Protocol

What are the risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy for penile cancer?

EAU Guidelines Panel on Penile Cancer

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Introduction

Description of the condition

Penile cancer is a rare cancer in the Western World, with an overall incidence in the USA and Europe of <1.0/100 000 males. Approximately 95% of penile cancers are of squamous cell histological type and around one third of cases are linked to human papilloma viral carcinogenesis [1]. The incidence of penile cancer is much higher in parts of the world where HPV infection is more prevalent, with rates of 8.3/100 000 men in Brazil. The incidence of penile cancer has been falling the USA since the 1970's and is stable in Europe, although increases have been described in the U.K. and Denmark [2]. The peak age of diagnosis is in the sixth decade of life [3].

Risk factors for penile cancer include:

- Phimosis
- Chronic inflammation and balanitis xerotica obliterans
- Sporalene and UVA phototherapy
- Smoking
- HPV infection
- Low socioeconomic status
- Unmarried
- Multiple sexual partners
- Early age of first intercourse

The treatment of penile cancer is divided into the management of the primary tumour and of the regional lymph nodes. The primary tumour can be managed by either: topical therapy, LASER therapy, surgery or radiotherapy. The choice of treatment is based upon the stage and grade of tumour and local practice.

Lymphatic metastatic spread of penile cancer is consistently predictable via the inguinal and pelvic lymph nodes, with the superficial and deep inguinal nodes being the first site of metastatic spread [4]. Lymph node management involves either: lymphadenectomy, lymph node sampling or surveillance. The choice, as for the primary tumour, is dictated by stage, grade and local practice. Radiotherapy may have a role in the palliative treatment of lymph node disease and in the adjuvant setting for high risk patients following inguinal lymphadenectomy. Adjuvant chemotherapy is currently recommended for high risk patients (pN2/3) and in the neo-adjuvant setting followed by surgery in those with initially non-resectable disease or recurrent lymph node disease [3].

Survival rates are reported in a number of heterogeneous studies and in which different management approaches have been utilised to treat a spectrum of disease stages. Overall 5 year survival rates in Europe are around 70%, but do reach 80% in some geographical regions [5]. Overall and cancer specific survival rates vary widely between 59-100% following penile preserving surgery [6]. Local recurrence following penile preserving surgery is not felt to affect survival [7]. The rates of local, regional and metastatic recurrence are prognosticated by the grade and stage of disease. Around 90% of local and regional recurrences occur within 2 years of treatment and recurrences beyond 5 years are rare. The presence of lymph node

metastases and lymph node recurrence is highly prognostic for distant metastatic disease, recurrence and survival. In contemporary series, the overall survival at 5 years is >90% in the absence of lymph node metastasesbut falls to 29-51% in the presence of lymph node involvement, and with pN3 disease 5-year survival rates are very low at 0-17% [8-10]. The outlook for those who develop nodal recurrence after lymphadenectomy is particularly poor with a median survival of only 4.5 months [11].

Description of the intervention

The intervention under evaluation in this review is the use of adjuvant inguinal radiotherapy following inguinal lymphadenectomy for patients with penile cancer who have pathologically proven inguinal lymph node involvement. Radical inguinal lymphadenectomy is currently the standard of treatment for patients with involvement of the inguinal lymph nodes. On the basis of lack of available data, the current EAU guidelines [3] has not stated a firm recommendation on the use of adjuvant radiotherapy, but the guidelines do suggest it can be considered in patients with extracapsular nodal extension of tumour in the inguinal nodes (pN3).

How the intervention might work

Radical inguinal lymphadenectomy for penile cancer involves the removal of the entire superficial and deep inguinal lymph node packet with the aim of removing all of the regional inguinal lymph nodes. Despite lymphadenectomy patients still develop recurrent disease in the inguinal region, which carries a very poor prognosis [11], even in the absence of recurrence of the primary tumour. Although radiotherapy is not the mainstay of primary treatment of penile cancer, SCC of the penis is sensitive to radiotherapy and this modality is used to treat the primary tumour [12]. Theoretically adjuvant radiotherapy to the inguinal region following lymphadenectomy may be able to treat residual microscopic disease, reducing the incidence of local, regional and distant recurrence.

Why it is important to do this review

The increased utilisation of penile preserving surgery and dynamic sentinel lymph node biopsy has reduced the morbidity of penile cancer treatment. Unfortunately survival rates for penile cancer have changed very little in the USA and Europe since 1990 [5]. This lack of progress with respect to survival is in part due to the absence of proven adjuvant treatments that have a major impact upon long term survival for patients with node positive or metastatic disease.

Aims and objectives

The aim is to perform a systematic review of the risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy for penile cancer

The objectives are:

- To undertake a systematic review of the published literature on penile cancer.
- To assess relapse-free survival associated with adjuvant radiotherapy
- To assess complications related to toxicity and associated with adjuvant radiotherapy

Trial Eligibility Criteria

Types of studies

- Study type: any
- For single-arm case series, minimum patient number is 10 patients.
- Restriction of date of publication: none
- Language restrictions: none

Types of participants

Inclusion criteria:

- Inguinal node-positive penile carcinoma patients pathologically staged
- Curative intent (will accept up to 10% having palliative treatment)
- Will accept 10% having urethral SCC
- Adjuvant EBRT after: surgery (neoadjuvant chemotherapy is not an exclusion criterion)

Exclusion criteria:

- Non squamous cell cancer (e.g. melanoma, sarcoma, paget's disease)
- Metastases
- Any prior radiation to the pelvic/groin area

Types of interventions

Experimental: Inguinal lymphadenectomy with ipsilateral adjuvant radiotherapy; with or without concurrent chemosensitisation.

Control: Inguinal lymphadenectomy alone.

Types of Outcomes measures

The primary harm outcome is: Toxicity from radiotherapy (lymphoedema)

The primary benefit outcome is: Relapse free survival (within 5 years from treatment)

The secondary outcomes are:

- Regional relapse
- Overall survival at 3 and 5 years
- Cancer specific survival at 3 and 5 years
- Complications
- Quality of life
- Sexual function
- Urinary function

- Chronic skin toxicity
- Need for salvage treatment
- Time from diagnosis to treatment (the pathway is much longer for radiation)

Subgroups of interest:

- Patients who have additional pelvic radiation vs inguinal radiation alone
- Dosimetry (i.e. standard (50-60gy) vs. non-standard)
- Chemo-radiotherapy vs radiotherapy alone
- Clinically positive nodal disease versus clinically negative disease at presentation

Material and Methods

Literature Search

The Medline, Embase and Cochrane controlled trials databases and clinicaltrial.gov will be searched for all relevant publications, with no language or date restriction.

The literature search will be carried out based on the search strategy provided in Appendix 1.

Data collection and analysis

Selection of studies

Following de-duplication, two review authors will independently screen the titles and abstracts of identified records for eligibility. The full-text of all potentially eligible records will be retrieved and screened independently by two review authors using a standardised form, linking together multiple records of the same study in the process. Any disagreements will be resolved by discussion or by consulting a third review author. The study selection process will be described using a PRISMA flow diagram [13].

Data extraction and management

Two review authors will independently extract outcome data. One review author will extract study characteristics and a second review author will check data extractions for accuracy. Any disagreements will be resolved by discussion or by consulting a third review author. A standardised data extraction form will be developed and piloted before its use. In case of any incompletely reported data, study authors will be contacted.

Data to be extracted and included in the 'characteristics of included studies' table are: study design; countries and institutions where the data were collected; dates defining start and end of patient recruitment and follow-up; participant demographic and clinical characteristics (essentially the same as pre-specified confounder variables shown in the 'risk of bias' section below); eligibility criteria for participants; study funding sources.

Assessment of risk of bias in included studies

The 'risk of bias' of each included study will be assessed by two review authors working independently. Any disagreements will be resolved by discussion or by consulting a third review author. The risk of bias in RCTs will be assessed by using the recommended tools in the *Cochrane Handbook for Systematic Reviews of Interventions* [14]. This includes the assessment of: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias.

Risk of bias in non-randomised comparative studies will be assessed using all the seven domains above, and an extra item to assess the risk of findings being explained by confounding. This is a pragmatic approach informed by methodological literature pertaining to assessing RoB in NRS [14, 15]. A list of the five most important potential confounders for harm and benefit outcomes was developed *a priori* with clinical content experts (EAU Penile Cancer guideline panel). For each study, we will determine whether each prognostic confounder was considered and whether, if necessary, the confounder was controlled for in analysis. The potential confounding factors are:

- Treatment in a palliative setting
- Co-morbidities
- BMI
- Bilateral disease
- Incomplete/old staging (older TNM staging and extracapsular extension)

Risk of bias in non-comparative studies, if included, cannot be assessed with the approach described above, which is designed to assess internal validity of comparative studies. Therefore, concern will be extended to addressing external validity (applicability of results to different people, places or time) of non-comparative studies by assessing whether study participants were selected consecutively or representative of a wider patient population and whether the specified confounding factors are comparable across studies reporting on the same intervention. This too is a pragmatic approach informed by the methodological literature [16, 17].

Measures of treatment effect

For time to event outcomes (e.g. survival analysis), we will use time-to-event estimates such as the median or the percent event free (survival rate) at time points such as 1 year, 3 years and 5 years. Hazard ratios (HR) will be used to estimate the size of intervention differences where available. For binary/dichotomous/categorical benefit or harm outcomes, we will use risk ratios (RR) or odds ratios (OR) where available. We will use mean difference (MD) or standardised mean difference (SMD) for continuous outcomes with corresponding 95% confidence intervals (CIs).

Unit of analysis issues

The primary analysis will be per participant (randomised). For studies with more than two intervention groups, only the intervention groups relevant to the review will be selected, or groups will be combined to create a single pair-wise comparison where possible.

Dealing with missing data

We will conduct an intention-to-treat analysis, if data are available; we will otherwise conduct an available case analysis. We will not impute missing data. In case of any incompletely reported data, we will attempt to contact authors.

Assessment of publications biases

The review authors aim to minimise potential publication bias by conducting a comprehensive literature search for eligible studies. If 10 or more studies investigating a particular outcome are included, we will use funnel plots to assess heterogeneity of study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We will therefore interpret results carefully.

Data synthesis

Meta-analysis will be performed if there is more than one randomised (or quasi-randomised) controlled trial reporting the same outcome. For studies with multiple publications, only the most up-to-date or complete data for each outcome will be utilized. Quantitative synthesis will not be undertaken for non-randomised studies. A fixed effects model will be used to calculate pooled estimates of treatment effect across similar studies and their 95% CIs.

For time-to-event data, the log (hazard ratio) and its variance will be combined using the generic inverse variance method. Dichotomous outcomes will be combined using the Mantel-Haenszel method for risk ratios or odds ratios. Continuous outcomes will be combined using the inverse variance mean difference method. If studies use different scales to assess the same continuous outcome, the standardized mean difference will be used instead of the mean difference.

If meta-analyses are inappropriate, we will use the narrative synthesis approach to summarise the results [18].

Assessment of heterogeneity and sensitivity analyses

If clinical, methodological or statistical heterogeneity is indicated then a random effects model will be used.

Heterogeneity between studies will be assessed by visual inspection of plots of the data, the Chi^2 test for heterogeneity and I^2 statistics [14]. We will consider substantial heterogeneity present if I^2 is greater than 50%. Possible reasons for heterogeneity will be explored, such as differences in the population studied, the intervention given, or the way in which the outcomes were assessed.

If there are sufficient data, subgroup analysis will be conducted to explore potential heterogeneity based on: tumour stage, patient age group and

If there are sufficient included studies, we will conduct a sensitivity analysis to assess the robustness of our review results by repeating the analysis only including studies with an overall medium to low risk of bias.

Acknowledgements

Acknowledgements will be stated in agreement with the rules set by the peer review journal that will publish this systematic review.

Contributions of authors

Contributions of authors will be stated in agreement with the rules set by the peer review journal that will publish this systematic review.

Declaration of conflicts of interest

Declaration of conflicts of interest will be stated in agreement with the rules set by the peer review journal that will publish this systematic review.

Administrative Aspects

Literature Search

The literature search will be carried out by Cathy Yuan using the search criteria specified in Appendix 1. Cathy Yuan will delete the duplicates to provide the final list of abstracts to be reviewed.

Study abstracts identified by the literature search will be reviewed by Richard Robinson and Alberto Coscione following the procedures described in Appendix 2.

Data Collection, Management and Quality Control

Data on patient and disease characteristics, treatment and patient outcome will be extracted (collected) for each study by Richard Robinson and Alberto Coscione

Data will be stored in Excel files on Dropbox.

Data quality control checks will be carried out by undertaking a review of the data in the review database. This will be undertaken 10% of the included data, selected at random.

Data Quality Control Committee

Data quality control will be carried out by Temitope Adewuyi.

Steering Committee

EAU Penile Cancer Guidelines Panel.

Writing Committee

EAU Penile Cancer Guidelines Panel in conjunction with reviewers involved in this systematic review.

Publication of the Results and Authorship

Publication of results will be in a peer review journal and authorship based on EAU Guidelines Office Authorship Rules.

Timelines

Literature search will be conducted in March 2015, Abstract and full text screening from April to June 2015, data extraction from July to August 2015 and summary analysis and drafting of systematic review article from August to September 2015.

Finances

This systematic review will be conducted through altruistic donation of time and knowledge from involved parties.

Appendix 1: Literature Search Strategy

The following databases will be searched using the provided search strategy:

Databases searched

- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Health Technology Assessment
- Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE
- Embase

Search Strategy

1 exp penis cancer/ or exp Penile Neoplasms

2 ((penile or penis) adj4 (cancer* or carcin* or malig* or tumor* or tumour* or neoplas* or SCC)).ti,ab,kw.

3 1 or 2

4 exp Lymph Node Excision/ or exp lymph node dissection

5 (lymphadenectom* or (lymph* and node*) or LN or LND or LNE).ti,ab,kw.

6 4 or 5

7 3 and 6

8 (Inguinal or groin).ti,ab,kw.

9 7 and 8

10 remove duplicates from 9

11 (exp animals/ not humans/) or ((rats or mice or mouse or cats or dogs or in vitro) not (human* or men or women)).ti.

12 10 not 11

13 (children/ not adult/) or ((children or pediatric* or paediatric*) not (aged or adult* or elder* or men or women)).ti.

14 12 not 13

15 note/ or editorial/ or letter/ or Comment/ or news

16 14 not 15

17 (case report/ or case reports/) not (case series or cases).ti,ab.

18 16 not 17

De-duplication of Identified Studies

Search results will be combined and duplicates removed by Cathy Yuan.

Appendix 2: Review of Studies Identified by the Literature Search and Searching Meeting Abstracts

The abstracts of studies that are identified by the literature search will be reviewed by a review team including:

Richard Robinson and Alberto Coscione

The studies identified by the literature search will be divided among reviewers such that two different reviewers independently review the abstract of each study.

Review of Studies Identified by the Literature Search

A separate Study Eligibility Form will be used as an aide in identifying eligible studies. It will be filled out by each reviewer for all studies that are identified as being potentially eligible or for which the eligibility is unclear based on their review of the abstract. This form will be e-mailed to Karin Plass / Cathy Yuan to request the full publication of the study in order to allow a more detailed assessment by the reviewer.

The unclear and potentially eligible studies will be entered into an Excel database by the reviewer in order to keep track of the study's status and final disposition. The Excel file will include information on whether or not the study is eligible and if not, the reason for exclusion. The columns will be: study ID, first author, and then the possible reasons for exclusion which

will be listed in the same order of the questions on the Study Eligibility Form. The Excel sheets from the various reviewers will be combined after collection from all of the reviewers.

Final Assessment of Study Eligibility

Disagreements between reviewers on study eligibility should be worked out between the reviewers whenever possible. The list of studies proposed as being eligible and the studies for which agreement between the reviewers could not be reached will be reviewed by at least one of the members of the Steering Committee.

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