



Original Article

Results from a prospective, randomised study on (accelerated) preoperative versus (conventional) postoperative radiotherapy in treatment of patients with resectable squamous cell carcinoma of the oral cavity – The ARTSCAN 2 study



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ABSTRACT

Background and purpose: An earlier prospective randomised multicentre study (ARTSCAN) in head and neck cancer patients that compared conventionally fractionated radiotherapy (CF) with accelerated radiotherapy (AF) was inconclusive. In the subgroup of oral cavity squamous cell cancer (OCSCC) a large absolute, but not statistically significant, difference in local control was seen in favour of AF. This difference was more pronounced in resectable tumours. The finding raised the hypothesis that AF could be beneficial for OCSCC patients. In addition, the longstanding controversy on pre- or postoperative radiotherapy was addressed.

Materials and methods: Patients with OCSCC, judged to withstand and likely benefit from combined therapy, were recruited. Subjects were randomised to either preoperative AF with 43 fractions given as a concomitant boost with two fractions/day to the tumour bearing volume to a total dose of 68 Gy in 4.5 weeks followed by surgery, or primary surgery with postoperative CF, total dose 60 or 66 Gy in 6–7 weeks. For patients whose tumours had high-risk features, 66 Gy and concomitant cisplatin was prescribed.

Results: 250 patients were randomised. Median follow-up was 5 years for locoregional control (LRC) and 9 years for overall survival (OS). There were no statistically significant differences between the two treatment arms regarding LRC and OS. LRC at five years was 73% (95% CI, 65–82) in preoperative AF and 78% (95% CI, 70–85) in postoperative CF.

Toxicity was more pronounced in preoperative AF.

Conclusion: This study does not support that AF prior to surgery improves outcome in oral cavity cancer compared with postoperative CF.

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Surgery or radiotherapy (RT), and in more advanced tumours a combination of the two modalities, is the standard approach for the curatively intended treatment of oral cavity squamous cell carcinoma (OCSCC). A long-standing controversy has been the order of sequence for surgery and RT; pre- or postoperative RT as to whether there is any advantage of this order in relation to tumour control, survival, toxicity, and functional outcome. There is a lack of randomised trials to settle this question. An early RTOG study [1] found an improvement in local control for postoperative compared with preoperative RT in patients with locally advanced head and neck SCC, but no differences in overall survival (OS) or morbidity. In a review from 1995, it was suggested that postoperative RT might give higher local control rates [2]. In a review [3] of studies of preoperative RT, with or without chemotherapy, of patients mainly with advanced oral cancer, it was concluded that the overall survival after preoperative treatment was remarkably good. Therefore, prospective randomised trials on the subject were recommended.

An earlier Swedish national prospective randomised multicentre study of RT as single treatment in locally advanced head and neck SCC patients compared conventionally fractionated RT (CF) with accelerated RT (AF) [4]. The study could not demonstrate any benefit with AF regarding locoregional control (LRC) or OS. Despite this, in the subgroup of OCSCC a comparatively large absolute, but not statistically significant, difference in local control was seen in favour of AF. This difference was even more pronounced in resectable tumours. The finding raised the hypothesis that AF could be of benefit in the treatment of patients with OCSCC.

To investigate this a multicentre randomised phase III study was initiated, comparing preoperative AF and radical surgery with the today often recommended “gold standard” postoperative CF [1,5]. The study was performed on behalf of the Swedish ARTSCAN study group.

Materials and methods

Study design and randomisation

The study was an open-label randomised controlled phase III study conducted in Sweden, with six participating centres. OCSCC patients planned for curative treatment with the combination of surgery and RT were eligible. Included patients were randomised 1:1 between either AF to 68.0 Gy during 4.5 weeks followed by surgery (preop AF), or surgery followed by CF (postop CF) to 60.0 or 66.0 Gy depending on the presence of the high risk features extracapsular spread and/or microscopic non-radical surgery (Fig. 1). High risk patients were recommended to receive concomitant weekly cisplatin. Randomisation was performed by a web-based randomisation system. Stratification was made between study

centre, tumour subsite (tongue or floor of mouth vs gingiva or other oral subsite) and clinical stage (I-II vs III-IV).

The study was approved by the regional ethics committee in Umeå, Sweden (07–178 M) and registered at <https://doi.org/10.1186/ISRCTN00608410>.

Objectives

The primary objective was to compare LRC between the treatment groups. Secondary objectives were to investigate pattern of failure, OS, disease-free survival (DFS), morbidity, and quality of life (QL) between the treatment groups.

Patients

Eligible patients had to be at least 18 years old, diagnosed with a previously untreated, resectable OCSCC without distant metastases and selected for curative treatment with the combination of surgery and RT. The patients had to have an expected survival of >6 months, understand information about the study and be amenable to follow-up. Patients with previous malignancy in the head and neck region were excluded. All patients received oral and written information about the study and gave a written informed consent before entering the trial.

Diagnostic procedures were CT or MRI of the head and neck region, CT or X-ray of the thorax, biopsy of the primary tumour and cytology of suspicious neck nodes (ultrasound-guided if needed). Assessment of resectability was made with endoscopy and palpation, if needed under general anaesthesia. Tumour staging was made according to UICC TNM classification, edition 7 [6].

Radiotherapy and chemotherapy

Treatment volumes

Preop AF

The GTV of the primary tumour and metastases should be encompassed by 0.5–1.5 cm (with the exception for anatomical barriers) to form the 68 Gy CTV. Elective treatment of lymph nodes included levels I–III, bilaterally. Unilateral lymph node treatment was allowed for T1–2N0 if the tumour was clearly lateralised (>1 cm from the midline). In N+ cases, the CTV encompassed one level distal to the lowest metastasis.

Postop CF

The tumour bed with a margin of ≥ 2 cm or, in the case of e.g., mobile tongue, the remaining mobile tongue was defined as the CTV. Anatomical barriers were respected. The elective lymph node treatment followed the same principles as in preop AF.

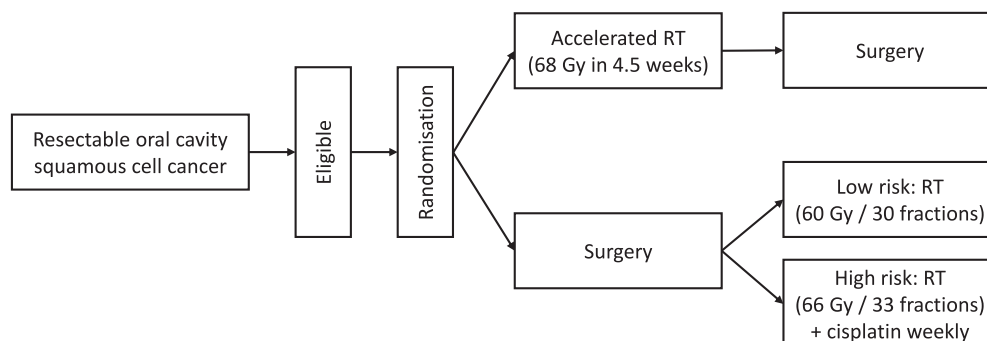


Fig. 1. Study design.

Radiotherapy fractionation and chemotherapy

Patients allocated to preop AF were prescribed 68.0 Gy in 43 fractions, b.i.d., with concomitant boost (1.1 Gy + 2 Gy) and a minimum of 7 hours between fractions, as described previously [4]. Total treatment time was 4.5–5 weeks. Patients receiving postop CF were prescribed conventionally fractionated treatment, 60.0 or 66.0 Gy in 30 or 33 fractions, 2.0 Gy per day, five fractions per week to the tumour bed and lymph node levels with metastatic nodes, and 50.0 Gy to elective lymph node volumes. For patients whose tumours showed high risk features (R1 resection and/or extracapsular lymph node spread) a dose of 66 Gy was planned in conjunction with concomitant cisplatin in weekly doses of 50 mg. Radiation was, in relevant cases, delivered with intensity modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT), but 3-dimensional conformal radiotherapy (3-DCRT) was allowed. RT should be started within 4 weeks (up to maximum 6 weeks) after surgery. Further radiotherapy details are described in the [Supplementary material](#).

Adverse events were monitored weekly during RT and graded according to the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria [7].

Surgery

To assure adequate surgery for patients randomised to preop AF, tumour borders were marked by injections of coal suspension around the macroscopic tumour before start of treatment. Surgical recommendations were local excisions for T1 and superficial T2 tumours. More advanced tongue and floor of mouth tumours were recommended pull-through resections. Free flap reconstructions and mandibulotomies were performed when indicated. In all cases, macroscopic tumour margins of 10 mm were recommended. Node negative (clinically and no suspicious nodes on CT/MRI) patients were not mandatory recommended a neck dissection. All N+ patients were treated with modified, or if necessary, radical neck dissections. For patients in the preop AF group surgery was to be performed within 4 weeks (up to maximum 6 weeks) after the end of RT. For all patients, surgical procedures and postoperative complications were recorded.

Follow up

After completion of the combined therapy the patients were scheduled for follow-up visits every three months during the first two years, and then every sixth months until five years. Tumour control was assessed and late toxicity was recorded and graded with selected items of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, RTOG Late Radiation Morbidity Scoring Criteria [7] and of the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT-SOMA) scales [8].

Quality of life questionnaires (European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30, general (EORTC QLQ-C30, version 2.0), EORTC QLQ-H&N35, specific for head and neck cancers, MD Anderson Dysphagia Inventory (MDADI) and the Hospital Anxiety and Depression scale (HADS)) were distributed before start of treatment, and on four more occasions during the first five years after treatment. Quality of life results will be reported separately.

Statistical analysis

The trial was designed as a superiority study that aimed to show a 25% absolute increase (from 50% to 75%) in local control

at two years for preop AF compared with postop CF. These figures were based on an early evaluation of the previously mentioned ARTSCAN study. To identify this difference with a power of 80% at a significance level of 0.05 a total of 240 patients needed to be randomly assigned. The intention-to-treat (ITT) population was used for efficacy analyses and contains all patients meeting the eligibility criteria. Five patients included and randomly assigned in the study who were later found to be not eligible for inclusion and five patients who withdrew consent before start of treatment were not included in the ITT population ([Fig. 2](#)).

Time to event was calculated from date of randomisation in all analyses. For the primary end point LRC, and for OS and DFS, the treatment groups were compared by means of a Cox proportional hazards model stratified for tumour site and clinical stage and adjusted for treatment centre. The postop CF group was considered the control arm in these calculations. Proportional hazards assumptions were tested by Schoenfeld residuals tests. The Kaplan-Meier method was used to illustrate LRC, OS and DFS, and the log-rank test was used to compare treatment groups. Cumulative incidence functions for locoregional control with distant metastases and death as competing events were estimated and compared by means of Gray's test. Adverse events were compared in the per-protocol population with Fisher's exact test. No corrections for multiple testing were applied.

Analyses were based on the study database as of Jan 12, 2021.

Results

Between March 2008 and February 2016, 250 patients were recruited. Ten patients were excluded before start of treatment, leaving 240 patients for the ITT analysis: 120 patients in each treatment group ([Fig. 2](#)). At time of analysis, median follow-up for LRC was 5.3 years (IQR 4.8–5.5), and median follow-up for OS was 9.4 years (IQR 7.0–11.2). Baseline characteristics were well balanced between the treatment groups ([Table 1](#)). Median age was 66 years, 62% were males and a majority were active or previous smokers. Sixty-nine percent of the patients had tumour location tongue or floor of mouth. Stage distribution was 50% stage I-II and 50% stage III-IV.

In the preop AF group 94% of the patients completed RT per protocol. One patient did not receive RT and treatment was prematurely interrupted in two patients. Two patients experienced progressive disease during RT and treatment was converted to chemoradiotherapy. Crossover was performed in two patients. Twelve patients in the preop AF group did not undergo surgery.

In the postop CF group three patients did not receive RT and one patient crossed over and received preop AF. Of the remaining patients in the postop CF group, one received 58.0 Gy, which was considered as per-protocol, and all other patients received at least 60.0 Gy. Surgery was not performed in one patient. Twenty-five patients had high-risk disease, and sixteen of these received concomitant cisplatin weekly during RT. Median number of cycles was seven (range 3–7).

In summary, 103 patients in the preop AF group and 115 patients in the postop CF group received treatment per-protocol.

Of clinically N0 patients, 39/83 (47%) in the preop AF group, and 50/90 (56%) in the postop CF group underwent elective neck dissection ($p = 0.29$, Fisher's exact test).

During the five-year follow-up, 29 locoregional failures were registered as first events in the preop AF group and 31 in the postop CF group. Estimated LRC at two years was 81% (95% CI 74–88) and 76% (69–84) in the preop AF and postop CF groups, respectively. Corresponding figures at five years were 73% (65–82) for both treatment groups (log-rank $p = 0.91$; adjusted cause-specific hazard ratio (HR) 1.00 (95% CI, 0.60–1.66), $p = 0.99$)

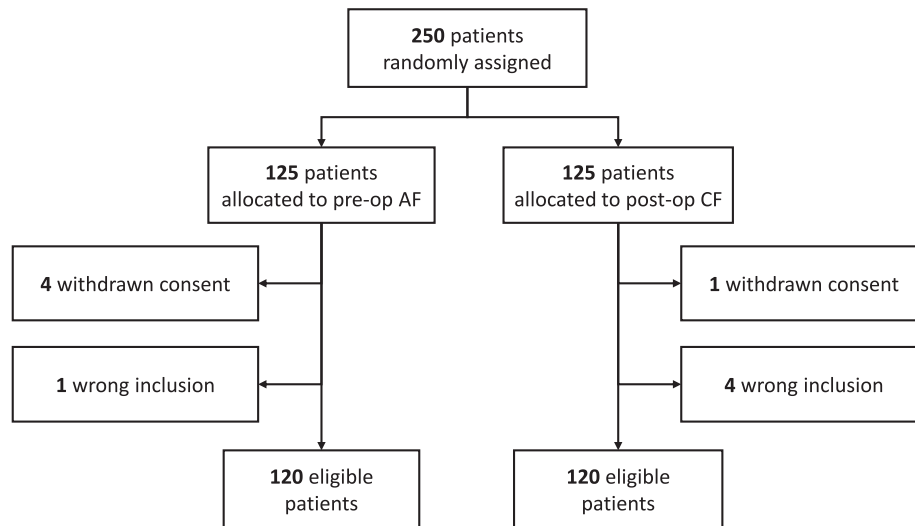


Fig. 2. Trial profile.

Table 1

Baseline demographics and clinical characteristics by randomised group for the Intention-to-Treat population (n = 240).

		Preoperative accelerated RT (n = 120)		Postoperative conventional RT (n = 120)	
Age, years	Median (range)	65	(31–84)	67	(23–85)
	≤55	21	(18%)	23	(19%)
	56–65	41	(34%)	34	(28%)
	≥66	58	(48%)	63	(53%)
Gender	Male	77	(64%)	72	(60%)
	Female	43	(36%)	48	(40%)
Performance status	WHO 0	107	(89%)	105	(88%)
	WHO 1–3	13	(11%)	15	(13%)
Smoker	No (never)	38	(32%)	50	(42%)
	Yes (active or previous)	80	(67%)	69	(58%)
	Unknown	2	(2%)	1	(1%)
Primary tumour site*	Tongue/floor of mouth	81	(68%)	84	(70%)
	Gingiva and other sites in oral cavity	39	(33%)	36	(30%)
T stage	T1	14	(12%)	14	(12%)
	T2	68	(57%)	63	(53%)
	T3	9	(8%)	17	(14%)
	T4	29	(24%)	26	(22%)
Nodal status	N0	83	(69%)	90	(75%)
	N1	14	(12%)	11	(9%)
	N2b	17	(14%)	16	(13%)
	N2c	5	(4%)	3	(3%)
	N3	1	(1%)	0	(0%)
Clinical stage*	I	10	(8%)	12	(10%)
	II	49	(41%)	50	(42%)
	III	16	(13%)	17	(14%)
	IV	45	(38%)	41	(34%)

*Stratification variables; tumour site (tongue/floor of mouth; gingiva or other oral subsite), clinical stage (I–II; III–IV).

(Fig. 3a). The cumulative incidence of locoregional failures with distant metastases and death as competing events did not differ between the treatment groups (Gray's test, $p = 0.73$), and is shown in [Supplementary Fig. 1](#). Distant failure as first event occurred in eight patients in the preop AF group, and in seven patients in the postop CF group. Distribution of first failures is described in [Supplementary Table 1](#), and DFS is shown in [Supplementary Fig. 2](#).

During the study period, 65 deaths occurred in the preop AF group and 56 in the postop CF group. OS at two years was 73% (95% CI, 66–82) and 78% (95% CI, 70–85), respectively, and at five years 57% (95% CI, 48–66) and 69% (95% CI, 61–78) (log-rank $p = 0.21$; adjusted HR = 1.27 (95% CI, 0.88–1.82; $p = 0.20$; [Fig. 3b](#)). Post-hoc subgroup analyses of LRC and OS are shown in [Supplementary Fig. 3a and b](#).

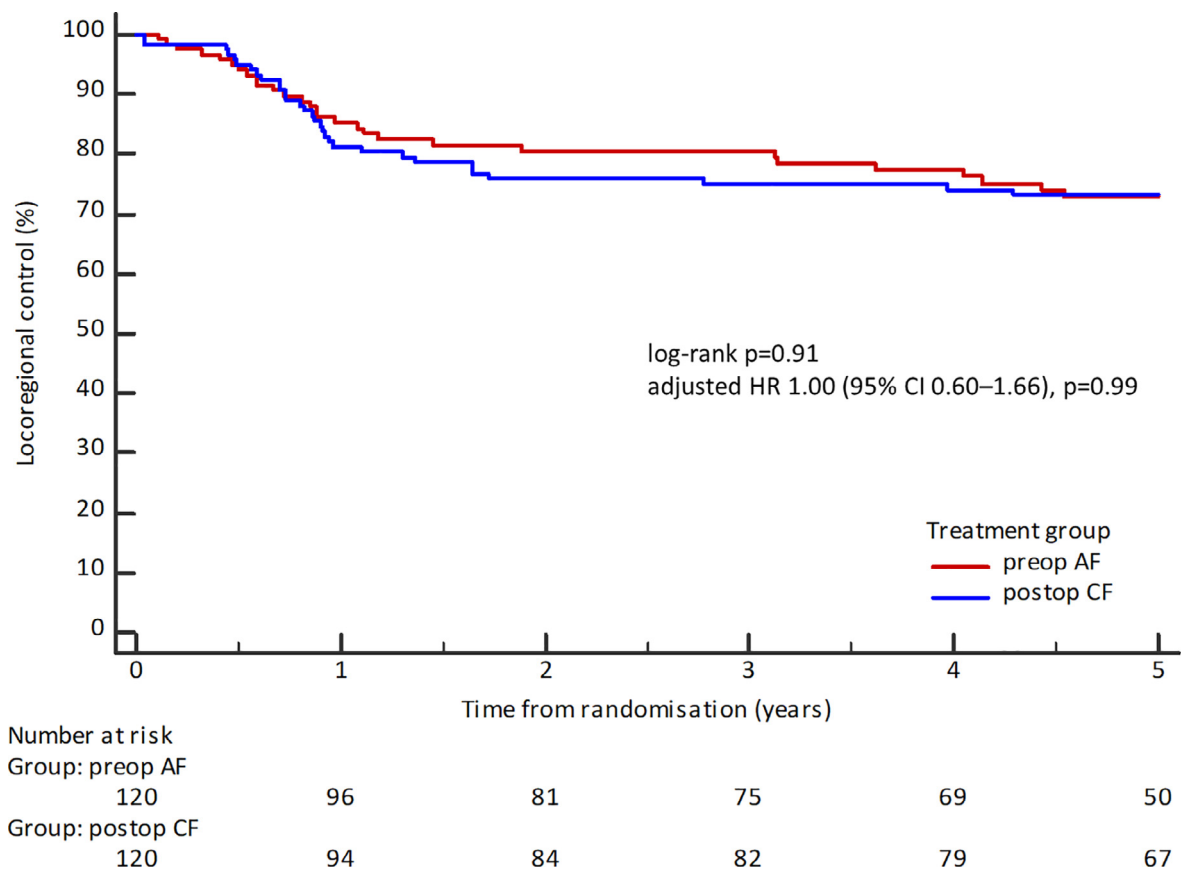


Fig. 3a. Locoregional control at two years was 81% (95% CI 74–88) and 76% (69–84) in the preop AF and postop CF groups, respectively. Corresponding figures at five years were 73% (65–82) for both treatment groups.

There were three early deaths (within 30 days after completion of treatment) in the preop AF group and one in the postop CF group. During RT significantly more patients in the preop AF group experienced grade 2–3 acute dysphagia and pain. Dependence of percutaneous endoscopic gastrostomy tubes (PEG)/nasogastric tubes was also more frequent in the preop AF group (Table 2). Post-treatment morbidity events grade 2–4 are presented in Table 3. Patients in the preop AF group had significantly more events of weight loss, laryngeal mucosa alterations and osteoradionecrosis, while remaining late morbidity events did not differ statistically significantly between the treatment groups.

Discussion

Our study did not reveal any statistically significant differences regarding LRC or OS between preop AF and postop CF. The outcome measures in our study are, however, well comparable with other reported treatment results. In a recently reported retrospective database analysis of OCSCC patients treated between 2011 and 2014, OS at three years was 70% for patients with late-stage disease [9]. In a study of neoadjuvant chemoradiotherapy followed by surgery in 134 patients with stage III – IV OCSCC reported in 2008, OS at two and five years were 65% and 45%, respectively [10]. In a phase III study comparing induction chemotherapy followed by surgery and postoperative RT vs. up-front surgery followed by RT in locally advanced OCSCC, the estimated 2-year OS was 68% and 69%, and DFS at two years was 64% and 62% in the control and experimental arms, respectively [11]. Corresponding figures for OS in our study were 73% and 57% at two and five years in the preop AF group, and 78% and 69% in the postop CF group. At the

time of the planning of the present study, it had been observed in several Swedish institutions that the prognosis for stage I-II oral cancer was poorer than expected. There was an unexpected number of recurrences after surgery alone for both T1 and especially T2 tumours. In some institutions the estimated depth of infiltration was used to select patients with T1 and T2 tumours to combined treatment. It should thus be noted that the inclusion of patients in the ARTSCAN II study was based on the clinical judgement that the combination of surgery and RT was indicated, and not strictly on clinical stage. Fifty percent of the patients in our study had stage I – II disease according to the UICC TNM classification, seventh edition. A retrospective reclassification, also including tumour depth according to TNM 8, is not possible in the present material.

The sequencing of surgery and RT in the combined treatment of HNSCC has long been a topic of debate. Only two prospective randomised controlled studies (RCT) have been published. They were performed in the 1960s and the 1970s. One compared pre- to post-operative RT in the treatment of hypopharyngeal SCC [12]. A low number of patients were included, and results were in favour of postoperative RT. The second RCT, published with a 10-year follow-up in 1991, comprised 277 patients with oral, oropharyngeal, supraglottic or hypopharyngeal SCC [1]. It showed superior LRC in favour of postoperative RT, but no difference in OS. There was no sub-group analysis with respect to tumour site. To our knowledge, no later RCTs on this subject have been performed. A number of non-randomised and retrospective studies have also compared preoperative and postoperative RT in OCSCC, but results have been conflicting [13,14]. It is well established that altered fractionation schemes can improve outcome in HNSCC [15]. In the ARTSCAN study, preceding the current trial, there was a non-

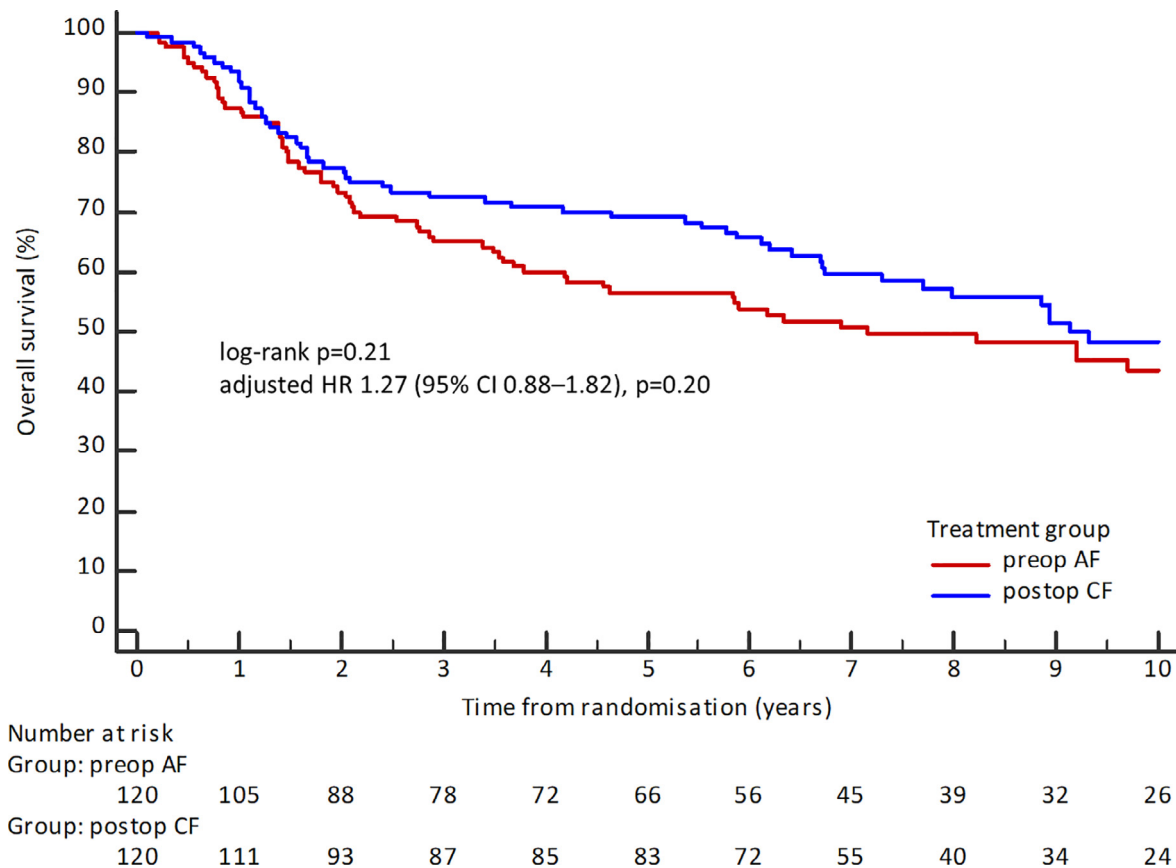


Fig. 3b. Overall survival at two years was 73% (95% CI, 66–82) and 78% (95% CI, 70–85) in the preop AF group and postop CF group, respectively. Corresponding figures at five years were 57% (95% CI, 48–66) and 69% (95% CI, 61–78).

Table 2

Toxicity during radiotherapy in the per-protocol population for the treatment groups. Data are presented as n/N where n is the number of patients with toxicity score registered at least once during RT and N is the number of patients.

Toxicity during RT	Scale/scores	Preop AF	Postop CF	<i>p</i>
Weight loss	CTCAE gr 2–3	9/101 (9%)	16/106 (15%)	0.204
Dysphagia	RTOG gr 2–3	91/103 (88%)	76/110 (69%)	0.001
Mucositis	RTOG gr 2–3	100/100 (100%)	104/111 (94%)	0.068
Pain	RTOG gr 2–3	103/103 (100%)	104/112 (93%)	0.007
Peg/nasogastric tube	Yes	61/103 (59%)	31/112 (28%)	0.000

Table 3

Toxicity after combined therapy registered in the per-protocol population for the treatment groups. Data are presented as n/N where n is the number of patients with toxicity score registered at least once during the planned follow-up visits and N is the number of patients. The follow-up is from median 5 months after end of combined therapy until tumour recurrence or until end of the planned five-year follow-up period.

Late toxicity	Scale/scores	Preop AF	Postop CF	<i>p</i>
Weight loss	CTCAE gr 2–3	62/92 (67%)	51/101 (50%)	0.020
Dysphagia	Grade 2–4	83/95 (87%)	86/109 (79%)	0.137
Laryngeal oedema	LENT-SOMA gr 3–4	19/95 (20%)	15/104 (14%)	0.348
Larynx mucosa status	LENT-SOMA gr 3–4	14/96 (15%)	6/107 (6%)	0.036
Respiration	LENT-SOMA gr 2–4	15/98 (15%)	8/107 (7%)	0.082
Tracheostomy	Yes	6/98 (6%)	5/108 (5%)	0.759
Trismus*	Yes	64/95 (67%)	61/106 (58%)	0.190
Osteoradionecrosis	LENT-SOMA gr 2–4	32/98 (33%)	20/109 (18%)	0.024
Xerostomia	RTOG gr 2–3	72/93 (77%)	82/105 (78%)	1.000
Saliva	LENT-SOMA gr 2–4	87/91 (96%)	98/103 (95%)	1.000
Taste alteration	LENT-SOMA gr 2–3	59/90 (66%)	59/98 (60%)	0.455
Oral mucosa status	LENT-SOMA gr 2–4	87/97 (90%)	92/107 (86%)	0.523

*Defined as maximal interincisal distance (MID) ≤ 35 mm.

significant improvement in LRC (58% vs. 41% ($p = 0.10$)) for OSCC patients ($n = 100$) treated with AF vs. CF. In contrast, no differences were seen for the tumour subsites larynx, hypopharynx and

oropharynx [4]. It was therefore hypothesised that intensified treatment with preoperative AF could be of benefit in OSCC. However, the results of the present randomised study do not support a

role for preoperative AF in this patient group. The comparatively small number of patients in our study leads to a low statistical power to detect small differences between the two treatment arms. As we found no tendency towards a better outcome for preoperative AF, it seems unlikely that a larger number of patients would reveal any clinically meaningful difference in favour of AF. Especially in the light of significantly more side effects than with CF.

The decision on a fixed weekly cisplatin dose may be controversial. Due to high reported toxicity and reduced compliance with high dose three-weekly cisplatin [15], lower weekly dose schedules were gaining ground at the time of the planning of the study. With the aim of reducing side effects, weekly cisplatin was chosen in this study. The total dose of cisplatin in the present study is comparatively low. Even if several studies have reported similar outcomes with weekly and three-weekly regimens of cisplatin [16–18], it cannot be ruled out that this might have influenced the outcomes.

In accordance with previous reports of altered fractionated RT [19–21], acute toxicity during RT was more pronounced in the preop AF group in our study. The increased late toxicity in this group was, however, unexpected, and not in agreement with earlier findings of altered fractionated RT as single treatment [19]. The higher prescribed RT dose to patients undergoing preoperative treatment may have contributed to this finding. Combined tissue trauma caused by RT-induced inflammation followed by surgery may be an alternative explanation, although the possible underlying mechanisms are not yet well understood. Although there was no significant difference in OS in the present study, there was a clear numerical difference between the treatment groups (57% vs. 69% at five years), and it cannot be ruled out that the higher toxicity in the preop AF group may have affected these figures. Also, severe late side effects can have a profound negative impact on the patients' QL [22]. Intense treatment schedules not translating into improved survival cannot be the preferred treatment, and thus the results of our study speak in favour of surgery followed by CF. The inclusion period for this study was long, which may have added uncertainties to the findings. Changes in clinical practice routines during this time include improvements in tumour staging, e.g. increased utilisation of PET-CT, and more developed IMRT techniques. These clinical improvements would, however, most likely have influenced both treatment groups similarly.

Conclusion

This study does not support that AF prior to surgery improves outcome in OCSCC compared with the “gold standard”, surgery followed by CF. The intense treatment schedule and the higher dose in the preop AF group increased the severity of acute and late side effects, and postoperative RT should remain the treatment of choice in the combined therapy of OCSCC.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2021.11.008>.

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