin [7,8]. However, an inverse association between HPV positivity and EGFR status exists [9], and therefore EGFR inhibition by cetuximab might not be as effective as chemotherapy in HPV-positive OPC.

With these premises, two Phase III trials, the De-ESCALaTE [10] and RTOG 1016 [11], have recently investigated, for the first time, the role of a deintensification approach in HPV-positive OPC patients. In the De-ESCALaTE trial [10], with an open-label randomized controlled design, locoregionally advanced patients with low-risk HPV-positive OPC were randomly assigned to receive either intravenous cisplatin (100 mg/m^2 on days 1, 22 and 43; n = 166) or intravenous cetuximab (400 mg/m^2 loading dose followed by 7 weekly administrations of 250 mg/m^2; n = 168) in addition to radiotherapy (70 Gy in 35 fractions). The primary outcome was the rate of overall (early and late) severe (grade 3–5) toxicity events at 24 months from the end of treatment: this rate did not differ significantly between treatment groups at 24 months (mean number of events per patient = 4.8, 95% CI: 4.2–5.4 with cisplatin vs 4.8, 95% CI: 4.2–5.4 with cetuximab; p = 0.98); a similar result was reported for all-grade toxicity. However,

there was a significant difference between cisplatin and cetuximab in terms of 2-year overall survival (OS; 97.5 vs 89.4%; hazard ratio [HR]: 5.0; 95% CI: 1.7–14.7; p = 0.001) and 2-year recurrence (6.0 vs 16.1%; HR: 3.4; 95% CI: 1.6–7.2; p = 0.0007).

Overall, similar findings were reported in the RTOG 1016, a randomized, multicenter, noninferiority trial in advanced patients with low- or intermediate-risk (29%) HPV-positive OPC [11]. Patients were assigned to receive either intravenous cetuximab (loading dose of 400 mg/m^2 5–7 days before radiotherapy initiation, followed by cetuximab 250 mg/m^2 weekly for seven doses; n = 399) or cisplatin (100 mg/m^2 on days 1 and 22; n = 406). All patients received accelerated intensity-modulated radiotherapy (70 Gy in 35 fractions over 6 weeks at six fractions per week). The primary end point was OS, with a noninferiority margin of 1.45. At a median follow-up of 4.5 years, radiotherapy plus cetuximab did not meet the noninferiority criteria for OS (HR: 1.45; 95% upper CI: 1.94; p = 0.5056 for noninferiority; p = 00163). Estimated 5-year OS was 77.9% (95% CI: 73.4–82.5) with cetuximab and 84.6% (95% CI: 80.6–88.6) with cisplatin. Progression-free survival and rate of locoregional failure were poorer with cetuximab. Moreover, proportions of acute moderate-to-severe toxicity (77.4%; 95% CI: 73.0–81.5 vs 81.7%; 95% CI: 77.5–85.3; p = 0.1586) and late moderate-to-severe toxicity (16.5%; 95% CI: 12.9–20.7 vs 20.4%; 95% CI: 16.4–24.8; p = 0.1904) were similar between cetuximab and cisplatin.

Overall, these findings, collected in well-conducted studies, show that for patients with HPV-positive OPC cetuximab + radiotherapy is associated with shorter survival and overall comparable toxicity profile compared with cisplatin + radiotherapy. Although outcome analysis was reported with different median follow-ups, given the natural history of the disease we do not expect further events.

Therefore, cisplatin + radiotherapy should be still considered the standard of care in this setting. Moreover, the results of the De-ESCALaTE and the RTOG 1016 trials support the notion that outcomes for HPV-positive OPC patients strongly depend on the type of treatment received.

How will the results of the De-ESCALaTE and the RTOG 1016 trials influence clinical research? Given their landmark results, we feel that the deintensification concepts of the three remaining different strategies currently under evaluation, namely deintensification with induction chemotherapy, deintensification with reduced intensity-modulated radiotherapy and deintensification with mininvasive surgery, should be challenged [12].

With respect to deintensification with induction chemotherapy, in the ECOG 1308 trial [13], cetuximab was employed concomitantly to 54 Gy in complete responders to induction chemotherapy. Considering only low-risk patients, 2-year progression-free survival and OS were 95 and 95%, respectively. Comparable data were observed in a second study [14], in which low-risk patients who responded to induction chemotherapy received paclitaxel with 54 Gy with locoregional failure of 2% and distant metastasis rate of 7%. In a third recent trial, induction chemotherapy with three cycles of carboplatin and nab-paclitaxel was followed by response-adapted dose and volume de-escalated radiation. Low-risk OPSCC patients with response ≥50% received radiotherapy alone consisting of 50 Gy and those with response less than 50% but ≥30% received 45 Gy with concomitant chemotherapy. Similar excellent oncologic outcomes were reported [15]. Since all these studies yield comparable results in low-risk subgroups as those observed in the chemotherapy arm of the De-ESCALaTE trial [10], one may wonder whether, within a de-escalation approach, if it is worth to trade full-dose induction chemotherapy for 16–20 Gy of radiotherapy or 25 Gy with concomitant chemotherapy.

For what concerns deintensification with reduced intensity-modulated radiotherapy dose, by reducing radiotherapy total dose with or without concomitant chemotherapy as in NRG HN002 study (NCT02254278), we expect that at least locoregional controls will be affected. Last, with respect to de-intensification with mininvasive surgery, the strategy adopted in low-risk patients defined by pathological staging assumes that surgery alone is sufficient. However, in light of the data under discussion we can hardly support the idea of opting out cisplatin at least to maintain an optimal distant control.

Overall, it appears that data from RTOG 1016 and De-ESCALaTE studies may produce a domino effect on the results of ongoing deintensification trials.

One crucial issue raised by the two trials concerns the appropriate selection of low-risk patients, which cannot be excluded, based on data on TNM stage and smoking status.

Interestingly, recent data suggest that distinct genetic HPV-related subtypes show clinically peculiar behaviors and potentially a differentiated chemosensitivity and radiosensitivity with resulting differences in treatment response and outcome [16,17]. In particular, recently, Gleber-Netto *et al.* assessed data from 80 OPSCC patients in the Cancer Genome Atlas, and found a panel of 582 HPV-correlated genes, which differentiate three prognostic categories with statistically significant survival differences: OPSCC-C1 or low-risk death HPV-positive group; OPSCC-C2

or high-risk death HPV-positive group; and OPSCC-C3 or HPV-negative group. Additional analysis discovered a panel of 38 transcripts that were able to distinguish the outcome between the two HPV-positive groups [17].

Moreover, potential targetable oncogenic alterations showed specific HPV-related complex mutational patterns that include loss of *TRAF3*, activating mutations of *PIK3CA* and amplification of *E2F1* [18].

In this scenario, we would advocate that future research focuses on identifying ideal HPV-positive de-escalation candidates by exploiting tumor genetic stratification in association with clinical features [12]. We believe that by adopting a more precise approach, we may maximize the probabilities of translating research efforts into an effective de-escalation.

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