Clinical and Translational Radiation Oncology 10 (2018) 1–6

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Methodology for tissue sample collection within a translational sub-study of the CHHiP trial (CRUK/06/016), a large randomised phase III trial in localised prostate cancer

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ARTICLE INFO

Article history:
Received 9 January 2018
Accepted 7 February 2018
Available online 16 February 2018

Keywords:
Sample collection methodology
Prostate cancer biopsies
Translational study

ABSTRACT

Background: This article presents the methodology for tissue sample collection in Trans-CHHiP, the main translational study within the CHHiP (Conventional or Hypofractionated High dose intensity modulated radiotherapy in Prostate cancer, ISRCTN 97182923) trial. The CHHiP trial randomised 3216 men with localised prostate cancer to 3 different radiotherapy fractionation schedules. Trans-CHHiP aims to identify biomarkers of fraction sensitivity.

Methods: We outline the process of tissue collection, including central review by a study-specific specialist uropathologist and comparison of the centrally-assigned Gleason grade group with that assigned by the recruiting-centre pathologist.

Results: 2047 patients provided tissue from 107 pathology departments between August 2012 and April 2014. A highly motivated Clinical Trials Unit chasing samples and a central Trans-CHHiP group that regularly reviewed progress were important for successful sample collection. Agreement in Gleason grade group assigned by the recruiting centre pathologist and the central study-specific uropathologist occurred in 886 out of 1854 (47.8%) cases. Key lessons learned were the need for prospective consent for tissue collection when recruiting patients to the main trial, and the importance of Material Transfer Agreement (MTA) integration into the initial trial site agreement.

Conclusions: This methodology enabled collection of 2047 patient samples from a large randomised radiotherapy trial. Central pathological review is important to minimise subjectivity in Gleason grade grouping and the impact of grade shift.

Background

The progression towards personalised medicine requires development and validation of robust predictive biomarkers. Phase III clinical trials provide an excellent opportunity to conduct translational biomarker studies as large numbers of patients with similar disease characteristics are randomised to different interventions and outcome data are collected prospectively through standard proforma. Efficient collection of patient samples is an obvious pre-requisite for biomarker studies and presents logistical challenges which are not well-represented in the published literature. Identifying strengths and weaknesses of methodologies for sample collection is increasingly important as technological innovation and improved understanding of tumour biology offer increased potential for introduction of biomarkers to routine clinical care.

Abbreviations: BATS, Blood and Tissue Samples database; BIDD, Biomarker and Imaging Discovery and Development Committee; CHHiP, Conventional or Hypofractionated High dose intensity modulated radiotherapy in Prostate cancer; CRN, Clinical Research Network; CTU, Clinical Trials Unit; H&E, Haematoxylin and Eosin; ICR-CTSU, Institute of Cancer Research Clinical Trials and Statistics Unit; ISUP, International Society of Urological Pathology; MTA, Material Transfer Agreement; NCCN, National Comprehensive Cancer Network; NCRI, National Cancer Research Institute; NHS, National Health Service; TMA, Tissue microarray; TMG, Trial Management Group; TSC, Trial Steering Committee; TURP, Trans-urethral resection of prostate.

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https://doi.org/10.1016/j.ctro.2018.02.002
2405-6308/

The CHHiP trial is a phase III non-inferiority trial that recruited 3216 men with localised prostate cancer from 71 centres to radiotherapy treatment between 2002 and 2011 [1]. Most men recruited to CHHiP had intermediate risk localised prostate cancer, a risk category where biochemical recurrence varies considerably from 10% to 40% [2], and our understanding of how to stratify patients is limited. Additionally, CHHiP is the largest trial of different radiotherapy fractionation schedules for prostate cancer to date; therefore it provides a unique opportunity for translational work to improve our understanding of the biological basis of fraction sensitivity.

Trans-CHHiP (CRUK A12518: An evaluation of biomarkers in hypofractionated and dose escalated prostate cancer radiotherapy) was established as the main translational study within the CHHiP trial. It aims to identify biomarkers of fraction sensitivity and improve risk stratification for patients with intermediate risk localised prostate cancer. Patient tissue samples were collected between 2012 and 2016, this article presents the methodology used for sample collection in Trans-CHHiP, together with lessons learned that could improve efficiency of sample collection in the future.

Methods

Study organisation

Trans CHHiP central group

Sample collection from participating centres was coordinated by a central Trans-CHHiP group based at the Institute of Cancer Research (ICR). This group met at least 3 monthly throughout the sample collection process to review progress, resolve problems and plan new aspects of sample collection. The group included members of the ICR Clinical Trials and Statistics Unit (ICR-CTSU) CHHiP team (scientific lead, trial managers, trial administrator and clinical research fellow), the trial Chief Investigator, a dedicated biomedical scientist and a study-specific diagnostic uropathologist.

Recruiting centres

67 recruiting CHHiP centres (excluding 4 trial centres outside the UK) from 58 National Health Service (NHS) Trusts were eligible for Trans-CHHiP. The ICR-CTSU communicated directly with recruiting centre pathology departments for sample collection (see below). All CHHiP centres were updated about Trans-CHHiP progress via annual teleconferences.

CHHiP governance groups

The CHHiP trial is overseen by a Trial Management Group (TMG) which meets 6 monthly, during which Trans-CHHiP updates are provided. In addition external data access requests for use of biological and/or clinical data are reviewed by the TMG and Trial Steering Committee (TSC) as they arise. The TSC is an independent oversight group comprising clinical and statistical members.

Study specific databases e.g. BATS, CHHiP Progeny

Two study-specific databases were created for Trans-CHHiP. Firstly the Blood and Tissue Samples database (BATS), which records the patient's histology number, unique trial number, recruiting CHHiP centre and pathology department where the tissue was held. It also contains details of Trans-CHHiP consent, whether samples have been requested, received and whether invoices for samples have been paid.

Secondly a customised version of Progeny software including the Sample Management module was created for Trans-CHHiP. This includes 11 pathology variables, and the Gleason score. It details the precise physical location of each sample within the CHHiP inventory. Progeny enables 2D barcoding for all slides, cassettes and eppendorf tubes, and creation of 91 disc digital tissue microarray (TMA) plates.

Patient consent, translational study contract and MTA

CHHiP was undertaken in 3 seamless stages with different consent for tissue donation between part I and parts II/III of the trial. For parts II/III consent for donation of tissue was included as an optional tick box clause in the main trial consent form. However, for Part I of the trial, this clause was not present and patients were re-consented (if possible) at a later date.

A Material Transfer Agreement (MTA) outlining terms and conditions of transfer of samples between academic organisations was required between the ICR and any NHS Trust donating tissue to Trans-CHHiP.

Funding and financial reimbursement

Sample collection was funded by a Cancer Research UK Biomarkers and Imaging Discovery and Development Committee (BIDD) grant (A12518) obtained in 2011. Cancer Research UK reimbursement to pathology departments was £15 per patient; having provided tissue, these departments submitted invoices directly to the ICR-CTSU. Invoices submitted at a higher cost per sample were reviewed by the Chief Investigator and funded where feasible. As CHHiP was within the National Institute for Health Research Clinical Research Network (NCRN) portfolio, pathology departments were encouraged to approach the CRN to help with additional resources for sample collection. Further funding for the central receiving laboratory at the ICR was provided by Prostate Cancer UK and the Movember Foundation.

Tissue collection process prior to arrival of tissue at central receiving laboratory

The steps for sample collection prior to arrival at the central receiving laboratory are summarised in Fig. 1. As sample location was unknown to the CHHiP team, a patient level "Sample location form" was created to enable recruiting centres to indicate where the sample was stored. A "Sample Transfer Form" was also created to ensure consistent record of sample transfer between the donating histopathology department, the central receiving Trans-CHHiP laboratory and the ICR-CTSU. (See appendix for both forms.)

A key requirement prior to the ICR-CTSU sending sample request letters to centres was that the MTA was in place between the ICR and the relevant NHS Trust. Several NHS Trusts wanted to renegotiate the terms of the original site agreement; set up of the MTA was, in some cases, a costly and lengthy process that significantly delayed sample collection. Some NHS Trusts comprised more than one recruiting CHHiP centre and a total of 58 NHS Trusts included the 67 recruiting centres for Trans-CHHiP. All 58 NHS Trusts did eventually complete the MTA, however the time taken for completion ranged from 6 to 777 days. Issues that arose during MTA negotiation included return of samples, change of NHS Trust names and splitting and merging of NHS Trusts since the original agreement. Additionally, some hospital pathology departments would not release blocks before seeing the relevant signed consent form, which required the ICR-CTSU to obtain and transfer the relevant form. A number of pathology departments had archived samples off site which further complicated obtaining tissue.

ICR-CTSU had a systematic programme for chasing up requested samples with an initial letter and subsequent phone calls if centres did not respond within one month of the letter. A substantial proportion of centres needed reminders. On average 3 reminders were required, but for some centres up to 6 repeated