Highlights in head and neck cancer

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Management of locoregional lymph nodes

The optimal management of the regional lymph nodes was studied in several elegant studies presented at ASCO this year. A single centre randomized trial conducted at Tata Memorial Centre, Mumbai, India and presented at the plenary session by Cruz on behalf of the Head and Neck Disease Management Group, demonstrated unequivocally that in patients with early-stage squamous cell carcinoma (SCC) of the oral cavity, elective neck dissection (ND) results in higher rates of overall survival (OS) and disease-free survival (DFS) than therapeutic ND.[1,2]

The trial was designed to answer 2 questions: the primary question was to evaluate the efficacy of elective ND versus wait policy in terms of OS (primary endpoint) and DFS in patients with early stages SCC of the oral cavity; the second question was to evaluate the role of ultrasonography in the early detection of neck node metastases during follow up. Initially, the trial was designed to detect an improvement of survival by 10% by elective ND assuming a baseline survival of 60% in the watch-and-wait arm with an 80% power and an α of 0.05, which required a sample size of 710 patients. However in June 2014, the data safety monitoring committee requested a second interim analysis after inclusion of 596 patients of which 500 with a minimum follow-up of 9 months were included in the current analysis. Eligible were patients with histologically proven treatment naïve cT1/T2No SCC of the oral cavity amenable to trans-oral excision with adequate margins (ideally 5 mm). Excluded were patients with tumors of the upper alveolus and palatal lesions or with heterogeneous leukoplakia requiring surgery or diffuse oral submucous fibrosis. Patients randomized in the elective ND arm underwent an ipsilateral selective ND clearing levels I- III. Surgery was extended to a modified ND involving level IV and V when positive nodes were found in the resection specimen. Patients randomized to elective ND arm underwent a modified therapeutic ND (level I-V) at the time of nodal recurrence. Adjuvant radiotherapy, according to the current guidelines, was administered in 58.5% of the patients (both arms). The majority (58.5%) had a primary tumor of the tongue and 55% had a T2 tumor. Median depth of invasion was 6 mm (range 0-20). In the elective ND patients, positive nodes on pathological examination were found in 29.6% (95%CI, 23.9 to 35.3) of the patients. The depth of invasion of the primary tumor was significantly associated with node positivity. There were 50 deaths (20.6%) in the elective ND group and 79 (31.2%) in the therapeutic ND group. The 3-year estimated OS rates were 80.0% (95% confidence interval [CI], 74.1 to 85.8) and 67.5% (95% CI, 61.0 to 73.9), respectively, (unadjusted hazard ratio [HR] for death in the elective-surgery group, 0.64; 95% CI, 0.45 to 0.92; p= 0.01; adjusted HR, 0.63; 95% CI, 0.44 to 0.90) (*Figure 1*). At 3 years, DFS rates were 69.5% (95%CI, 63.1 to 76.0) and 45.9% (95%CI, 39.4 to 52.3%), respectively, (unadjusted HR, 0.45; 95%CI, 0.34 to 0.59; p<0.001; adjusted HR, 0.44; 95% CI, 0.33 to 0.57).

Of the 114 patients with cervical-lymph-node relapse in the therapeutic-surgery group, 60 (52.6%) died of

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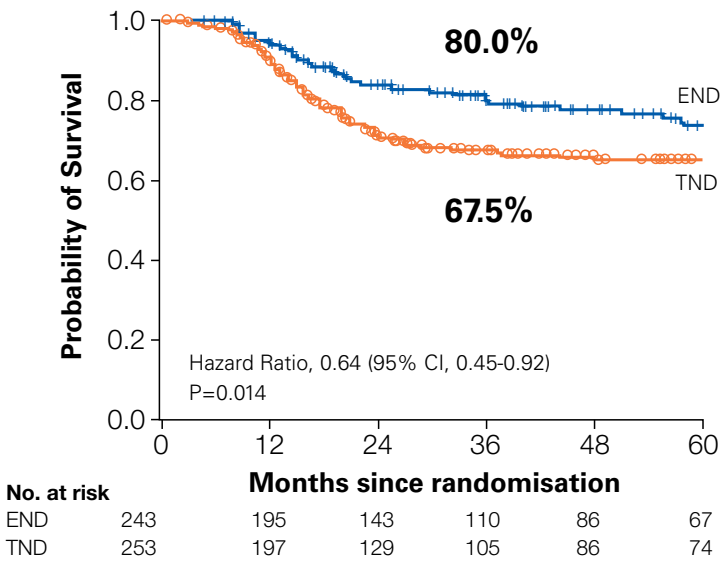

	END	TND
Events	50	79
Total	243	253

Figure 1. Elective neck dissection is associated with a longer overall survival in patients with early-stage squamous cell carcinoma (SCC) of the oral cavity.

disease progression. The majority of first events (114 events in 146 patients [78.1%]) were nodal relapses in the therapeutic-surgery group. In contrast, the majority of first events (42 events [51.9%]) in the elective ND arm were non-nodal recurrences.[2] The outcome in this randomized trial are consistent with the results of a previously published meta-analysis.[3]

Planned ND after definitive chemoradiation for patients with locally advanced nodal metastases remains controversial. The PET-NECK study was a multicentre, randomized, phase III, controlled trial comparing PET-CT guided active surveillance with planned ND for locally advanced (N2/N3) nodal metastases (LANM) in SCC of the head and neck (HNSCC) treated with primary definitive chemoradiation.[4] Patients with LANM of oropharynx, hypopharynx, larynx, oral cavity, or occult primary, and fit for ND were randomized to planned ND before or after chemoradiation, or chemoradiation followed by FDG-PET-CT 10-12 weeks post chemoradiation with ND if PET-CT showed incomplete or equivocal response of nodal disease (intervention arm). The primary endpoint was OS. The study aimed to detect non-inferior OS in the intervention arm with 80% power, Type I error 5%, defining non-inferiority as having a HR no higher than 1.50.

In total, 564 patients were recruited: 17% N2a, 61% N2b, 18% N2c, 3% N3. Of them 84% had oropharyngeal cancer and 75% of tested cases were p16-positive. Median follow-up was 36 months. The HR for OS was 0.92 (95% CI: 0.65, 1.32) indicating non-inferiority. HR margin of 1.50 lies at the 99.6 percentile of this estimate (p= 0.004). There were no differences by p16 status. Fifty-four NDs were performed in the intervention arm with 22 surgical complications versus 221 NDs with 85 complications in the control arm. Results of the economic evaluation indicated that PET-CT surveillance is cost-effective over a short term. Results over a longer term are less clear.[5]

Quality of head and neck surgery has thus far focused on adherence to clinical national guidelines and margin status. For other solid tumors, an association has been found between lymph node counts from regional ND on and outcome and lymph node counts have been proposed as an indicator for quality of surgery. A secondary analysis of patients in RTOG trials 9501 and 0234 was performed.[6] The number of lymph nodes counted from regional ND was evaluated for its prognostic impact on OS using a multivariate Cox model adjusted for demographic, tumor, and lymph node data, and stratified by postoperative treatment group: (1) radiation, (2) chemoradiation on RTOG 9501 or (3) chemoradiation and cetuximab on RTOG 0234. In total, 572 patients were analyzed. Median FU for surviving patients was eight years. Median number of lymph nodes recorded on the left and right sides were

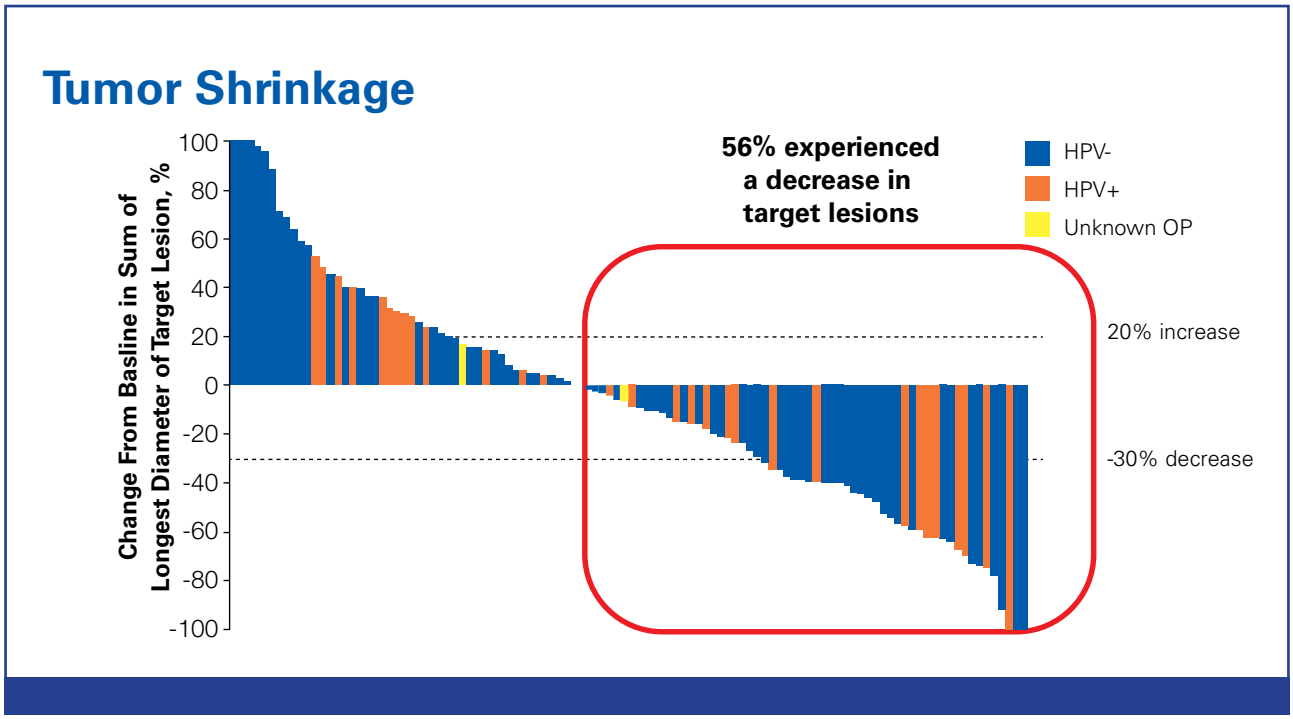

Figure 2. Pembrolizumab decreases the target lesions in 56% of advanced HNSCC patients.

24 and 25, respectively. Fewer than 18 nodes was associated with significantly worse OS relative to ≥18 nodes (HR 1.38, 95%CI 1.09-1.74, p= 0.007). The model with this cut point had minimum AIC of all possible models indicating optimal fit. The difference appears to be driven by local-regional failure (HR 1.46, 95%CI 1.02-2.08, p= 0.04) but not distant metastasis (HR 1.08, 95%CI 0.77-1.53, p= 0.65). The effect of node counts is not different by p16 status (p-value for interaction 0.99). The removal and identification of at least 18 lymph nodes can be considered as a measure of quality in neck dissections for HNSCC.

Locoregionally advanced squamous cell carcinoma of the head and neck

Concurrent administration of anti-EGFR monoclonal antibody with radiotherapy (RT) increases survival compared to RT alone in patients with locoregionally advanced HNSCC (LA-HNSCC). Thus far, no prospective data are available comparing bioradiation to standard chemoradiation. Siu et al. presented the results of NCIC Clinical Trials Group HN6 trial. Three hundred and twenty patients with TanyN+MO or T3-T4 LA-SCCHN (oropharynx 81%, larynx 11%, hypopharynx 6%,oral cavity 2%) were randomized to receive standard fractionation (SFX) (70Gy/35 over 7 weeks) plus cisplatin 100 mg/m^2 for 3 doses on weeks 1, 4, and 7, or accelerated fractionation (AFX) (70 Gy/35 over 6 weeks) plus panitumumab at 9 mg/kg on weeks 1, 3, and 6. At a median follow-up of 46,4 months, progression-free survival (PFS) (primary endpoint) with AFX plus panitumumab was not superior to SFX plus cisplatin. Non-inferiority was not proven as the upper bound of hazard ratios exceeded the pre-specified non-inferiority margin. Incidence of any grade ≥3 non-hematological adverse events was similar in both arms.[7]

Janoray et al. presented the long-term results of GORTEC 2000-01, a multicentre randomized phase III trial of induction chemotherapy with 3 cycles of cisplatin plus 5-fluorouracil, with or without docetaxel, for larynx preservation in patients with operable stage stage III or IV SCC of the larynx or hypopharynx, who required a total laryngectomy.[8] Long-term follow-up confirms that induction chemotherapy with TPF increases larynx-preservation rate and larynx dysfunction-free survival (LDFS). Two hundred and thirteen patients were treated and the median follow-up was 105 months. The 5- and 10-year larynx preservation rates were 74.0% (95%CI, 0.64-0.82) *vs.* 58.1% (95%CI, 0.47-0.68) and 70.3% (95%CI, 0.58-0.8) *vs.* 46.5% (95%CI, 0.31-0.63, p = 0.01) in TPF versus PF arm, respectively. The 5- and 10-year LDFS rates were 67.2% (95%CI, 0.57-0.76) *vs.* 46.5% (95%CI, 0.36-0.57) and 63.7% (95%CI, 0.52-0.74) versus 37.2% (95%CI, 0.24-0.52, p= 0.001), respectively. Moreover, significantly fewer grade 3-4 late toxicities of the larynx occurred with the TPF regimen

compared to the PF arm (9.3% *vs.* 17.1%, g-test p=0.038). Kish et al. examined the effect of age on outcome in 3 prospective, phase III NRG Oncology/RTOG trials of radiotherapy with or without chemotherapy in patients with LA-SCCHN.[9] The analysis included 2.688 patients with a median FU of 5.2 years for surviving patients. Patients aged ≥70 represented only 11.5 % of the enrolled population. They were more likely to be female with poorer performance status, heavier smoking history and p16 negative status. Adjusting for covariates, patients aged ≥70 had worse survival regardless of smoking or p16 status. This was more apparent in combined modality cisplatin-based trials. Maximum grade stomatitis and other toxicities were similar by age cohort and treatment arms on RTOG 9003, which compared 3 altered fractionation radiation schedu-les versus SFX. In the cisplatin-based studies, patients ≥70 experienced more grade 3-5 thrombocytopenia, anaemia, nephrotoxcity, and possibly ototoxicity (p= 0.06) but less mucositis.

A large multicentre cohort study suggests that cisplatin dose intensity < 200 mg/m^2 has a detrimental impact on OS in HPV-negative LA-HNSCC, while the impact in HPV-positive patients was not significant. However, prospective validation of de-intensification of treatment in patients with HPV-positive tumors is warranted prior to implementation outside clinical trials.[10]

In ECOG 1308 reduction of IMRT dose from 69.3 Gy to 54 Gy appeared to ameliorate late toxicities in locally advanced HPV-positive HNSCC as measured using the Vanderbilt Head and Neck Symptom Survey version 2 (VHNSS V2), suggesting that de-intensification could lead to meaningful reduction of late toxicity.[11]

Metastatic squamous cell carcinoma of the head and neck

Pembrolizumab had previously demonstrated activity in patients with recurrent or metastatic (R/M) HNSCCN enriched for PD-L1 expression or HPV status. Seiwert et al. now reported on a large expansion cohort of 132 advanced HNSCC patients, irrespective of biomarker status.[12] In this trial, 56.6% of the patients received at least 2 lines of prior therapy for recurrent disease. One hundred and seventeen patients were available for this efficacy analysis. Overall response rate (primary endpoint) was 24.8% (95%CI, 17.3-33.6). Stable disease was observed in 24.8% of the patients (*Figure 2*). Overall response rate was similar in HPV- and HPV+ patients. Responses were durable as 86% of responding patients remain in response.[12]

'Inflamed phenotype' signatures, as demonstrated by using 4 previously established gene signatures, are strong predictors of clinical benefit from anti-PD-1 treatment for HNSCC, even among a group of patients already considered to be PD-L1 positive.[13] Koutsodontis et al reported a highly sensitive, specific and reproducible quantitative real-time RT-qPCR assay for the assessment of PDL1 expression in circulating tumor cells in HNSCC.[14]

Nasopharyngeal carcinoma

A study by Lee et al. showed a strong relationship between post-IMRT 8th week and 6th month undetectable plasma EBV DNA and 3-year survival outcomes in non-metastatic nasopharyngeal carcinoma (NPC).[15] PD-L1 expression was found in 72% of EBV positive NPC, supporting development of anti-PD1/PD-L1 antibody in NPC.[16]

Thyroid cancer

The final OS analysis of EXAM, a double-blind, randomized, placebo-controlled phase III trial of cabozantinib in locally advanced or metastatic medullary thyroid carcinoma (MTC) patients with documented RECIST progression within 14 months of screening were presented after a median follow-up of 52.4 months.[17] The trial had already met its primary endpoint with a significant improvement in PFS (HR: 0.28, p< 0.001). The estimated median OS was 26.6 months for cabozantinib versus 21.1 months for placebo (HR: 0.85; p= 0.241). For 126 patients with known RET M918T mutations, median OS was 44.3 months with cabozantinib versus 18.9 months with placebo (HR: 0.60, p= 0.026). Lenvantinib significantly prolonged PFS versus placebo in the phase III SELECT trial of patients with ^{131}I-refractory differentiated thyroid cancer. Newbold et al. reported the pre-specified analysis of lenvantinib-treated patients based on prior VEGF-targeted therapy exposure.[18] Seventy-five percent of lenvantinib-treated and 79% of placebo-treated patients were naive to VEGF-targeted therapy. However, lenvantinib conferred comparable efficacy in patients with and without prior exposure to VEGF-targeted therapy, with similar safety profiles.

Tahara et al. investigated serum circulating cytokine/angiogenic factors (CAFs) (Ang2, VEGF, sTie2, and FGF23) as potential pharmacodynamic biomarkers for lenvantinib efficacy and disease progression in SELECT. From cycle 1 VEGF levels were consistently elevated for patients on lenvantinib, whereas Ang2 and sTie2 levels were consistently decreased compared with placebo.

FGF23 levels increased by 20.8% (C1D15) and 28.6% (C2D1). Although throglobuline decreases in lenvantinib patients were correlated with tumor shrinkage and objective response rate, thyroglobuline decreases also occurred in patients with stable or progressive disease. Increased VEGF and decreased Ang2 and sTie2 levels also correlated with tumor shrinkage, but not with ORR. Preliminary analyses of patients who progressed on lenvantinib indicated elevated levels of Ang2 and sTie2.

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