Cost-effectiveness Analysis of Pre- *Versus* Post-operative Radiotherapy for Patients With Oral Cancer

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Abstract

Background: Treatment for resectable oral cavity cancer (OCC) often includes combinations of surgery and radiotherapy (RT), but there is no conclusive information on by which order these measures are best administered. The aim of this study was to assess cost-effectiveness of two alternative treatment regimens for patients with OCC, reflecting pre-and post-operative RT.

Methods: The study was performed on data from the ARTSCAN 2 randomised, controlled trial, which compares pre-operative accelerated RT with post-operative conventionally fractionated RT. Two-hundred-fifty patients were randomised and 240 were eligible for treatment outcomes. Costs were retrieved from the hospital's economic systems and national registries. The incremental cost-effectiveness ratio (ICER) was calculated, and a sensitivity analysis was performed. Overall survival (OS) was used as effect measure in the analysis.

Results: Two-hundred-nine patients completed the treatment and had retrievable data on costs. There was no statistically significant difference in OS between the treatment modalities (log-rank $p=0.23$). OS at three years was 67% and 74% for pre- and post-operative RT, respectively. Mean direct costs per patient were € 65 958 for pre-operative RT and € 53 172 for post-operative RT, while indirect costs were € 75 874 and € 73 184, respectively. All projected results indicated that post-operative RT was cost-effective in comparison to pre-operative RT.

Conclusions: Post-operative RT for patients with resectable OCC is cost-effective compared to pre-operative RT.

Background

The incidence of oral cavity cancer (OCC) in Sweden is 11.3 per 100 000 individuals (1), but the condition is more common globally (2). Treatment for resectable OCC often includes combinations of surgery and radiotherapy, but there is so far no conclusive evidence on by which order these measures are best administered (3, 4). This issue was addressed in the multicentre ARTSCAN 2 randomised controlled trial (RCT) (5), where the primary outcome was locoregional control (LRC) and where secondary objectives included overall survival (OS). There were no statistically significant differences in either LRC or OS between the treatment regimens. Median follow-up times were five years for LRC and nine years for OS (5).

Apart from tumour control, survival, and the morbidity caused by OCC and its treatment, other healthcare considerations are of key importance, including societal costs (i.e., health care resources and production loss due to disease-related sick-leave and early retirement) (6). In order to assess the cost-effectiveness of a treatment, the incremental cost-effectiveness ratio (ICER) may be calculated (7). To the best of our knowledge, cost-effectiveness concerning treatment order of surgery and radiotherapy for OCC has not previously been assessed.

The aim of this study is to assess the cost-effectiveness of two alternative treatment regimens for patients with OCC of the ARTSCAN 2 RCT, which reflect pre- and post-operative RT, i.e., pre-operative accelerated RT and post-operative conventional RT.

Methods

Patients and design

Two-hundred-fifty patients were randomised in the multicentre ARTSCAN 2 RCT, which involved combined therapy with surgery and RT for advanced, resectable OCC from 2008 through 2016 (5). Patients were randomised 1:1 to either accelerated RT (68 Gy in 4.5 weeks) followed by surgery, or surgery followed by conventionally fractionated RT (60 Gy in 6 weeks to low-risk patients; 66 Gy in 6.5 weeks plus concomitant cisplatin to high-risk patients). Two-hundred-forty patients were eligible for intention-to-treat analysis (120 patients in each treatment group).

Data on costs and OS from the randomisation date and three years onwards were assessed. Direct costs (i.e., for work-up and treatment) were analysed for the patient cohort of the Southern Healthcare Region of Sweden treated at Skåne University Hospital (i.e., 79 patients), for whom such data were available. Indirect costs (i.e., for sick-leave and early retirement) were retrieved for 69 out of the 209 patients, i.e., retired individuals and those on early retirement for other causes were excluded.

Costs

All costs were converted into Euro (€) using the mean exchange rate for 2019, i.e., SEK 10.59 for 1€ (8). According to recommendation (9), cost originating from the years 2008 through 2018 were discounted by 3%.

Direct costs, specified per inpatient and outpatient care, were retrieved from the hospital's economic systems for patients treated at Skåne University Hospital and data were cross-checked against the patients' medical records. Through this "bottom-up" analysis, OCC-specific costs were cleared from costs produced by comorbidities. Data were expressed as mean individual cost per treatment regimen.

Indirect costs, for sick-leave and early retirement due to post-treatment morbidity, were retrieved for the entire study population from the Swedish Social Insurance Agency for persons of working age, i.e., between 18-65 years old (10). The number of days (sick-leave and early retirement) were estimated per patient and multiplied by an average daily income salary (based on a monthly salary of SEK 35 300) including costs for social services at 2019-year's level (37.06%) (9). Sick leaves due to other illnesses were disregarded.

Effectiveness of therapy

The primary effect measure for the ARTSCAN 2 RCT was LRC, and secondary measures included aspects of morbidity and survival, including OS. OS at three years, as a fundamental outcome reflecting the

effectiveness of the treatment, was used as effect measure in the cost-effectiveness analysis.

Incremental cost-effectiveness ratio

The incremental cost (IC) and incremental effectiveness (IE) was calculated as the difference in cost and effect measure, respectively, between the two treatment regimens. The ICER was then calculated as IC/IE, which represents the cost per additional unit of effect.

$$ICER = \frac{\text{Costs for preoperative RT (€)} - \text{Costs for postoperative RT (€)}}{\text{Effects of preoperative RT (\%)} - \text{Effects of postoperative RT (\%)}}$$

Sensitivity analysis

Furthermore, to evaluate the impact of the included parameters, a one-way sensitivity analysis was performed and presented as a Tornado diagram. This type of diagram shows the effect of one parameter while the other parameters are being held steady (10). We applied the categorical thresholds for willingness to pay (WTP) suggested by the Swedish National Board of Health and Welfare (1).

Statistical analysis

Data are presented as means and standard deviations. The Kaplan-Meier method was used to estimate (from date of randomisation) OS and the log-rank test for comparing OS between the treatment regimens (MedCalc Software, Ostend, Belgium). Differences in cost between the regimens were analysed with the unpaired t-test (SPSS Version 26, IBM, Armonk, NY). Cost-effectiveness between the treatment regimens was assessed using a uni-variate sensitivity analysis (TreeAge Pro, TreeAge Software, Williamstown, MA). P-values <0.05 were considered statistically significant.

Results

Out of the 240 patients eligible for intention-to-treat analysis, 31 dropped out during the study due to failure to complete the intended treatment or because of missing data on costs. The reasons for withdrawal are indicated in Figure 1. Three patients were offered to switch from pre- to post-operative RT or *vice versa* due to temporarily extended waiting times to start of intended treatment. Accordingly, 209 patients were eligible for assessment of direct and indirect costs as well as for analysis of cost-effectiveness, i.e., 98 in the pre-operative RT group and 111 in the post-operative RT group.

Data on demographics for the study population (used to assess indirect costs) are indicated in Table 1 and the subgroup of patients from the Southern Health Care Region of Sweden (used to assess direct costs) in Table 2.

Table 1
Characteristics of patients eligible for cost assessment.

	Pre-operative RT (n=98)	Post-operative RT (n=111)	TOTAL (n=209)
Mean age, (range)	65 (31-84)	64 (23-84)	65 (23-84)
Female/Male No.	33/65	43/68	76/133
Long-term sick-leave ¹ No. (%)	5 (5%)	3 (3%)	8 (4%)
Retired No. (%)	59 (60%)	66 (59%)	125 (60%)
Early retirement ¹ No. (%)	3 (3%)	4 (4%)	7 (3%)
Clinical stage No. (%)			
– I	11 (11%)	10 (9%)	21 (10%)
– II	39 (40%)	46 (41%)	85 (41%)
– III	14 (14%)	17 (15%)	31 (15%)
– IVa	34 (35%)	38 (34%)	72 (34%)
¹ Long-term sick-leave or retirement for comorbidity. <i>Abbreviation:</i> RT, radiotherapy.			

The mean age of the patients was 65 years (65 years for pre-operative RT and 64 years for post-operative RT), which was not different from data from the subgroup of patients from the Southern Health Care Region of Sweden used to assess direct costs.

In the pre-operative RT group, 60% were already retired when diagnosed with OCC (*cf.* 59% in the post-operative RT group). In the pre- and post-operative RT groups, respectively, 89% and 90% were diagnosed with stage II lesions or higher (Table 1).

Table 2

Characteristics of patients of the Southern Healthcare Region of Sweden eligible for assessment of direct costs.

	Pre-operative RT (n=35)	Post-operative RT (n=44)	TOTAL (n=79)
Mean age, (range)	65 (36-80)	61 (23-84)	63 (23-84)
Female/Male, No.	12/23	17/27	29/50
Clinical stage, No. (%)			
– I	2 (6%)	0 (0%)	2 (3%)
– II	16 (46%)	28 (64%)	44 (56%)
– III	5 (14%)	4 (9%)	9 (11%)
– IVa	12 (34%)	12 (27%)	24 (30%)
<i>Abbreviation:</i> RT, radiotherapy.			

There was a trend towards a difference in OS between the treatment regimens (in favour of post-operative RT), which failed to reach statistical significance (log-rank $p=0.23$). OS at three years was 67% (95% CI 59-77) and 74% (95% CI 66-83), respectively, for pre- and post-operative RT (Figure 2).

Direct and indirect costs are presented in Table 3. The total direct cost for work-up and treatment was greater for pre-operative RT (€ 65 958) *cf.* post-operative RT (€ 53 172), and this difference reached statistical significance ($p=0.029$). Similarly, the subset of direct costs representing out-patient care was greater for pre-operative RT *cf.* post-operative RT ($p=0.047$). The subset of direct costs for in-patient care was also greater for pre-operative RT (*cf.* post-operative RT), but this trend failed to reach statistical significance. Mean hospital stay was 28 days for pre-operative RT *cf.* 22 days for post-operative RT. The indirect costs for sick-leave and early retirement were similar between the groups. The mean number of sick-leave days was 311 for pre-operative RT and 300 for post-operative RT.

Table 3

Mean (SD) direct and indirect costs per patient and treatment regimen for resectable OCC. Direct costs from the population of the Southern Health Care Region of Sweden (n=79). Indirect costs from the population eligible for cost evaluation for which data were retrievable (n=69).

	Pre-operative RT	Post-operative RT	P-value
Direct costs	65 958 (25 240)	53 172 (25 335)	0.029
– Out-patient care	23 310 (7 408)	19 758 (8 022)	0.047
– In-patient care	42 649 (24 115)	33 414 (22 724)	0.085
Indirect costs	75 874 (43 126)	73 184 (55 543)	0.826
<i>Abbreviations:</i> SD, standard deviation; RT, radiotherapy.			

Post-operative RT was more effective in terms of OS (although not statistically significant) and less costly compared with pre-operative RT, meaning that post-operative RT dominates pre-operative RT. Hence, all projected results from the one-way sensitivity analysis indicated that post-operative RT was the most cost-effective regimen. According to the one-way sensitivity analysis, indirect costs followed by inpatient costs and outpatient costs were the parameters with the greatest impact on the ICER (Figure 3).

Discussion

An overall analysis of the ARTSCAN 2 RCT indicates that pre- and post-operative RT are equally effective alternatives for resectable OCC regarding LRC and OS when combinations of surgery of RT are considered (5). The present analysis based on this trial demonstrates that post-operative RT is cost-effective in comparison to pre-operative RT. Arguably, the information will aid to support or refute a specific treatment order of surgery and RT for resectable OCC.

The main finding of this study is that post-operative RT is cost-effective in comparison to pre-operative RT. According to the sensitivity analysis, indirect costs arising from sick-leave and early retirement are primary factors influencing the ICER. The fact that this is revealed despite the minor differences in nominal costs between the treatment regimens reflects the strength of the methodology and indicates the importance of such analyses in addition to mere descriptions of actual cost in assessments of diseases and their associated healthcare measures. Furthermore, differences in costs between pre- and post-operative RT are in keeping with the cost-effectiveness analysis, i.e., a trend for higher costs for the former and lower for the latter, with a statistical significance reached for a 1.24-fold greater direct costs for work-up and treatment for pre-operative RT.

A major strength of the present analysis is that it is based on an RCT, which is a desired design for comparisons of clinical effects and, consequently, for analyses of effectiveness of health care interventions. The patients in an RCT are randomly allocated to a treatment regimen, resulting in

estimates of treatment effects that are considered to have high internal validity. This is because patients randomised to different groups will be similar in terms of observed characteristics (i.e., factors affecting the outcome) as well as unobserved characteristics (i.e., factors affecting the outcome but are unknown to the analyst) (7).

There are two previous studies focusing on treatment order of surgery and radiotherapy in head and neck cancer (11, 12), both arguing for post-operative RT, but they do not specifically focus on OCC. Accordingly, this is the first RCT for OCC that can be analysed regarding treatment order when a combination of surgery and RT is considered appropriate. Data from the ARTSCAN 2 RCT are now in press showing a numerical difference in OS (although not statistically significant) in favour of post-operative RT (5). While further data on patient-reported quality-of-life outcome associated with OCC and its treatment will be produced later by the ARTSCAN 2 Study Group, the present analysis compares costs and cost-effectiveness between the treatment regimens. As such the analysis, which is the first of its kind, may be of particular interest to head and neck surgeons/oncologists and health care officials alike, when deciding on how resectable OCC may best be treated from a societal perspective.

There are several studies focusing on societal costs for head and neck cancer, but none exclusively on OCC and the cost-effectiveness of its various treatment options. Furthermore, previous cost studies on head and neck cancer, in general, have key drawbacks. First, they report only direct or indirect costs (13-20). Second, they are “top-down” analyses of registry data, not curated against medical records (18-20). In contrast, the present study assesses costs specifically for OCC including direct medical costs of work-up and treatment from a “bottom-up” perspective and indirect costs (e.g., costs due to sick-leave and early retirement), cleared from costs of co-existing conditions. The advantage of having patient-specific data on both societal costs and outcome is that these can be further used in cost-utility-analyses with a lifetime perspective to determine whether a treatment is justified in terms of health gains for patients with OCC. However, further data on lifetime expectancy, health-related quality of life, palliative care, pharmaceuticals in out-patient care, informal care, and transportation are warranted.

The “bottom-up” analysis of direct costs for OCC and its treatment was of importance to the present analysis and enabled us to clear the data from costs produced by conditions other than, or considered not associated with, OCC. As this detailed level of information was not available for the study population as a whole, we focused on the patient cohort of the Southern Healthcare Region of Sweden. There were no statistically significant differences between this cohort and the remainder of the study population regarding age, gender, and stage distribution. Therefore, the data were extrapolated to the study population as a whole. Furthermore, as the parts of the combined treatment for OCC, i.e., surgery and RT, is executed similarly in Sweden and exclusively by the public health care system, we have no reason to believe that the direct costs retrieved for the Southern Healthcare Region are not representative for Sweden in general. Taken together, our observations arguably represent an accurate assessment of direct and indirect costs associated with resectable oral cancer specified per treatment regimen.

Conclusions

Based on data from the ARTSCAN 2 RCT, we conclude that post-operative RT for resectable OCC is cost-effective *cf.* pre-operative RT, while OS at three years is not significantly different between the two treatment regimens.

List Of Abbreviations

AF Accelerated fractionation

CF Conventionally fractionation

EV Expected value

IC Incremental cost

ICER Incremental cost-effectiveness ratio

IE Incremental effectiveness

ITT Intention to treat

LRC Locoregional control

OCC Oral cavity cancer

OS Overall survival

RCT Randomised controlled trial

RT Radiotherapy

SD Standard deviation

WTP Willingness to pay

Declarations

Ethics approval and consent to participate

The RCT study was approved by the regional ethic committee (Etikprövningsmyndigheten) in Umeå, Sweden (07-178M) and registered at <https://doi.org/10.1186/ISRCTN00608410> and the amendment for the cost-effectiveness analysis protocol was approved by the regional ethic committee (Etikprövningsmyndigheten) in Uppsala, Sweden (no: 2019-05768). All the methods in the study were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all persons who entered the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interest.

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Authors' contributions

M.S., L.G., E.Ö., and J.S. conceived the study.

All authors contributed to its design.

M.S., L.G., P.N., E.Ö., and J.S. analysed the data.

M.S., L.G., P.N., B.Z., E.Ö., and J.S. drafted the manuscript.

All authors reviewed the manuscript and approved the final version.

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Not applicable

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Figures

Figure 1

Flowchart for the 240 patients eligible for intention-to-treat population analysis. The number of dropouts was 21 in the pre-operative RT group and 10 in the post-operative RT group. Incomplete and missing data refer to a lack of information on indirect costs. Abbreviations: ITT, intention to treat; RT, radiotherapy.

Number at risk

Group: pre-op AF RT

98 88 73 66 61 56 47 38 33 27 23

Group: post-op CF RT

111 103 87 82 81 80 69 54 38 32 22

Figure 2

Overall survival (%) for accelerated RT (68 Gy) followed by surgery, or surgery followed by conventionally fractionated RT (60 Gy to low-risk patients; 66 Gy plus weekly chemotherapy to high-risk patients) for the population (n=209). Abbreviations: AF, accelerated fractionation; CF, conventional fractionation.

Figure 3

Tornado diagram showing the incremental cost-effectiveness ratio (ICER) of the range of values for each variable tested in the one-way sensitivity analysis, i.e., the lowest and highest recorded values (in brackets). The left-hand side vertical grey line corresponds to all the uncertain parameters being at their base values. The red portion of the bars represents the ICER range when the parameter is higher than its base case value, and the blue portion the ICER range when the parameter is lower than its base case value. The right-hand side vertical grey line indicates WTP, i.e., € 10 000. Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; WTP, willingness to pay; RT, radiotherapy; EV, expected value.