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

Submission date
01/08/2011

Recruitment status
No longer recruiting

Registration date
31/08/2011

Overall study status
Completed

Last Edited
05/09/2016

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
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 fractonation. 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

Primary study design
Interventional

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

Study type(s)
Treatment

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 posible, 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 patological 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 radioterapy.

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 hydratation 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 ate 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(s)
Cumulative incidence of locoregional recurrence

Key secondary outcome(s)
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)

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 clearence of more than 50 ml per minute
9. Aminotransferase and bilirubin values below twice the normal upper limit

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

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. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology
Gliwice
Poland
44 100

Sponsor information

Organisation
Polish Ministry of Science and Higher Education (Poland)

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

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?
Results article	results	01/02/2016		Yes	No