

Study information		Board Submission Form	
Title	Phase III study assessing The “best of” radiotherapy compared to the “best of” surgery (trans-oral surgery (TOS) in patients with T1-T2, N0 oropharyngeal carcinoma		
Study Number	EORTC – 13xx -	Collaborating Group(s)	GORTEC
Date Board review		Is this a resubmission	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Study Coordinator	Name: Pr Simon Pr Bourhis	Institution: 457 - CHUV/UNIL, Lausanne, Switzerland	
Non-EORTC group(s) involved	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Leading: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Group name: GORTEC
Sponsorship			
Concept		Board Submission Form	
Rationale (clinical need)	<p>The current standard treatment for early stage oropharyngeal carcinoma is based on either surgery and/or radiotherapy. Both surgery and radiotherapy are associated with comparable and high tumor control probability rates but also with different constraints and potential side effects. The choice between these two treatment options is generally based on the experience accumulated in each individual centre, but not based on evidence based level 1 comparisons. Since both novel surgical and radiation techniques can offer a better ratio in terms of tolerance/efficacy, it is also essential to evaluate which of these novel approaches would be superior to each other in terms of functional out-come. It is hence important to revisit, which of them could appear as generally more appropriate as first treatment choice. To answer this question, we propose a randomized trial to evaluate the respective benefits and disadvantages of these treatments.</p>		
Hypothesis (rationale trt)	<p>The general hypothesis is that both treatments will have equivalent tumor control probabilities, but could have a different functional outcome. The general aim hence is to assess and compare in patients with early stage oropharyngeal carcinomas dysphagia, shoulder function, xerostomia, and general quality of life after the two treatments.</p>		
Pt population (5 main criteria)	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Squamous cell carcinoma, biopsy proven • Tumor located in the oropharynx, including one or several of the following sub-sites: base of tongue, lateral wall, tonsil, glosso-tonsillar 		

	<p>sulcus.</p> <ul style="list-style-type: none"> • TNM stage I or II : T1 or T2 N0, as evaluated both clinically, and on CT scanner w contrast and/or MRI and US w FNA (to r/o N1) • Age 18 years or older, • Treatment naïve patient with confirmed diagnosis of squamous cell carcinoma of the oropharynx • ECOG PS =< 1. • Written informed consent. • HPV status available • Smoking status available <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Patient not suitable for general aenesthesia • Any previous anti-cancer therapy for HNSCC (chemo or radiotherapy or molecular targeted therapy). • Serious illness or concomitant non-oncological disease considered by the investigator to be incompatible with the protocol. • Contra-indication to the use of cisplatin (renal, cardio-vascular, auditive) • Poor transoral exposure of the tumor during panendoscopy • Patients unable to comply with the protocol.
<p>Primary endpoint(s)</p>	<p>Mean of the total MDADI score at 3 and 6 months.</p> <p>The total MDADI score is a composite endpoint reported and scored by the patient for dysphagia. It is composed of 19 items: Emotional (6 questions), Functional (5 questions), and Physical (8 questions). The MDADI total score ranges from 20 (extremely low functioning) to 100 (high functioning). References: Chen, JAMA Otolaryngology–Head & Neck Surgery , 2001 ; Carlsson et al, Dysphagia, 2012.</p> <p>MDADI has been validated in previous clinical trials and is the standard test to assess dysphagia, used currently in the ECOG 3311 and RTOG 1221 clinical trials)</p>
<p>Secondary endpoint(s)</p>	<ul style="list-style-type: none"> - Total MDADI score at 1 and 2 years. - Local tumor control rate at 1 and 2 years - Regional tumor control rate at 1 and 2 years - Overall Survival rate at 1 and 2 years - Quality of life (PSS-HN, EORTC-HN35 and -QLQ, NDII, DASH, Xerostomia score) at 3 and 6 months, and at 1 and 2 years - Cost benefit analysis
<p>Trial design (phase, trt arms, schedule & duration)</p>	<p>This is a phase III, multicenter, randomized study. The following stratification factors are under consideration: institution, HPV-status, smoking, T-stage, sub-site is foreseen.</p> <p>ARM1:</p> <p>Radiotherapy: Simultaneous integrated boost Intensity modulated radiation therapy (IMRT) (SIB) with a definitive dose of 70Gy and an elective dose of 52.8 Gy in 6 weeks (moderately accelerated IMRT with parotid and constrictor</p>

	<p>muscles sparing and uni- or bilateral level II-IV elective nodal irradiation for T1 and T2-OPCs.</p> <p>ARM2:</p> <p>Surgery : Trans-oral surgery (Any trans-oral approach such as trans-oral laser microsurgery, conventional trans-oral surgery (only for OPC of the tonsil) or trans-oral robotic surgery) combined with a bilateral selective neck dissection level 2, 3 and 4 for T2 base of tongue cancers closer then 0.5cm to the midline and unilateral selective neck dissection level 2, 3, and 4 for T1 and T2 tonsil, lateral pharyngeal wall and all other T1 and T2 base of tongue cancers.</p>
<p>Brief stat considerations inc. approx. sample size</p>	<p>Statistical design is based on a formal comparison between the two treatment arms, based on the mean of the total MDADI score at 3 and 6 months.</p> <p>Sample size is based on the following preliminary assumptions:</p> <ul style="list-style-type: none"> - Difference of 8 points at 3 months between the two arms (difference at 6 months still under discussion). - Normal distribution of total MDADI score - Standard deviation = 15 points (Carlsson et al) - Correlation between subsequent assessments 3 months apart = 0.71 - Alpha: 0.05 (two-sided) - Power: 80% <p>The statistical analysis will be adjusted for baseline total MDADI score.</p> <p>The total sample size will be 80 to 160 patients, depending on the final assumptions retained.</p> <p>Study duration: 2 year recruitment, 2 years follow-up Total: 4 years</p>
<p>TR and/or biobanking</p>	<p>Ancillary studies with specific budget upon availability: subgroup analysis according to HPV status (P16 by immuno histo chemistry, IHC) and EGFr expression (IHC), smoking status.</p> <p>Analysis of genetic and phenotypic tumor heterogeneity to determine mutational landscapes and architecture (only upon availability of a specific budget)</p>
<p>Preliminary feasibility:</p> <ul style="list-style-type: none"> - pt access, approx No. centers: - competing studies: - funding: 	<p>Partial funding through Fondation Dreyfus, Lausanne, Suisse</p>
<p>Why is EORTC the organization to do this study? (max 3 criteria)</p>	<ol style="list-style-type: none"> 1. EORTC is the only organization that offers access to a pan European network in this rare disease 2. Given this trial compares two therapeutic approaches without drugs companies may not be interested in supporting this study so it is up to academic organisations like EORTC to take up this cause 3. This trial is potentially practice changing with an agenda to improve the outcome of patients being treated
<p>CRP completes how project is in line with EORTC strategy</p>	<p>Clinical trials addressing the comparison of multimodal treatment strategy</p>