

# Seven days a week postoperative radiotherapy versus postoperative radiochemotherapy in cancer of the oral cavity or oropharynx

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| <b>Submission date</b><br>01/08/2011   | <b>Recruitment status</b><br>No longer recruiting | <input checked="" type="checkbox"/> Prospectively registered<br><input type="checkbox"/> Protocol |
| <b>Registration date</b><br>31/08/2011 | <b>Overall study status</b><br>Completed          | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results |
| <b>Last Edited</b><br>05/09/2016       | <b>Condition category</b><br>Cancer               | <input type="checkbox"/> Individual participant data  |

## Plain English summary of protocol

### Background and study aims

Despite improvements in surgery and radiation treatment (radiotherapy), cancers of the mouth and oropharynx (part of the throat) often come back. Combined chemotherapy and radiotherapy (radiochemotherapy) after surgery is the new standard treatment for such patients. However, radiochemotherapy has more side effects than standard radiotherapy. Radiotherapy given over a shortened treatment time (e.g. 7 days a week) may provide a similar effect to radiochemotherapy, but without some of the side effects. Also, markers could be identified in tumors that may help to select patients for accelerated radiotherapy. The aim of this study is to compare the effectiveness of 7-days-a-week radiotherapy versus 5-days-a-week radiochemotherapy for cancer of the mouth/oropharynx, and to also search for tumor markers that would help to guide future treatment.

### Who can participate?

Patients aged 18 and over who have undergone surgery to remove squamous cell cancer of the mouth or oropharynx

### What does the study involve?

Participants are randomly allocated to be treated with either 7-days-a-week radiotherapy or 5-days-a-week radiochemotherapy. Cancer recurrence, treatment side effects, tumour markers and patient survival are evaluated in both groups.

### What are the possible benefits and risks of participating?

Participation carries the risks that are typical for radiotherapy or radiochemotherapy treatment. Long-term side effects of accelerated radiotherapy may include dry mouth, mild fibrosis (scarring) of the skin, tooth decay and in rare circumstances mandibular necrosis (severe bone disease of the jaw). Radiochemotherapy has frequent side effects such as nausea and fatigue as well as hematological (blood) reactions.

Where is the study run from?

Center of Oncology, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology,  
Gliwice Branch (Poland)

When is the study starting and how long is it expected to run for?

September 2011 to September 2014

Who is funding the study?

Polish Ministry of Science and Higher Education

Who is the main contact?

Prof. Rafal Suwinski

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## Contact information

### Type(s)

Scientific

### Contact name

Prof Rafal Suwinski

### Contact details

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## Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

MSCMCI Gliwice N402 1801 34

## Study information

### Scientific Title

Randomized clinical trial on seven days a week postoperative radiotherapy versus postoperative radiochemotherapy in locally advanced cancer of the oral cavity or oropharynx

## **Acronym**

p-CAIR vs p-RTCT

## **Study objectives**

Despite improvements in surgical and radiation techniques locoregional recurrences remain among the major causes of failure in combined treatment of locally advanced cancer of the oropharynx and oral cavity. Two large randomized clinical trials demonstrated that postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than postoperative radiotherapy alone. This resulted in a widespread acceptance of postoperative radiochemotherapy as a new standard in adjuvant treatment after surgery for high risk head and neck cancer. The combined treatment that incorporates concurrent radiotherapy and chemotherapy is, however, associated with a substantial increase in adverse effects.

An alternative approach in attempts to enhance the effectiveness of combined treatment for locally advanced cancer of the head and neck is represented by the trials in which the overall radiation treatment time of postoperative radiotherapy was shortened, compared to standard fractionation. This may improve locoregional tumor control by hampering tumor repopulation that can be triggered by cell depletion from surgery and successive fractions of radiotherapy. The outcome of these trials is largely conflicting, with some of them demonstrating a significant improvement in locoregional control that favors accelerated postoperative radiotherapy, some demonstrating a non-significant trend towards such improvement, while other show no beneficial effect of accelerated postoperative radiotherapy. Such disparity can be explained by relatively small sample size of these trials, heterogeneity in patient selection criteria and, thus risk of recurrence, diversity in dose-fractionation schedules and heterogeneity in both individual time intervals surgery-radiotherapy and average values reported in the trials.

The largest trial that compared accelerated versus conventional postoperative radiotherapy for high-risk head and neck cancer was performed in our institution and recruited 279 patients with cancer of the larynx, oral cavity and oropharynx. The results of this trial have shown a non significant trend towards improvement in locoregional control in a whole group of 279 patients. A significant improvement in LRC attributable to acceleration of postoperative radiotherapy was, however, demonstrated in a subgroup of 121 patients with cancer of the oropharynx/oral cavity. Also, we were able to identify, based on molecular marker profiles, subgroup of the patients with even more significant improvement in locoregional control from accelerated postoperative radiotherapy. By contrast, patients with cancer of the larynx, and those with a molecular profile unfavorable for accelerated radiotherapy, did not have any clinical benefit. Our supposed ability to select the patients who may benefit from accelerated postoperative radiotherapy (i.e. mainly those with cancer of the oral cavity/oropharynx) created the basis for the present trial.

The hypothesis to be tested is that the patients with cancer of the oral cavity/oropharynx treated with postoperative accelerated radiotherapy (or some subsets of these patients that can be identified by molecular profiling) may have a comparable locoregional tumor control to those treated with postoperative chemoradiotherapy, but may have a favorable tolerance of treatment.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Bioethical Committee at Center of Oncology, M. Sklodowska-Curie Memorial Cancer Center

### **Study design**

Random assignment to continuous seven days a week postoperative radiotherapy (p-CAIR) or conventionally fractionated postoperative concurrent radiochemotherapy (p-RTCT)

### **Primary study design**

Interventional

### **Secondary study design**

Randomised controlled trial

### **Study setting(s)**

Hospital

### **Study type(s)**

Treatment

### **Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

### **Health condition(s) or problem(s) studied**

Squamous-cell cancer of the oral cavity or oropharynx

### **Interventions**

Patients will have to be appointed for radiotherapy shortly after the surgery, i.e. as soon as the pathological specimens are evaluated. Postoperative radiotherapy will begin as soon as possible, i.e. as adequate healing occurs and radiation treatment plan is set and approved. This may optimally occur 4-6 weeks after the surgery. Randomization will be performed at the time of appointment for radiotherapy by telephone call to the trial office. The patients will be randomly assigned to receive continuous seven days a week postoperative radiotherapy (p-CAIR) or conventionally fractionated postoperative concurrent radiochemotherapy (p-RTCT).

The prescribed total dose, dose per fraction and radiation treatment technique will be the same in both arms of the trial; the assigned treatments will differ, however, with respect to the overall radiation treatment time: it will be 5 weeks in p-CAIR and 7 weeks in p-RTCT. The total dose at sites considered to be at intermediate/high risk of recurrence will be 63 Gy in 1.8 Gy per fraction, i.e. the same as used in our earlier trial that compared continuous 7-days-a-week postoperative radiotherapy (p-CAIR) and conventional postoperative radiotherapy (p-CF) [7]. A support for such dose selection provided earlier study that had been performed in MD Anderson, Houston. The dose delivered to electively treated areas will be 45 Gy, supraclavicular nodes will be electively treated whenever pathological specimen reveal involvement of the neck nodes. In patients assigned to continuous 7-days-a-week postoperative radiotherapy (p-CAIR) 'large' portals covering CTV will be irradiated to the total dose of 45 Gy and will be treated 5 days -a-week (from Monday to Friday). By contrast, 'small' portals, limited to the areas considered at intermediate/high risk of recurrence will exclude the spinal cord and will be treated 7 days -a-week.

In patients assigned to conventional postoperative radiochemotherapy 'large' portals will be irradiated 5-days-a-week to the total dose of 45 Gy i.e. over the first 5 weeks of treatment, while 'small fields' will be irradiated at weeks 6-7. Orphit masks will be used for immobilization. The patients will be treated using linear accelerators with 6 MV photons. The quality assurance

procedures will include repeated in vivo dosimetry, IGRT procedures (kV or Cone Beam CT), double check of treatment plans and portals and pre-treatment and weekly audits during therapy.

The protocol will allow use of IMRT or 3D conformal radiotherapy.

Chemotherapy will consist of 80-100 mg per square meter of body-surface area on days 1, 22 and 43 of the course of radiotherapy. Prophylactic hydration and antiemetic agents will be given to patients that receive chemotherapy. Acute mucosal reactions will be scored using modified Dische system. This system places emphasis on both morphological and functional radiation effects. The score will be evaluated every week during radiotherapy, and 2, 4 and 8 weeks after its completion. Hematological reactions will be evaluated with the same frequency using RTOG scoring system. For skin, mucosal, salivary glands, bones and spinal cord late radiation morbidity RTOG/EORTC scoring system will be used.

Supportive anti-inflammatory treatment will be given whenever the severity score of acute mucositis exceeds 10. This will include non-steroid anti-inflammatory drugs, local corticosteroids, and antiseptic liquids. When the severity score will exceed 16 systemic corticosteroids and antibiotics will be prescribed. The evaluation of molecular marker expression will be a part of the study. The expression of p53, Ki67, Bcl2, EGFR, PTEN, p16 will be immunohistochemically assessed. The expression of molecular marker will be correlated with the rate of locoregional tumor control and distant metastases. Loco-regional failure will be defined as the recurrence of cancer at the primary tumor site, within the neck or supraclavicular nodes, and distant metastases as the recurrence elsewhere. The survival curves will be plotted using Kaplan-Meier method, and the cumulative incidence of recurrence will be compared using Grays test. Multivariate Cox regression model will be used to further explore the data. An interim analysis is planned after recruitment of 100 patients to evaluate acute normal tissue reactions and locoregional tumor control. Should significant differences in locoregional control appear ( $p < 0.05$ ) the recruitment will be stopped due to ethical reasons.

### **Intervention Type**

Mixed

### **Primary outcome measure**

Cumulative incidence of locoregional recurrence

### **Secondary outcome measures**

Local control, nodal control, metastases-free survival, disease-free survival, second cancer free survival, overall survival, acute mucosal reaction score (Dische system), acute radiation and hematological morbidity (RTOG scoring system), late radiation morbidity (RTOG/EORTC scoring system)

### **Overall study start date**

01/09/2011

### **Completion date**

01/09/2014

## **Eligibility**

### **Key inclusion criteria**

1. Squamous-cell cancer of the oral cavity or oropharynx
2. Age at least 18 years

3. A written informed consent for participation in a trial
4. Macroscopically complete major surgery
5. Good performance status (ZUBROD 0-1)
6. White-cell count of at least 3500 per cubic millimeter
7. Platelet count of at least 100,000 per cubic millimeter
8. Creatinine clearance of more than 50 ml per minute
9. Aminotransferase and bilirubin values below twice the normal upper limit

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

270

**Key exclusion criteria**

1. Patients after reconstructive surgery with free-style flaps
2. Patients with stage pT1N0 disease
3. History of invasive cancer (except for nonmelanoma skin cancer)
4. Prior treatment
5. Distant metastases
6. For female participants, pregnant

**Date of first enrolment**

01/09/2011

**Date of final enrolment**

01/09/2014

**Locations****Countries of recruitment**

Poland

**Study participating centre**

M. Skłodowska-Curie Memorial Cancer Center and Institute of Oncology

Gliwice

Poland

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# Sponsor information

## Organisation

Polish Ministry of Science and Higher Education (Poland)

## Sponsor details

Wspolna 1/3

Warsaw

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## Sponsor type

Government

## Website

<http://www.nauka.gov.pl/home/>

## ROR

<https://ror.org/05dwvd537>

# Funder(s)

## Funder type

Government

## Funder Name

Ministerstwo Nauki i Szkolnictwa Wyższego (ref: N402 1801 34)

## Alternative Name(s)

Ministerstwo Nauki i Szkolnictwa Wyższego, Ministry of Science and Higher Education, Ministry of Science and Higher Education, Republic of Poland, MNiSW

## Funding Body Type

Government organisation

## Funding Body Subtype

National government

## Location

Poland

# Results and Publications

## Publication and dissemination plan

Not provided at time of registration

## Intention to publish date

## Individual participant data (IPD) sharing plan

## IPD sharing plan summary

Not provided at time of registration

## Study outputs

| Output type                     | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---------------------------------|---------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a> | results | 01/02/2016   |            | Yes            | No              |