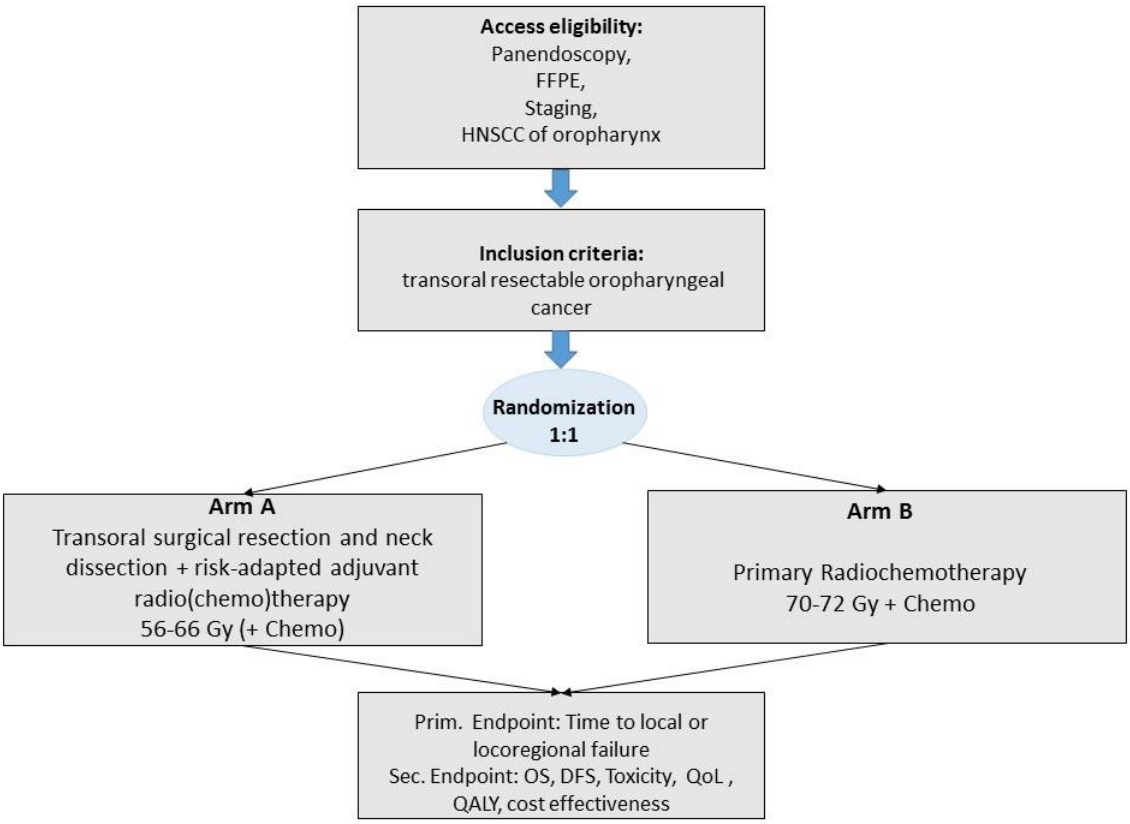
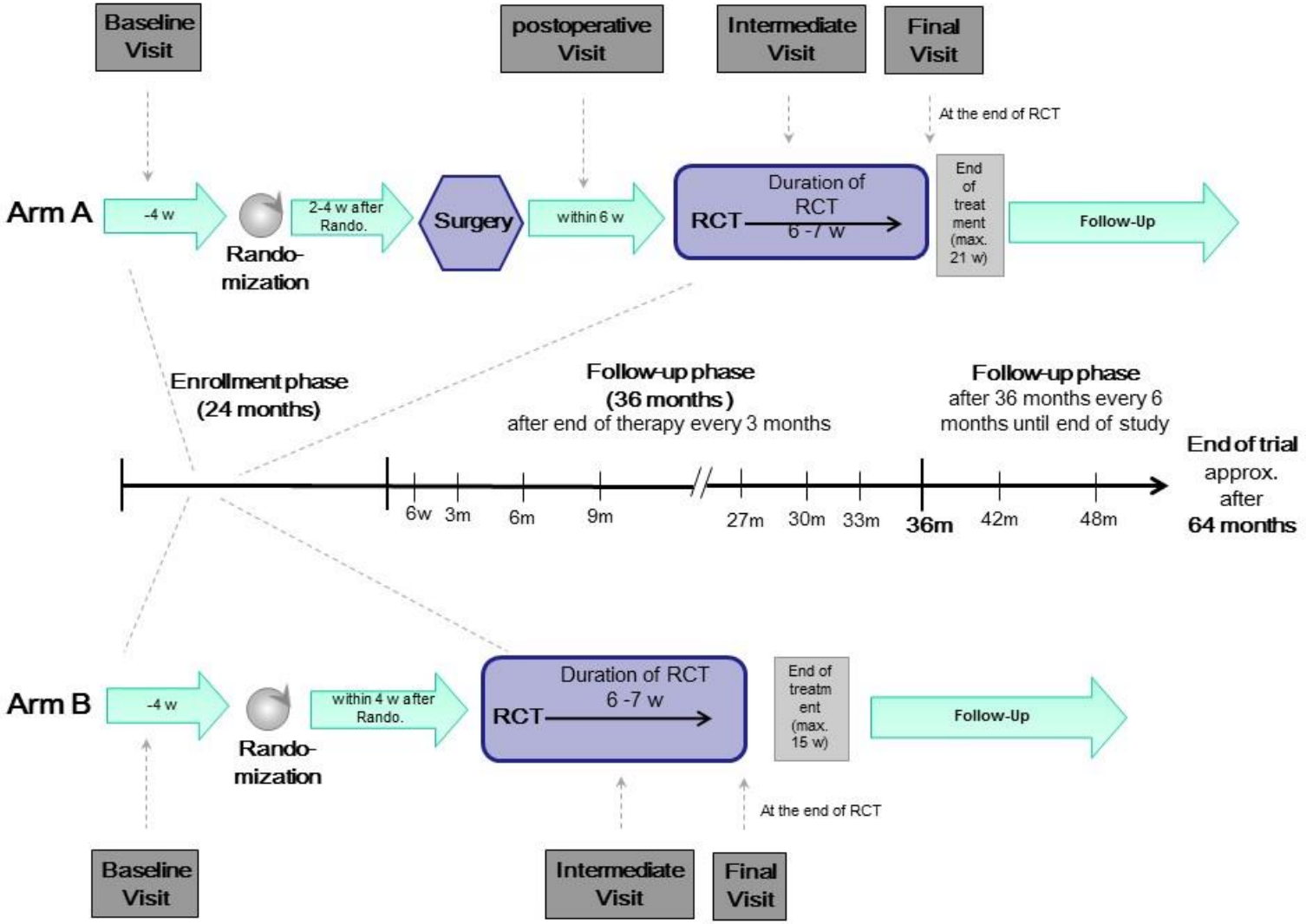
Study title	Comparative Effectiveness Trial of Transoral Head and Neck Surgery followed by adjuvant Radio(chemo)therapy versus primary Radiochemotherapy for Oropharyngeal Cancer
Short title	TopROC ; TOS vs. CRTX
Indication	Locally advanced, transorally resectable oropharyngeal cancer
Primary objectives	To evaluate the effectiveness of primary surgical versus non-surgical treatment of locally advanced, but transorally resectable oropharyngeal cancer in terms of time to local or locoregional failure or death from any cause (LRF)
Secondary objectives	Effectiveness of primary surgical versus non-surgical treatment of locally advanced, but transorally resectable oropharyngeal cancer with respect to • overall and disease-free survival of both treatments • acute toxicity and late morbidity (including swallowing function) until 3 years after randomization • Quality of life • Cost-effectiveness/ cost-utility analysis
Tertiary objectives	Comparison of treatment effects • between HPV+ and HPV- oropharynx carcinoma • between different treatment modalities (surgery, radiotherapy and chemotherapy protocols)
Study design	Prospective, two-arm, open label, multicenter, randomized, controlled comparative effectiveness study. The trial is based on an event-driven design: the final analysis will be performed when all events have been observed or the study was terminated at one of the interim analyses.
Study population	**Main inclusion criteria:** • Histologically proven SCC of the oropharynx; T1, N2a-c, M0; T2, N1-2c, M0; T3, N0-2c, M0, with only amendable to transoral resection) • Primary tumor must be resectable through transoral approach • p16 immunohistochemitry by local pathology or FFPE tissue must be available for central HPV diagnostic • Written and signed informed consent • Briefing through surgeon and radiation oncologist • ECOG PS ≤2, Karnofsky PS ≥ 60 % • Age ≥ 18 • Curative treatment intent • Adequate bone marrow function: leucocytes $\geq$ 3.0 x 10^9/L, neutrophils $\geq$ 1.5 x 10^9/L, platelets $\geq$ 80 x 10^9/L, hemoglobin $\geq$ 9.5 g/dL • Adequate liver function: Bilirubin $\leq$ 2.0 g/dL, SGOT, SGPT, $\leq$ 3 x ULN • If of childbearing potential, willingness to use effective contraceptive method for the study duration and 2 months post-dosing. • dental examination and appropriate dental therapy if needed prior to beginning of radiotherapy • Nutritional evaluation prior to initiation of therapy and optional prophylactic gastrostomy (PEG) tube placement

	Main exclusion criteria: • Prior invasive malignancy except controlled skin cancer or carcinoma in situ of cervix • Unknown primary (CUP), nasopharynx, hypopharynx, laryngeal or salivary gland cancer • Metastatic disease • Serious co-morbidity, e.g. high-grade carotid artery stenosis, congestive heart failure NYHA grade 3 and 4, liver cirrhosis CHILD C • Hemoglobin level <9.5g/dl within 4 weeks before randomization • Pregnancy or lactation • Women of child-bearing potential with unclear contraception • Previous treatment with chemotherapy, radiotherapy, EGFR-targeting agents or surgery exceeding biopsy in head and neck • Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to study screening • Social situations that limit compliance with study requirements or patients with an unstable condition (e.g., psychiatric disorder, a recent history of drug or alcohol abuse, interfering with study compliance, within 6 months prior to screening) or otherwise thought to be unreliable or incapable of complying with the requirements of the protocol • Patients institutionalized by official means or court order • Deficient dental preservation status or not accomplished wound healing
Number of Subjects	280 patients will be randomly assigned to one of the two treatment groups.
Study treatment	**Arm A:** • Transoral surgical resection within 4 weeks after randomization • Neck dissection can be performed during resection of the primary tumor or within 4 weeks after randomization • 6-7 weeks standard risk-adapted adjuvant radio(-chemo)therapy 56-66 Gy (chemotherapy according to arm B if necessary), start within 6 weeks post-surgery **Arm B:** • 6-7 weeks standard radiotherapy (IMRT-technique), start within 4 weeks after randomization • 70-72 Gy, SIB possible • Cisplatin 100 mg/m^2 on days 1, 22, 43 or Cisplatin once weekly (30-40 mg/m^2) on days 1, 8, 15, 22, 29, 36 or Mitomycin C 10 mg/m^2 d1, 29 and 5-FU 600 mg/m^2/day iv on days 1-5 or Cisplatin 20 mg/m^2 + 5-FU 600 mg/m^2/day iv d 1-5 and 29-33 • +/- Salvage neck dissection 12±2 weeks after treatment

Primary endpoint	Time to local or locoregional failure (LRF) (defined as time from randomization to local or locoregional failure or death from any cause, whatever occurs first)
Secondary endpoints/ analyses	• Overall and disease-free survival • Therapy-associated toxicity including swallowing function • QoL and QALY • Direct and indirect costs
Tertiary analyses	• Subgroup analysis of HPV+ and HPV- oropharynx carcinoma • Subgroup analysis of different treatment modalities (surgery, radiotherapy and chemotherapy protocols)
Statistical methods	**Sample size calculations:** The trial is based on an event-driven design with a planned observational period of five years (recruitment time two years and follow-up time 3 years). The event rate in the definitive chemoradiotherapy for oropharyngeal cancer group is assumed to be 50% after 36 month. The transoral head and neck surgery followed by adjuvant (chemo)radiotherapy is assumed to reduce the event rate for the primary outcome to 35%. It is assumed that the hazard rate is constant over time. Under these assumptions, 142 events have to be observed during the planned observation period, which will result in a sample size of 280 patients. In both arms a 3% lost to follow-up during the study is estimated. After recruiting 250 patients a blinded interim analysis will be performed. The steering committee will decide on adaptation of the sample size/ recruiting time. Additionally, based on results of the planned unblinded interim analysis after 50% and 75% of available observed events, the steering committee will decide on adaptation of the recruiting/follow up time or to allow an early stopping of the trial for success. The recruitment will be stopped immediately if the needed number of events is reached. **Statistical analysis:** The primary analysis is in the full analysis set population, consisting of all randomized patients. Analysis of time to event with Cox regression and Kaplan-Meier curves for both arms, adjusted to the group sequential design in a way that a two-sided overall significance level of 5% is kept. Descriptive statistics for all patients and separately for both arms.
Timeline	• Treatment period: Arm A 8-17 weeks; Arm B 6-11 weeks • Recruitment period: 2 years • Follow-up: 3 years after end of treatment of the last patient • Total duration of trial: approximately 64 months
Study centers	Ca. 20 centers in Germany


Access eligibility:
Panendoscopy,
FFPE,
Staging,
HNSCC of oropharynx
Inclusion criteria:
transoral resectable oropharyngeal cancer
Randomization
1:1
Arm A
Transoral surgical resection and neck dissection + risk-adapted adjuvant radio(chemo)therapy
56-66 Gy (+ Chemo)
Arm B
Primary Radiochemotherapy
70-72 Gy + Chemo
Prim. Endpoint: Time to local or locoregional failure
Sec. Endpoint: OS, DFS, Toxicity, QoL , QALY, cost effectiveness


Baseline Visit
postoperative Visit
Intermediate Visit
Final Visit
At the end of RCT
Arm A
-4 w
Rando-mization
2-4 w after Rando.
Surgery
within 6 w
RCT
Duration of RCT 6 -7 w
End of treat ment (max. 21 w)
Follow-Up
Enrollment phase (24 months)
Follow-up phase (36 months) after end of therapy every 3 months
Follow-up phase after 36 months every 6 months until end of study
End of trial approx. after 64 months
6w
3m
6m
9m
27m
30m
33m
36m
42m
48m
Arm B
-4 w
Rando-mization
within 4 w after Rando.
RCT
Duration of RCT 6 -7 w
End of treatm ent (max. 15 w)
Follow-Up
At the end of RCT
Baseline Visit
Intermediate Visit
Final Visit