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Refining the definition of mandibular osteoradionecrosis in clinical trials: The cancer research UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis)

Richard Shaw [a,b,*], Binyam Tesfaye [b], Matt Bickerstaff [b], Paul Silcocks [b], Christopher Butterworth [a,c]

[a] Department of Molecular and Clinical Cancer Medicine, University of Liverpool & Head & Neck Division, Aintree University Hospital NHS Foundation Trust, Liverpool L9 7AL, UK
[b] Cancer Research UK Liverpool Cancer Trials Unit, University of Liverpool Cancer Research Centre, University of Liverpool, Block C Waterhouse Building, 1-3 Brownlow Street, L69 3GL, UK
[c] Department of Restorative Dentistry, Liverpool University Dental Hospital, Pembroke Place, Liverpool L3 5PS, UK

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ABSTRACT

Introduction: Mandibular osteoradionecrosis (ORN) is a common and serious complication of head and neck radiotherapy for which there is little reliable evidence for prevention or treatment. The diagnosis and classification of ORN have been inconsistently and imprecisely defined, even in clinical trials.
Methods: A systematic review of diagnosis and classifications of ORN with specific focus on clinical trials is presented. The most suitable classification was evaluated for consistency using blinded independent review of outcome data (clinical photographs and radiographs) in the HOPON trial.
Results: Of 16 ORN classifications found, only one (Notani) appeared suitable as an endpoint in clinical trials. Clinical records of 217 timepoints were analysed amongst 94 randomised patients in the HOPON trial. The only inconsistency in classification arose where minor bone spicules (MBS) were apparent, which occurred in 19% of patients. Some trial investigators judged MBS as clinically unimportant and not reflecting ORN, others classified as ORN based on rigid definitions in common clinical use. When MBS was added as a distinct category to the Notani classification this ambiguity was resolved and agreement between observers was achieved.
Discussion: Most definitions and clinical classifications are based on retrospective case series and may be unsuitable for prospective interventional trials of ORN prevention or treatment. When ORN is used as a primary or secondary outcome in prospective clinical trials, the use of Notani classification with the additional category of MBS is recommended as it avoids subjectivity and enhances reliability and consistency of reporting.

Introduction

Mandibular osteoradionecrosis (ORN) is a common complication of radiotherapy for head and neck malignancy whereby the bone undergoes necrosis, becoming exposed. This is usually symptomatic and may cause intra- or extra-oral fistulae, infection, pain and eventually pathological fracture [1]. The consequences of these complications include malnutrition, opiate dependency, haemorrhage, sepsis, with progressive disfigurement and deterioration in quality of life. The incidence of head and neck cancer, survival and proportion receiving radiotherapy are all increasing, in part, due to Human Papillomavirus related cases [2,3]. As such, the 'at risk' population for ORN is increasing and it has justifiably become a focus for clinical trials.

Classifications of mandibular ORN vary significantly in their aims but have been developed in order to help the clinician categorise and manage ORN in routine clinical practice rather than as endpoints in clinical trials. The emergence of formally conducted prospective randomized trials addressing ORN, such as HOPON [4], DAHANCA21 [4], ORN96 [5] & those of Delanian [6], highlights the requirement for more objective and valid endpoints. This would facilitate reproducibility across multiple trial sites and validation by independent blinded panels even in the absence of the patient, irrespective of the treatment arm assigned. Suggested criteria for definition and classification of ORN in clinical trials are listed in Table 1.

* Corresponding author at: Department of Molecular and Clinical Cancer Medicine, University of Liverpool & Head & Neck Division, Aintree University Hospital NHS Foundation Trust, Liverpool L9 7AL, UK.
E-mail address: richard.shaw@liverpool.ac.uk (R. Shaw).

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Table 1
Criteria for definition and classification of ORN in clinical trials.

	Domain	Criteria
a	Response	Does not assume outcome or response to the use of a defined prior treatment modality or protocol
b	Trend	Can be completed at a single time point and without knowledge of prior ORN or future progression/ prognosis
c	Prescription	Do not make assumptions about indications for, or methods of, subsequent treatment
d	Blinding	Can be readily reproduced for validation by independent blinded assessor or panel
e	Precision	Are not subject to subjectivity or vague definitions
f	Validation	Not dependent on unvalidated patient reported outcomes or symptom severity
g	Exposure	Mandates the presence of exposed bone, ie. presence of radiological changes *alone* are insufficient to diagnose ORN

The HOPON trial (Hyperbaric Oxygen in the Prevention of Osteoradionecrosis) addresses the prophylactic benefit of hyperbaric oxygen in preventing osteoradionecrosis accompanying surgical procedures to the irradiated mandible. Patients are eligible for HOPON who require dental extractions in the posterior mandible or implant placement and are at high risk of ORN following radiotherapy for head and neck malignancy. In developing the protocol for the HOPON trial, it has become apparent that a robust classification of osteoradionecrosis has not yet been well resolved within clinical trials.

The aims of this study are to review, refine and validate suitable classifications of ORN within the setting of clinical trials. A systematic review of published classifications of mandibular ORN will be conducted with specific reference to their suitability as a clinical trial endpoint, with reference to the criteria listed in Table 1. These criteria have been assembled as an assumed gold-standard in trials with osteoradionecrosis as an endpoint. The most suitable method (s) will subsequently validated using data from the CR-UK HOPON trial (ISRCTN39634732), focusing on inconsistencies in categorization by a blinded independent expert review panel.

Methods

Systematic review

The published literature was reviewed for articles relating to classification of mandibular osteoradionecrosis 1970–2016. Pubmed was searched for articles using the terms ‘‘osteoradionec rosis”, ‘‘mandible”, ‘‘classification”, ‘‘definition” and also with Mesh term ‘‘Osteoradionecrosis” and Mesh subheadings: ‘‘diagnosis”, ‘‘analysis” and ‘‘classification”. 350 resultant manuscripts in the English language were hand sorted, and cross-checked by scanning their reference lists. The criteria for selection were original, independent and distinct definitions and classifications of mandibular osteoradionecrosis. The 13 resultant articles that presented original classifications were additionally subject to scrutiny according to criteria laid out above and this data tabulated (Table S1). Additionally, the classification of mandibular ORN from the last three NIH Common Terminology Criteria for Adverse Events (CTCAE) [7–9] were separately tabulated (Table S2). The classification method most nearly fitting the criteria established in Table 1, was used in the second part of the study.

Validation

Anonymised patient records (clinical photographs and radiographs) from 94 patients randomised to the HOPON trial were reviewed independently by two blinded independent clinicians (RJS & CB). Cases were classified according to Notani et al. [10] and this was compared with the research site principal investor's assessment as annotated on the trial clinical record forms (CRFs). These records constituted a clinical photograph at 3, 6 and 12 month post-surgery time-points, and accompanying radiographs for the 6 month time-point (and 3 or 12 months, if ORN was clinically diagnosed). A dedicated software package on the trials unit's web portal was created so that both clinicians could independently access paired clinical photographs and radiographs for the defined endpoints for each patient. Any cases with discrepancies within the 3 independent assessments, or with any comments highlighting difficulty in classifying outcome in the free-text were noted for further analysis. Due to some incomplete data and immaturity of all data collection (and exclusion of two ineligible patients), a total of 217 clinical assessments were reviewed from a potential total of 336 (65% complete). The photographs and radiographs from each assessment were made *without* knowledge of timing or of which arm of the trial (HBO vs standard therapy) the patients was in, as the trial is ongoing at the time of writing.

Results

Systematic review: Definition of ORN

Many authors offer a description [11] rather than a definition of ORN, however a number of subtly differing definitions have been offered in the published literature. The cited definitions found in the literature generally appear to originate from three published versions [12–14]. Harris [12] defines mandibular ORN as ‘‘*exposed irradiated bone that fails to heal over a period of 3 months in the absence of local tumour*”. Marx [13] offers a definition of ‘‘*an area greater than 1cm of exposed bone in a field of radiation that has failed to show any evidence of healing for at least 6 months*”. The definitions of ORN show some consensus around an area of exposed bone for a minimum time period in an irradiated field and in the absence of tumour. The specific extent of exposed bone or time period specified vary and are presented in Table 2. Store and Boysen [14] include radiological change without exposed bone within diagnostic criteria, whilst this is specifically excluded by Harris & Marx [12,13] so this is evidently an area of controversy.

Classification of ORN

Although there was evident overlap between the principles of classification seen, 13 distinct classifications [10,11,13–23] (Table S1) were identified between 1983 and 2015 and 3 differing classifications were offered by CTCAE (Table S2) in 1999, 2006 and 2010. None of the peer reviewed publications were designed with the stated aim to evaluate treatments under investigation in prospective clinical trials, and indeed all were evaluated retrospectively from their authors' own institutional case series. The degree to which the classifications met the specified criteria varied considerably. As the Notani et al. [10] classification does not rely on assumptions about response to previous treatment or subsequent prescription bias, additionally it does not assume knowledge of

Table 2
Common diagnostic criteria for mandibular ORN.

Criteria	Specified thresholds
Presence of exposed bone [12,13]	Minimum dimension 1 cm [13]
Previously irradiated [12–14]	*(dose not specified in any definition)*
Minimum period of exposed bone	2 months [25,26]
	3 months [12,27,28]
	6 months [13]
Absence of recurrent tumour [12–14]	*(diagnostic criteria not stated in any definition)*