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## Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis


Lacas B, Bourhis J, Overgaard J, et al



*from **Lancet Oncology**, September 2017*



**BACKGROUND**
The Meta-Analysis of Radiotherapy in squamous cell Carcinomas of Head and neck (MARCH) showed that altered fractionation radiotherapy is associated with improved overall and progression-free survival compared with conventional radiotherapy, with hyperfractionated radiotherapy showing the greatest benefit. This update aims to confirm and explain the superiority of hyperfractionated radiotherapy over other altered fractionation radiotherapy regimens and to assess the benefit of altered fractionation within the context of concomitant chemotherapy with the inclusion of new trials.

**METHODS:**
For this updated meta-analysis, we searched bibliography databases, trials registries, and meeting proceedings for published or unpublished randomised trials done between Jan 1, 2009, and July 15, 2015, comparing primary or postoperative conventional fractionation radiotherapy versus altered fractionation radiotherapy (comparison 1) or conventional fractionation radiotherapy plus concomitant chemotherapy versus altered fractionation radiotherapy alone (comparison 2). Eligible trials had to start randomization on or after Jan 1, 1970, and completed accrual before Dec 31, 2010; had to have been randomized in a way that precluded prior knowledge of treatment assignment; and had to include patients with non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx undergoing first-line curative treatment. Trials including a non-conventional radiotherapy control group, investigating hypofractionated radiotherapy, or including mostly nasopharyngeal carcinomas were excluded. Trials were grouped in three types of altered fractionation: hyperfractionated, moderately accelerated, and very accelerated. Individual patient data were collected and combined with a fixed-effects model based on the intention-to-treat principle. The primary endpoint was overall survival.

**FINDINGS:**

Comparison 1 (conventional fractionation radiotherapy vs altered fractionation radiotherapy) included 33 trials and 11 423 patients. Altered fractionation radiotherapy was associated with a significant benefit on overall survival (hazard ratio [HR] 0·94, 95% CI 0·90-0·98; p=0·0033), with an absolute difference at 5 years of 3·1% (95% CI 1·3-4·9) and at 10 years of 1·2% (-0·8 to 3·2). We found a significant interaction (p=0·051) between type of fractionation and treatment effect, the overall survival benefit being restricted to the hyperfractionated group (HR 0·83, 0·74-0·92), with absolute differences at 5 years of 8·1% (3·4 to 12·8) and at 10 years of 3·9% (-0·6 to 8·4). Comparison 2 (conventional fractionation radiotherapy plus concomitant chemotherapy versus altered fractionation radiotherapy alone) included five trials and 986 patients. Overall survival was significantly worse with altered fractionation radiotherapy compared with concomitant chemoradiotherapy (HR 1·22, 1·05-1·42; p=0·0098), with absolute differences at 5 years of -5·8% (-11·9 to 0·3) and at 10 years of -5·1% (-13·0 to 2·8).

**INTERPRETATION**:
This update confirms, with more patients and a longer follow-up than the first version of MARCH, that hyperfractionated radiotherapy is, along with concomitant chemoradiotherapy, a standard of care for the treatment of locally advanced head and neck squamous cell cancers. The comparison between hyperfractionated radiotherapy and concomitant chemoradiotherapy remains to be specifically tested.

Strengths

- Large scale, multi-institutional meta-analysis with use of individual patient data from the trials
- Long term analyses on patient data >10 years
- Inclusion of short and long term toxicity data
- Absolute differences in survival demonstrated with hyperfractionation

Limitations

- Inclusion of trials with outdated XRT techniques
- Lack of HPV and smoking data
- Inability to compare hyperfractionation to concomitant chemoradiotherapy (aka the data suggest that hyperfractionation should only be used when CRT not able to be administered, and due to the superior survival over conventional fractionation)

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## Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomized, phase3 trial.

Harrington KJ, Ferris RL, Blumenschein G Jr, Colevas AD, Fayette J, Licitra L, Kasper S, Even C, Vokes EE, Worden F, Saba NF, Kiyota N, Haddad R, Tahara M, Grünwald V, Shaw JW, Monga M, Lynch M, Taylor F, DeRosa M, Morrissey L, Cocks K, Gillison ML, Guigay J.

*from **Lancet Oncology**, August 2017*

**BACKGROUND:**
Patients with platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck have few treatment options and poor prognosis. Nivolumab significantly improved survival of this patient population when compared with standard single-agent therapy of investigator's choice in Checkmate141; here we report the effect of nivolumab on patient-reported outcomes (PROs).

**METHODS:**
CheckMate 141 was a randomised, open-label, phase 3 trial in patients with recurrent or metastatic squamous cell carcinoma of the head and neck who progressed within 6 months after platinum-based chemotherapy. Patients were randomly assigned (2:1) to nivolumab 3 mg/kg every 2 weeks (n=240) or investigator's choice (n=121) of methotrexate (40-60 mg/m2 of body surface area), docetaxel (30-40 mg/m2), or cetuximab (250 mg/m2 after a loading dose of 400 mg/m2) until disease progression, intolerable toxicity, or withdrawal of consent. On Jan 26, 2016, the independent data monitoring committee reviewed the data at theplanned interim analysis and declared overall survival superiority for nivolumab over investigator's choicetherapy (primary endpoint; described previously). The protocol was amended to allow patients in theinvestigator's choice group to cross over to nivolumab. All patients not on active therapy are being followed for survival. As an exploratory endpoint, PROs were assessed at baseline, week 9, and every 6 weeks thereafter using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of LifeQuestionnaire-Core 30 (QLQ-C30), the EORTC head and neck cancer-specific module (EORTC QLQ-H&N35), and the three-level European Quality of Life-5 Dimensions (EQ-5D) questionnaire. Differences within and between treatment groups in PROs were analysed by ANCOVA among patients with baseline and at least one other assessment.

All randomised patients were included in the time to clinically meaningful deterioration analyses. Median time to clinically meaningful deterioration was analysed by Kaplan-Meier methods. CheckMate 141 was registered with ClinicalTrials.org, number NCT02105636.

**FINDINGS:**
Patients were enrolled between May 29, 2014, and July 31, 2015, and subsequently 361 patients were randomly assigned to receive nivolumab (n=240) or investigator's choice (n=121). Among them, 129 patients (93 in the nivolumab group and 36 in the investigator's choice group) completed any of the PRO questionnaires at baseline and at least one other assessment. Treatment with nivolumab resulted in adjusted mean changes from baseline to week 15 ranging from -2·1 to 5·4 across functional and symptom domains measured by the EORTC QLQ-C30, with no domains indicating clinically meaningful deterioration. By contrast, eight (53%) of the 15 domains in the investigator's choice group showed clinically meaningful deterioration (10 points or more) at week 15 (change from baseline range, -24·5 to 2·4). Similarly, on the EORTC QLQ-H&N35, clinically meaningful worsening at week 15 was seen in no domains in the nivolumab group and eight (44%) of 18 domains in the investigator's choice group. Patients in the nivolumab group had a clinically meaningful improvement (according to a difference of 7 points or greater) in adjusted mean change from baseline to week 15 on the EQ-5D visual analogue scale, in contrast to a clinically meaningful deterioration in the investigator'schoice group (7·3 vs -7·8). Differences between groups were significant and clinically meaningful at weeks 9 and 15 in favour of nivolumab for role functioning, social functioning, fatigue, dyspnoea, and appetite loss on the EORTC QLQ-C30 and pain and sensory problems on the EORTC QLQ-H&N35. Median time to deterioration was significantly longer with nivolumab versus investigator's choice for 13 (37%) of 35 domains assessed across the three questionnaires.

**INTERPRETATION:**
In this exploratory analysis of CheckMate 141, nivolumab stabilised symptoms and functioning from baseline to weeks 9 and 15, whereas investigator's choice led to clinically meaningful deterioration. Nivolumab delayed time to deterioration of patient-reported quality-of-life outcomes compared with single-agent therapy of investigator's choice in patients with platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck. In view of the major unmet need in this population and theimportance of maintaining or improving quality of life for patients with

recurrent or metastatic squamous cell carcinoma of the head and neck, these data support nivolumab as a new standard-of-care option in this setting.

**Summary statements**
This is the Quality of life evaluation for patients enrolled in the checkmate study of Nivolumab vs other agents for platinum refractory patients. Patient Reported outcomes were assessed using the EORTC, QLQ-C30 questionnaires

**Strengths**
- Statistical difference was noted not only in the survival but also in QOL
- Further rationale is provided to consider immunotherapy for this population with advanced disease

**Weaknesses**
- Of the 361 initial patients only 129 patients (93 in the nivolumab group and 36 in the investigator's choice group) completed any of the PRO questionnaires at baseline and at least one other assessment
- Limited data points especially in the investigators choice group

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## Human Papillomavirus 16 E6 Antibodies Are Sensitive for Human Papillomavirus–Driven Oropharyngeal Cancer and Are Associated With Recurrence

Skillington SA, Lang Kuhs KA, Kreimer AR, Trivedi S, Holzinger D, Pawlita M, Pfeiffer RM, Gibson SP, Schmitt NC, Hildesheim A, Waterboer T, Ferris RL.

*from **Cancer**, November 2017*

**BACKGROUND:**
Human papillomavirus 16 (HPV16) E6 antibodies may be an early marker of the diagnosis and recurrence of human papillomavirus-driven oropharyngeal cancer (HPV-OPC).

**METHODS:**
This study identified 161 incident oropharyngeal cancer (OPC) cases diagnosed at the University of Pittsburgh (2003-2013) with pretreatment serum. One hundred twelve had preexisting clinical HPV testing with p16 immunohistochemistry and HPV in situ hybridization (87 were dual-positive [HPV-OPC], and 25 were dual-negative [HPV-negative]); 62 had at least 1 posttreatment serum sample. Eighty-six of the 161 tumors were available for additional HPV16 DNA/RNA testing (45 were dual-positive [HPV16-OPC], and 19 were dual-negative [HPV16-negative). HPV16 E6 antibody testing was conducted with multiplex serology. The following were evaluated: 1) the sensitivity and specificity of HPV16 E6 serology for distinguishing HPV-OPC and HPV16-OPC from HPV-negative OPC, 2) HPV16 E6 antibody decay after treatment with linear models accommodating correlations in variance estimates, and 3) pre- and posttreatment HPV16 E6 levels and the risk of recurrence with Cox proportional hazards models.

**RESULTS:**
Seventy-eight of 87 HPV-OPCs were HPV16 E6-seropositive (sensitivity, 89.7%; 95% confidence interval [CI], 81.3%-95.2%), and 24 of 25 HPV-negative OPCs were HPV16 E6-seronegative

(specificity, 96.0%; 95% CI, 79.6%-99.9%). Forty-two of 45 HPV16-OPCs were HPV16 E6-seropositive (sensitivity, 93.3%; 95% CI, 81.7%-98.6%), and 18 of 19 HPV16-negative OPCs were HPV16 E6-seronegative (specificity, 94.7%; 95% CI, 74.0%-99.9%). Posttreatment HPV16 E6 antibody levels did not decrease significantly from the baseline (P = .575; median follow-up, 307 days) and were not associated with the risk of recurrence. However, pretreatment HPV16 E6 seropositivity was associated with an 86% reduced risk of local/regional recurrence (hazard ratio, 0.14; 95% CI, 0.03-0.68; P = .015).

**CONCLUSIONS:**
HPV16 E6 antibodies may have potential clinical utility for the diagnosis and/or prognosis of HPV-OPC

**Strengths**

- Well-designed study with a relatively large sample size
- Use of both HPV ISH and p16 testing, which is reported by the authors as the "gold standard" method for assigning HPV status
- Results showing high specificity and sensitivity for the detection of HPV OPC

**Limitations**

- The vast majority of patients mounted an immune response making the test highly sensitive for diagnosis, but not necessarily great for prognostic discrimination
- Low rates of recurrence and post-treatment samples makes conclusions regarding the utility of HPV 15 E6 antibody testing for prognostic and recurrence information difficult to make
- Lack of multivariable analysis due to above reason

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## Definitive Chemoradiotherapy With Carboplatin for Squamous Cell Carcinoma of the Head and Neck

Nagasaka M, Zaki M, Issa M, Kim H, Abrams J, Sukari A.

*from **Laryngoscope**, October 2017*

Objective: Definitive concurrent chemoradiotherapy (CRT) is considered the standard of care for organ preservation and is the only potentially curative therapy for surgically unresectable patients with stage III to IVb locally advanced squamous cell carcinoma of the head and neck. In patients with high risks for adverse events utilizing cisplatin, carboplatin has been empirically substituted. The objective of this study was to estimate the locoregional control rate, progression-free survival, overall survival, and adverse events in locally advanced squamous cell carcinoma of the head and neck patients treated with CRT utilizing carboplatin.

Study Design: A retrospective single-arm analysis.

Methods: Data on consecutive patients who fit the eligibility criteria were collected. Eligible patients were treated with 70 Gy of radiation therapy and at least two cycles of carboplatin (area of curve [AUC] of 5 between January 2007 to December 2013.

Results: Fifty-four patients were identified. Overall locoregional control rate was 50% (95% confidence interval [CI] 37%–63%). Median progression-free and overall survival were 21 (CI 11–33) and 40 (CI 33–NA) months, respectively. One, 3, and 5-year overall survival were 81% (CI 67%–89%), 59% (CI 41%–73%), and 42% (CI 22%–61%), respectively. Stage III/IVa patients (n = 45) had a median survival

of 62 (CI 37–NA months) and 3 years of 71% (CI 53%–84%), whereas stage IVb (n = 9) had a median survival of 31 (CI 4–NA) months and none survived to 3 years.

Conclusion: Definitive CRT with carboplatin for locally advanced squamous cell carcinoma of the head and neck was well tolerated and demonstrated comparable results to CRT with cisplatin.

Summary: 54 patients with locally advanced (stage III to IVb) SCCA of multiple subsites (most were laryngeal and oropharynx) treated with concurrent carboplatin and radiation were retrospectively studied. Patients with renal insufficiency and hearing loss were included. Locoregional control rates and OS were comparable to historical concurrent cisplatin and radiation rates.

Strengths:

- Study included a wide range of patient ages and comorbities including patients >70 and those with renal insufficiency and hearing loss.
- Advanced stage disease was included (Stage IVa and IVb)
- Excellent review of the major historical studies comparing cisplatin, cetubimab and radiation (RTOG 99-11, RTOG 05-22, Bonner trial, etc).

Weaknesses:

- Retrospective study
- Small sample size = 54 patients
- 35% of patients had oropharyngeal primaries. No mention of p16 status or outcome differences in these patients.

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