OC-0389 Individualized prophylactic irradiation based on sentinel lymph node(s) identification in cN0 HNSCC

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Purpose or Objective
The DAHANCA9 hyperfractionation study and the MARCH meta-analysis (Bourhis et al, Lancet 2006) on altered fractionation showed that Hyperfractionated Accelerated Radiotherapy (HART) is superior in terms of loco-regional control (LRC) and overall survival (OS) compared to conventional or moderately accelerated radiotherapy for Head and Neck Squamous Cell Carcinomas (HNSCC). Since 2007, HART has been included as a treatment option in the Danish DAHANCA radiotherapy guidelines. The aim of the present study was to evaluate this treatment strategy using LRC, OS and late morbidity as endpoints.
Material and Methods
Prospectively registered patients (pts) with HNSCC treated with HART according to national guidelines prescribed as 76Gy/56fx, 10 fx/week, as primary treatment were identified in the DAHANCA database and updated. The study was evaluated as intention to treat and elective neck-dissection was not an option.
Results
From July 2007 to December 2017, 271 pts with HNSCC treated with HART were identified in four national cancer centers that on a regular basis offers HART according to treatment guidelines. The median age was 64 years (32-81 years) and 74% were males. The majority of pts were WHO PS 0-1 (94%) and only 6% were WHO PS ≥2. Most (84%) were current or previous smokers with a smoking history of median 42 pack-years (1-140 pack-years). The primary site was larynx in 65 cases (24%); 176 cases were in the pharynx (65%) and 30 pts had oral cavity cancer (11%). In total, 62% of the cases were stage III-IV (UICC7). In the pharynx, 138 cases (78%) were of oropharyngeal origin and of those, 48% were HPV/p16+. The proportion of pts receiving HART as planned was 96%. No patients received adjuvant or concomitant chemotherapy. As per September 1st 2018, 50 loco-regional failures (19% of the pts) were detected with a median follow-up time of 29 months: 47 occurred in T-site and 15 in N-site. Among those, 12 pts had both T- and N-site failure.Three-year actuarial LRC was 81% and OS was 68%. LRC at three years was significantly different for stage I-II and stage III-IV HNSCC (90% vs. 74%, HR 0.44 (range 0.23-0.81)) but not significantly better for HPV/p16+ oropharyngeal carcinomas compared to the HPV/p16- oropharynx pts (94% vs 89%).The proportion of pts reporting severe late dysphagia was 16%, and 9% reported late, severe dryness of the mouth; 8% were observed with late tardive edema of the larynx, 10% with severe mucosal atrophy and 5% with severe fibrosis of the subcutaneous tissue in the neck region.
Conclusion
Hyperfractionated accelerated radiotherapy is an attractive treatment approach in patients with HNSCC. Three-year loco-regional control as observed in this study is more than 80% and that is reflected in an acceptable overall survival. In this study, HART produced equally good results for HPV/p16+ and HPV/p16- oropharyngeal cancer patients. Severe late morbidity is reasonably low and comparable to treatment with chemo-radiotherapy.

OC-0389 Individualized prophylactic irradiation based on sentinel lymph node(s) identification in cN0 HNSCC

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Purpose or Objective
Due to a risk of occult nodal metastases in clinically node-negative (cN0) head and neck squamous cell carcinoma (HNSCC) patients, prophylactic and often bilateral neck irradiation is mandatory. However, it leads to a large irradiation of healthy tissues and could miss unexpected nodal basins drained by the tumor. This prospective, non-randomized, interventional phase II study investigated how sentinel lymph node (SLN) mapping by SPECT/CT may help to individualize prophylactic neck irradiation and its potential impact on radiation-related toxicities and tumor control. The final results are presented.
Material and Methods
Forty-four patients with newly diagnosed cN0 squamous cell carcinoma of the oral cavity, oropharynx, larynx or hypopharynx were included and treated with upfront (chemo)radiotherapy with a curative intent. After simulation, all patients were imaged in treatment position with SPECT/CT after ^{99m}Tc nanocolloid injection around the tumor. The neck levels containing up to four hottest SLN were selected for prophylactic irradiation (CTVn-LS). A comparative virtual planning was performed by including the levels selected on the basis of the current international guidelines (CTVn-IG). Dosimetric data to the different organs-at-risk (OAR) were compared between both plans. Normal tissue complication probability (NTCP) models for xerostomia and dysphagia as well as quality of life assessments (EORTC C30 and H&N35 scales) are being investigated to predict the clinical benefit of this technique.
Results
Lymphatic migration was observed in all of the 44 patients. Four patients (9%) presented an unpredicted lymphatic drainage and 21 patients (48%) had only an unilateral drainage. The volumes of CTVn-LS and PTVn-LS (median volumes of 91.8 cc and 219.1 cc, respectively) were systematically smaller than CTVn-IG and PTVn-IG (median volumes of 188.3 cc and 405.3 cc, respectively). This led to a significant dose decrease in identified OAR, particularly to the controlateral parotid gland, controlateral submandibular gland, inferior constrictor muscle for oral/oropharynx tumors and superior constrictor muscle for larynx/hypopharynx tumors (Table 1). NTCP values and QoL data processing is still work in progress and will be presented during the congress. At a median follow-up of 42 months, 3 patients experienced a regional relapse: 2 in an irradiated area (4.5%) and 1 in a non-irradiated area (2.3%). Currently, 4 patients had a local reccurence and 6 patients died (2 patients from geriatric degradation and 4 patients experienced fatal local relapse).

Comparative dosimetry of clinically significant organs-at-risk

OARs	IG plan Median Dmean (Gy)	LS plan Median Dmean (Gy)	p-Value*	Median ΔDmean (Gy)
Unilateral lymph drainage on SPECT/CT (n = 21)				
Oral cavity and oropharynx carcinoma				
Parotid gland (ipsilateral)	28.5	29.7	0.69	-0.1
Parotid gland (contralateral)	25.3	18.0	0.03	10.4
Submandibular gland (ipsilateral)	54.0	52.1	0.87	0.4
Submandibular gland (contralateral)	40.8	20.9	<0.01	24.0
Superior PCM	57.3	53.2	0.09	5.0
Middle PCM	38.2	32.2	0.44	7.1
Inferior PCM	33.8	13.4	0.01	22.5
Hypopharynx and larynx carcinoma				
Parotid gland (ipsilateral)	18.9	16.0	0.03	1.9
Parotid gland (contralateral)	19.5	4.0	<0.01	15.2
Submandibular gland (ipsilateral)	39.2	36.5	0.08	3.1
Submandibular gland (contralateral)	41.6	11.9	<0.01	28.1
Superior PCM	35.0	20.9	<0.01	14.4
Middle PCM	49.1	42.5	0.22	4.2
Inferior PCM	58.6	57.3	0.66	2.2
Bilateral lymph drainage on SPECT/CT (n = 23)				
Oral cavity and oropharynx carcinoma				
Parotid gland (ipsilateral)	27.15	25.75	0.43	1.5
Parotid gland (contralateral)	25.05	23.0	0.45	1.7
Submandibular gland (ipsilateral)	50.15	46.3	0.55	0.4
Submandibular gland (contralateral)	42.1	38.4	0.34	1.5
Superior PCM	64.25	63.5	0.66	0.0
Middle PCM	47.6	44.2	0.70	0.8
Inferior PCM	46.7	19.05	<0.01	24.9
Hypopharynx and larynx carcinoma				
Parotid gland (ipsilateral)	20.7	18.9	0.02	0.3
Parotid gland (contralateral)	20.2	18.7	0.02	0.6
Submandibular gland (ipsilateral)	39.5	35.95	0.06	1.3
Submandibular gland (contralateral)	37.25	33.55	0.04	2.8
Superior PCM	36.95	30.55	0.05	6.9
Middle PCM	56.5	56.15	0.47	0.5
Inferior PCM	60.05	58.3	0.74	0.3

Abbreviations: IG: International guidelines; LS: Lymphoscintigraphie; PCM: pharyngeal constrictor muscle
* Mann-Whitney-U test, two-sided test.

Conclusion
SLN mapping using SPECT/CT allowed to significantly reduce the prophylactically irradiated neck volumes in cN0 HNSCC patients. This resulted in a significant dose decrease in OAR, especially in patients presenting an unilateral lymphatic drainage, while uncompromising the

oncological outcome. The final analysis of the clinical impact of dose reduction to OAR will be presented.

OC-0390 TCGA molecular subclassification is prognostic for LRC of HNSCC after postoperative RCTx

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Purpose or Objective

The Cancer Genome Atlas (TCGA) recently provided a molecular subclassification of head and neck squamous cell carcinomas (HNSCC) including an atypical, classical, basal and mesenchymal subtype. The aims of the present study are to investigate (I) the impact of this subclassification on loco-regional control (LRC) in patients with locally advanced HNSCC who received postoperative radiochemotherapy (RCTx); and (II) the enrichment of those subtypes in radiobiologically relevant aspects such as hypoxia, epithelial-mesenchymal transition (EMT) and cancer stem cells (CSCs).

Material and Methods

In this retrospective multicentre study, 195 patients with locally advanced squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx were included. All patients received surgery followed by postoperative RCTx between 2005 and 2011. Their median follow-up was about 26 months. Whole transcriptome analysis was performed using the HTA 2.0 Array (Affymetrix). Tumours were classified into the four subtypes atypical, classical, basal or mesenchymal, based on four cluster centres of the expressions of 838 genes that were previously reported. A clear classification was possible for 141 out of 195 patients. Hypoxia was assessed using an established hypoxia-associated 15-gene signature. For EMT, a previously developed 31-gene signature was applied and for the analysis of CSC markers, previously reported putative CSC markers *CD44*, *SLC3A2* and *MET* were used since no CSC signature is available to date. Primary endpoint was loco-regional control (LRC).

Results

Tumours were classified into all four subtypes (43% atypical, 19% classical, 15% basal and 23% mesenchymal). The atypical subtype represented the subgroup with the highest LRC, while the mesenchymal subtype showed the lowest LRC (p=0.002, log-rank test). The basal and classical subtypes represented intermediate subgroups. Interestingly, the atypical subtype showed low expressions of the EMT signature, the hypoxia signature as well as low expressions of CSC markers. In contrast, the mesenchymal subtype was associated with increased expression of the EMT signature as well as hypoxia-associated genes and CSC markers.

Conclusion

We have shown for the first time, that the molecular subclassification reported for the TCGA HNSCC cohort allows for stratification of patients who were treated with postoperative RCTx regarding their loco-regional control. This was further supported by the enrichment of radiobiologically relevant aspects within those subtypes.

OC-0391 Treatment outcome of 265 patients with sinonasal adenoid cystic carcinoma (ACC)

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