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Validation of the ICON-S staging for HPV-associated oropharyngeal carcinoma using a pre-defined treatment policy

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ABSTRACT

Objectives: To determine whether the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) for HPV associated oropharyngeal carcinoma (HPV + OPC) is a better discriminator of overall survival (OS), compared with the 7th edition (7th Ed) AJCC/UICC TNM staging following curative radiotherapy (RT).

Material and methods: The 5-year OS for all patients with non-metastatic (M0) p16-confirmed OPC treated between 2005 and 2015 was determined and grouped based on the 7th Ed AJCC/UICC TNM and ICON-S staging.

Results: A total of 279 patients met the inclusion criteria. The 5-year OS with the 7th Ed TNM classification were Stage I/II 88.9% (95% CI; 70.6–100%), Stage III 93.8% (95% CI; 85.9–100%), Stage IVa 86.4% (95% CI; 81.6–91.5%) and Stage IVb 62.3% (95% CI; 46.8–82.8%). On multivariate Cox regression analysis there was no statistically significant OS difference when comparing Stage I/II with, Stage III ($p = 0.98$, HR = 0.97, 95% CI; 0.11–8.64), IVa ($p = 0.67$, HR = 1.56, 95% CI; 0.2–11.94) and IVb ($p = 0.11$, HR = 5.54, 95% CI; 0.69–44.52), respectively.

The 5-year OS with ICON-S staging were Stage I 93.6% (95% CI; 89.4–98.0%), Stage II 81.9% (95% CI; 73.7–91.1%) and Stage III 69.1% (95%; 57.9–82.6%). There was a consistent decrease of OS with increasing stage. On multivariate Cox regression analysis, when compared to Stage I, OS was significantly lower for stage II ($p = 0.007$, HR = 2.84, 95% CI; 1.33–6.05) and stage III ($p < 0.001$, HR = 3.78, 95% CI; 1.81–7.92), respectively.

Conclusion: The ICON-S staging provides better OS stratification for HPV + OPC following RT compared with the 7th Ed TNM staging.

Introduction

Since the recognition of Human Papillomavirus (HPV) associated oropharyngeal cancer (OPC) (HPV + OPC) as a distinct entity, clinicians have long observed the limitations of the current 7th edition (7th Ed) American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging ability to reflect survival outcomes in this group of patients. This is not surprising, as the staging system was developed to account for outcomes of patients with traditional smoking-related mucosal head and neck cancer (HNC), whose demographics, risk factors, carcinogenesis and response to therapy differ to HPV + OPC [1–5].

Recently, Huang and colleagues proposed a new staging system for this group of patients based on a retrospective analysis from the Princess Margaret Hospital (PMH) [6].

The PMH staging proposal formed the basis of the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S) involving institutions across North America and Europe [7]. This multicentre cohort study retrospectively examined the outcomes of over 1900 HPV + OPC patients based on this proposed staging classification treated in a variety of manner including surgery and post-operative radiotherapy (RT) and definitive RT. A

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statistical analysis of the outcomes resulted in the further refinement of a new staging classification, ICON-S. This staging classification appears to better reflect the survival outcomes compared with the current 7th Ed TNM staging. The ICON-S group staging are: Stage I (T1-2N0-N1), Stage II (T1-2N2 or T3N0-2), Stage III (T4 or N3) and Stage IV (M1). N-category was re-classified to: N0, no lymph nodes; N1, ipsilateral lymph nodes; N2, bilateral or contralateral lymph nodes; N3, nodes larger than 6 cm.

While the collaboration resulted in a large sample size allowing detailed analysis, it is likely that there would have been for the same disease stage substantial heterogeneity of treatment policies amongst centres, with respect to indications for surgery, treatment intensification, RT scheduling and total dose, use of unilateral versus bilateral neck irradiation, and re-staging policy and management of the neck. These variations may have influenced survival outcomes. Further, it is important to test the applicability of any staging proposal independently from the initial cohort used to develop it.

This study applies the proposed ICON-S staging to a cohort of patients treated at a single institution with a pre-defined treatment policy depending on pre-treatment disease extent, with respect to treatment intensification, RT scheduling, total RT dose, and re-staging policy.

Methods and materials

Study population

The study was a retrospective analysis of a prospectively collected database of all newly diagnosed, histopathologically confirmed loco-regionally confined HPV + OPC treated with curative intent RT and a pre-defined treatment policy for all patients between 1st December 2005 and 30th December 2015 at the Princess Alexandra Hospital, Brisbane, Australia. Patients treated with primary surgery were excluded. The study received institutional ethics approval.

All patients underwent routine assessment by the multidisciplinary tumour board, which included at a minimum, a head and neck surgeon, radiation and medical oncologist, pathologist and radiologist, and were staged on the basis of clinical examination, panendoscopy and whole body 18-fluorine fluoro-deoxy-glucose (FDG) positron emission tomography (PET)/contrast enhanced computed tomography (CT). Magnetic resonance imaging (MRI) was included in those where there was uncertainty regarding tumour infiltration into surrounding tissues/structures.

p16 Immunohistochemistry (IHC)

Patients were considered to have HPV + OPC on the basis of p16 IHC. p16 IHC was performed using paraffin-embedded tumour tissue and defined as positive if there was strong and diffuse nuclear and cytoplasmic staining in $\geqslant$70% of tumour. Patients who presented without a clinically evident primary lesion despite biopsies of the oropharynx and a p16 positive core biopsy of an involved node were excluded from the analysis, as they are not included in either the 7th Ed TNM or ICON-S classifications.

Treatment

All patients, independent of treating radiation oncologist, were managed according to a pre-defined treatment policy. Patients with T1N0 disease were offered definitive surgical management with primary resection via transoral laser or robotic surgery and selective neck dissection (excluded from study). Patients with this disease were only treated with definitive RT if they refused or had a contraindication to surgery. Patients with T1N1-2a, T2N0 and T2N1 were treated with RT alone (68 Gy in 6 weeks to gross disease, as per DAHANCA fractionation). With regards to systemic therapy, consisting of either cytotoxic chemotherapy or anti-epidermal growth factor, patients were typically offered concurrent cisplatin (100 mg/m^2) and 70 Gy over 7 weeks to the gross disease. Patients ineligible for high-dose cisplatin were offered cetuximab (loading dose 400 mg/m^2, 250 mg/m^2 weekly with RT) and 68 Gy over 6 weeks. In 2012, eligible patients were considered for enrolment onto the Trans Tasman Radiation Oncology Group (TROG) low-risk HPV + OPC de-escalation trial (TROG 12.01, NCT01855451) randomizing patients to receive either concurrent low dose weekly cisplatin (40 mg/m^2) or cetuximab (as described above), and 70 Gy over 7 weeks.

Patients with lateralized (>1 cm lateral to the midline) tonsil/-soft palate tumours T1-2 N0-2a were treated with unilateral neck treatment. All other tonsil tumours and base of tongue (BOT) tumours received bilateral neck irradiation. Retropharyngeal nodes were treated electively in the presence of >T2 tonsil/soft palate tumours with any N-category, T1 tonsil/soft palate and $\geqslant$N2b, $\geqslant$T3 BOT with any N-category, and any T-category with N3 disease.

RT was delivered with either Intensity Modulated RT (IMRT) or Volumetric Modulated Arc Therapy (VMAT). The head and neck radiation oncology team reviewed all RT volumes at the weekly quality assurance meeting to ensure compliance with treatment protocol and appropriate tumour coverage.

Patients were followed up and re-staged according to our previously described PET policy [8,9]. In brief, all patients were reviewed 4–6 weeks post therapy to determine response to treatment. In the absence of disease progression of the primary tumour and/or neck, patients underwent a 12-week clinical examination and PET-CT. Patients with residual primary disease underwent surgical salvage. In patients who achieved a complete response of the primary lesion, the neck was managed based on the PET-CT findings. If PET positive, they underwent a neck dissection, if negative they were observed regardless of any structural residual abnormality, and if PET equivocal they underwent a repeat PET-CT 4–6 weeks later, and if still equivocal underwent a neck dissection.

Statistical considerations

The closeout date of the study was 30th June 2016. Survival was calculated from commencement of treatment to the date of death from any cause, or the closeout date. As this study was designed to determine the utility of the ICON-S staging, the outcome focused solely on OS. Estimated OS based on 7th Ed TNM and ICON-S group staging classification was calculated using the Kaplan-Meier method with 95% confidence intervals (CI). Within each staging classification, 7th Ed TNM or ICON-S, the group stages were compared using the log-rank test. The 5-year OS were calculated and reported by stage. To identify survival differences between stages for either staging classification, and account for potential factors of age, addition of systemic therapy, and smoking history, a multivariate cox regression analysis was performed and hazard ratios (HR) with 95% CI were reported for each variable.

Age was assessed as a continuous variable. Systemic therapy was assessed initially including both cytotoxic chemotherapy and cetuximab. A further analysis was preformed assessing cytotoxic chemotherapy alone, excluding patients treated with cetuximab alone. Smoking was assessed by the following categories; never smoked, $\leqslant$10 pack/years and >10 pack/years.

All analyses were performed using the R statistical software and p-values were two-tailed with $p < 0.05$ considered statistically significant [10].