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[Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer \(De-ESCALaTE HPV\): an open-label randomised controlled phase 3 trial.](#)

Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, Dalby M, Mistry P, Sen M, O'Toole L, Al Booz H, Dyker K, Moleron R, Whitaker S, Brennan S, Cook A, Griffin M, Aynsley E, Rolles M, De Winton E, Chan A, Srinivasan D, Nixon I, Grumett J, Leemans CR, Buter J, Henderson J, Harrington K, McConkey C, Gray A, Dunn J; De-ESCALaTE HPV Trial Group.

from Lancet, January 2019

BACKGROUND: The incidence of human papillomavirus (HPV)-positive oropharyngeal cancer, a disease affecting younger patients, is rapidly increasing. Cetuximab, an epidermal growth factor receptor inhibitor, has been proposed for treatment de-escalation in this setting to reduce the toxicity of standard cisplatin treatment, but no randomised evidence exists for the efficacy of this strategy.

METHODS: We did an open-label randomised controlled phase 3 trial at 32 head and neck treatment centres in Ireland, the Netherlands, and the UK, in patients aged 18 years or older with HPV-positive low-risk oropharyngeal cancer (non-smokers or lifetime smokers with a smoking history of <10 pack-years). Eligible patients were randomly assigned (1:1) to receive, in addition to radiotherapy (70 Gy in 35 fractions), either intravenous cisplatin (100 mg/m² on days 1, 22, and 43 of radiotherapy) or intravenous cetuximab (400 mg/m² loading dose followed by seven weekly infusions of 250 mg/m²). The primary outcome was overall severe (grade 3-5) toxicity events at 24 months from the end of treatment. The primary outcome was assessed by intention-to-treat and per-protocol analyses. This trial is registered with the ISRCTN registry, number ISRCTN33522080.

FINDINGS: Between Nov 12, 2012, and Oct 1, 2016, 334 patients were recruited (166 in the cisplatin group and 168 in the cetuximab group). Overall (acute and late) severe (grade 3-5)

toxicity 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 [4.2-5.4] with cetuximab; $p=0.98$). At 24 months, overall all-grade toxicity did not differ significantly either (mean number of events per patient 29.2 [95% CI 27.3-31.0] with cisplatin vs 30.1 [28.3-31.9] with cetuximab; $p=0.49$). However, there was a significant difference between cisplatin and cetuximab in 2-year overall survival (97.5% vs 89.4%, hazard ratio 5.0 [95% CI 1.7-14.7]; $p=0.001$) and 2-year recurrence (6.0% vs 16.1%, 3.4 [1.6-7.2]; $p=0.0007$).

INTERPRETATION: Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control. Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

Strengths:

- Phase 3 data adequately powered with low-risk disease only
- Multi-institutional across many different centers/countries with well-designed protocol and no major differences between treatment arms
- Clear differences in locoregional control, distant mets, and disease free survival between the two treatment arms in favor of platinum-based chemo
- Good QOL and toxicity data showing no differences between the two arms (aka no decrease in toxicity with cetuximab)

Limitations:

- use of HPV ISH instead of HPV PCR which is considered the “gold standard”
- more adverse events in acute toxicity with cisplatin. Less patients completed full chemo regimen of cisplatin → however, still with improved survival

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[Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma \(KEYNOTE-040\): a randomised, open-label, phase 3 study.](#)

Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, Soria A, Machiels JP, Mach N, Mehra R, Burtness B, Zhang P, Cheng J, Swaby RF, Harrington KJ; KEYNOTE-040 investigators

from *Lancet*, January 2019

BACKGROUND: There are few effective treatment options for patients with recurrent or metastatic head-and-neck squamous cell carcinoma. Pembrolizumab showed antitumour activity and manageable toxicity in early-phase trials. We aimed to compare the efficacy and safety of pembrolizumab versus standard-of-care therapy for the treatment of head-and-neck squamous cell carcinoma.

METHODS: We did a randomized, open-label, phase 3 study at 97 medical centres in 20 countries. Patients with head-and-neck squamous cell carcinoma that progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease

recurred or progressed within 3-6 months of previous multimodal therapy containing platinum for locally advanced disease, were randomly assigned (1:1) in blocks of four per stratum with an interactive voice-response and integrated web-response system to receive pembrolizumab 200 mg every 3 weeks intravenously or investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab intravenously (standard-of-care group). The primary endpoint was overall survival in the intention-to-treat population. Safety was analysed in the as-treated population. This trial is registered with ClinicalTrials.gov, number NCT02252042, and is no longer enrolling patients.

FINDINGS: Between Dec 24, 2014, and May 13, 2016, 247 patients were randomly allocated to pembrolizumab and 248 were randomly allocated to standard of care. As of May 15, 2017, 181 (73%) of 247 patients in the pembrolizumab group and 207 (83%) of 248 patients in the standard-of-care group had died. Median overall survival in the intention-to-treat population was 8.4 months (95% CI 6.4-9.4) with pembrolizumab and 6.9 months (5.9-8.0) with standard of care (hazard ratio 0.80, 0.65-0.98; nominal $p=0.0161$). Fewer patients treated with pembrolizumab than with standard of care had grade 3 or worse treatment-related adverse events (33 [13%] of 246 vs 85 [36%] of 234). The most common treatment-related adverse event was hypothyroidism with pembrolizumab (in 33 [13%] patients) and fatigue with standard of care (in 43 [18%]). Treatment-related death occurred in four patients treated with pembrolizumab (unspecified cause, large intestine perforation, malignant neoplasm progression, and Stevens-Johnson syndrome) and two patients treated with standard of care (malignant neoplasm progression and pneumonia).

INTERPRETATION: The clinically meaningful prolongation of overall survival and favourable safety profile of pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma support the further evaluation of pembrolizumab as a monotherapy and as part of combination therapy in earlier stages of disease.

Strengths:

- First phase 3 study looking at pembro in the recurrent or metastatic setting
- Multi-institutional across many different disease subsites
- PD-L1 expression data available from tumor samples helped determine how this can be used as a risk stratifier and improve patient selection.
- Those who did respond seemed to have a much greater chance of sustained response (18.4 months in the pembrolizumab group, compared with only 5.0 months in the standard-of-care group).

Limitations:

- Heterogeneity of the control arm (3 different possible chemos that the investigators could chose from)
- Post-study crossover may have actually influenced the outcomes and decreased the magnitude of benefit of Pembro
- No difference in progression-free survival between the groups in the total population; only when stratified by PD-L1 tumor proportion score >50%.
- Higher number of treatment-related deaths (4 vs 2), but fewer number of adverse events/grade 3-5 toxicities in the pembro group.

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[¹⁸F-FDG PET/C for locoregional surveillance following definitive treatment of head and neck cancer: A meta-analysis of reported studies](#)

Wong ET, Dmytriw AA, Yu E, Waldron J, Lu L., Fazelzad R, de Almeida JR, Veit-Haibach P, O'Sullivan B, Xu W, Huang SH.

from **Head & Neck**, February 2019

¹⁸F-FDG PET/CT has been used for staging and to assess tumor response after multimodality treatment of advanced stage head and neck cancer. However, false-positive results due to treatment-related inflammation and false negative results mainly due to dental artifacts are frequently reported. Early detection of persistent or recurrent disease using CT or MRI can be difficult also due to local treatment effects. ¹⁸F-FDG PET/CT done beyond 12 weeks after treatment have a high negative predictive value (NPV) and then contribute to the reduction of the indication of neck dissection after chemoradiation, minimizing treatment morbidity. On the other side, early detection of recurrent disease increases the chance of salvage treatment. The aim of Wong et al. study was to report the diagnostic performance of ¹⁸F-FDG PET/CT in identifying residual/recurrent disease stratified by the site of failure and timing of imaging.

The authors followed recommended guidelines to perform a comprehensive literature search to identify studies published in Medline, Epub Ahead of Print and In-Process & Other Non-Indexed Citations, EMBASE and Cochrane Central Register of Controlled Trials from January 2010 to August 2016. They included prospective and retrospective studies published in the English language literature with more than 30 patients who underwent surgery (alone or with adjuvant radiotherapy or radiochemotherapy), radiotherapy or chemoradiotherapy. Diagnostic performance of ¹⁸F-FDG PET/CT was evaluated for local or regional failures stratified by treatment-to-scan time interval (≤ 3 versus > 3 months).

A total of 3088 studies were initially identified. Only 24 studies met the inclusion criteria for data extraction and analysis. More than 80% of the 2627 reported patients underwent primary radiochemotherapy. HPV status was reported in 6 studies. Local failures were reported in 10 studies, regional failures in 13 studies and locoregional failures in 15 studies (with or without distant metastasis). Compared to ≤ 3 months, ¹⁸F-FDG PET/CT performed > 3 months showed significantly improved sensitivity (87% vs 60%, $P = 0.020$) and specificity (93% vs 84%, $P < 0.001$) for local failure. There was no significant difference in sensitivity (79% vs 56%, $P = 0.100$) or specificity (95% vs 97%, $P = 0.35$) for regional failure > 3 versus ≤ 3 months.

The authors conclude that post treatment ¹⁸F-FDG PET/CT in patients with head and neck squamous cell carcinoma has high NPV and can obviate the need for invasive surgical procedures or unnecessary follow-up imaging in the case of a negative ¹⁸F-FDG PET/CT result. The reported sensitivity and specificity for detection of local failures were significantly improved when it was performed after 3 months. This data supports the notion that the optimal window for an initial ¹⁸F-FDG PET/CT follow-up must extend beyond the usually accepted 2 to 3 months in select patients at low risk for failure, to around 3 months following completion of curative treatment. They suggest that only a large-scale prospective study of ¹⁸F-FDG PET/CT



surveillance with factor stratification would further help define the optimal timing of follow-up for individual patients.

Strengths:

- This is a well-designed meta-analysis of recent literature. Comparing with a previous meta-analysis on the same subject, the present one showed favorable NPVs, although different protocols were used in each participant institution,.
- It is the best evidence today confirming that a complete metabolic response 3 months after radiotherapy or radiochemotherapy can rule out residual disease and favor observation instead of invasive biopsy or neck dissection.

Weakness:

- Although more than 80% of the patients underwent radiation or chemoradiation as primary treatment, most of the included studies were retrospective.
- Several different ^{18}F -FDG PET/CT protocols were used in different institutions.
- Failure rates ranged from 0% up to 56%, possibly associated with the population studied and follow up time.
- The purpose of post-treatment imaging was not clearly described in most studies, it was not possible to perform subgroup analysis to explore the diagnostic performance of ^{18}F -FDG PET/CT in surveillance or residual disease versus recurrent disease.
- The ≤ 3 months subgroups for local and regional failure analysis contained data from only three studies each, which were relatively few compared to the > 3 months subgroups.

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[The Impact of Adjuvant Chemoradiotherapy Timing on Survival of Head and Neck Cancers](#)

Tam M, Wu SP, Gerber NK, Lee A, Schreiber D, Givi B, Hu K.

from *Laryngoscope*, October 2018

Background: Delays in postoperative head and neck (HN) radiotherapy have been associated with decreased overall survival; however, the impact of delays in postoperative HN chemoradiotherapy remains undefined.

Methods: All patients with nonmetastatic HN cancer (oral cavity, oropharynx, larynx, hypopharynx) who underwent curative intent surgery and received adjuvant chemoradiotherapy were identified from the National Cancer Database (2005–2012). Overall treatment time (OTT) was defined as the time from surgery to the end of radiation therapy. Statistical methods included Cox proportional hazards modeling, which adjusted for clinicopathologic, demographic, and socioeconomic factors. Recursive partitioning analysis (RPA) identified the optimal threshold of OTT via conditional inference trees to estimate the greatest differences in overall survival (OS) on the basis of randomly selected training and validation sets.

Results: A total of 16,733 patients were included, with a median follow-up of 37 months. Median OS for OTT in a predefined threshold of < 13 weeks was 10.1 years (95% confidence interval [CI], 9.8 years; not reached) compared with 8.7 years (95% CI, 8.2–9.2 years) in > 13 weeks. On



multivariate analysis, OTT of >13 weeks versus <13 weeks independently increased mortality risk (hazard ratio, 1.10; 95% CI, 1.04–1.17; P5<0.001). RPA identified an optimal OTT threshold of 97 days (interquartile range: 96–98 days). The OTT threshold of 97 days was confirmed in a full Cox regression model estimating the risk of death according to overall treatment time as a continuous variable.

Conclusion: In this large hospital-based national data, an OTT of greater than approximately 14 weeks most consistently increased the risk of death.

Summary: 16,733 patients, diagnosed with SCCA of the OP, OC, larynx or hypopharynx treated with surgery and post op chemoradiation without distant metastasis, were studied retrospectively over a 7 year period. Overall treatment time (OTT) was defined as the time from surgery to the end of radiation therapy. The unadjusted median OS for OTT in <13 weeks was 10.1 years compared with 8.7 years in >13 weeks, thus OTT of >97 days (14 weeks) increased risk of death.

Strengths:

- Single institution, large patient cohort
- Establishes a threshold of <13 weeks for completion of treatment (surgery to end of chemoradiation) for optimal survival.
- This study highlights the importance of a multidisciplinary team approach in optimizing logistics and providing adequate support for head and neck cancer patients.

Weaknesses:

- 25% of patients were stage I or II
- 57% of patients had ECE or positive margins. Thus what was the indication for post op chemoradiation in the remaining 43%? (If indications for post op chemoradiation are positive margins or ECE)
- 1/3 of patients in this review completed treatment in <13 weeks. This represents an opportunity for improved patient care.
- locoregional control and distant metastasis were not recorded by NCDB, selection bias, incomplete data, coding errors, and unreported data

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