Clinical Oncology 26 (2014) 344–347

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

NIMRAD – A Phase III Trial to Investigate the Use of Nimorazole Hypoxia Modification with Intensity-modulated Radiotherapy in Head and Neck Cancer

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Received 25 February 2014; accepted 3 March 2014

NIMRAD is a randomised placebo-controlled trial of synchronous nimorazole versus radiotherapy alone in patients with locally advanced head and neck oropharyngeal, hypopharyngeal and laryngeal squamous cell carcinoma not suitable for synchronous chemotherapy or cetuximab. Eighteen UK centres aim to recruit a total of 470 patients over the next 4 years. The trial aims are to: (i) assess the benefit of hypoxia modification in those unsuitable for standard synchronous systemic therapies, including elderly or less fit patients; (ii) determine the effectiveness and tolerability of synchronous nimorazole when used with contemporary advanced radiotherapy techniques (fixed beam or rotational intensity-modulated radiotherapy, IMRT); (iii) validate a hypoxia gene signature for use in the clinic as a predictive biomarker; and (iv) standardise the UK approach to the definition of head and neck IMRT treatment volumes. A radiotherapy quality assurance programme for head and neck volume delineation and IMRT treatment planning has been specifically developed for NIMRAD, which aims to maintain the quality of treatment delivery while minimising quality assurance repetition.

Locally Advanced Head and Neck Squamous Cell Carcinoma

The reported UK annual prevalence of head and neck squamous cell carcinoma (HNSCC) between 2011 and 2012 was 8272 [1], representing 2.5% of all cancers [2]. Of these, the total prevalence of oropharyngeal, laryngeal and hypopharyngeal cancers was 4659 [1]. The crude 2 year overall survival rates were 70, 73 and 42%, respectively [1]. However, most (60–70%) patients present with locally advanced disease and have a comparatively poor outlook, with an estimated 5 year relative conditional survival of 44% [3]. The standard of care for this group is various combinations of surgery, radiotherapy and systemic treatments. A non-surgical approach is used for patients unsuitable/unfit for surgery or with the aim of function preservation and is preferred as first definitive treatment in around 50% of patients [1,4]. However, elderly or less fit patients are often unsuitable for combined radical radiotherapy with synchronous chemotherapy or cetuximab and receive radiotherapy alone [5,6].

An estimated 24% of patients with HNSCC are over the age of 70 years [7]. Elderly patients are under-represented in chemotherapy clinical trials [8]. However, in a meta-analysis, the 692 patients over the age of 71 years derived no overall survival benefit from the addition of synchronous chemotherapy to radiotherapy [5]. This lack of benefit may be due to increased toxicity and an excess of non-cancer deaths [8]. Similarly, in the registration study of synchronous cetuximab with radiotherapy, the 26% of patients ≥65 years did not benefit from combined modality treatment [6]. In the UK, about 8–13% of patients with HNSCC have a performance status of 2 at presentation [1]. This less fit group of patients may receive radical radiotherapy, but generally without synchronous chemotherapy or cetuximab, as the evidence suggests that they may not benefit from it [5,6]. There is, therefore, a need to improve therapy for patients with locally advanced HNSCC who are currently treated with radical radiotherapy alone.

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http://dx.doi.org/10.1016/j.clon.2014.03.003

Hypoxia Modification in the Treatment of Head and Neck Squamous Cell Carcinoma

A meta-analysis published in 2011 showed level 1a evidence in favour of adding hypoxia modification to radiotherapy in patients with HNSCC [9]. This included published and unpublished data from 4805 patients enrolled in 32 randomised clinical trials using several hypoxia modification strategies (hyperbaric oxygen, carbogen, carbogen plus nicotinamide and radiosensitisers). Hypoxia modification improved locoregional control (odds ratio 0.71; 95% confidence interval 0.63–0.80; $P < 0.001$), disease-specific survival (odds ratio 0.73; 95% confidence interval 0.64–0.82; $P < 0.001$) and overall survival (odds ratio 0.87; 95% confidence interval 0.77–0.98; $P = 0.03$) without increasing late complications (odds ratio 1.00; 95% confidence interval 0.82–1.23; $P = 0.96$). The improvement in locoregional control was independent of the type of hypoxia modification. However, at present, hypoxia modification is not routinely used in clinical practice, except for nimorazole in Denmark [10].

Nimorazole belongs to a class of chemicals known as 5-nitroimidazoles and acts as a hypoxic radiosensitiser. The Danish Head And Neck Cancer (DAHANCA)-5 randomised, placebo-controlled, double-blind phase III study of synchronous nimorazole with primary radiotherapy was carried out in 414 patients with supraglottic larynx and pharynx carcinoma from 1986 to 1990 and published in 1998 [11]. This study showed improved locoregional tumour control (5 year actuarial rates of 49% versus 33%; $P < 0.002$) and a non-significant trend to improved overall survival (10 year actuarial rates of 26% versus 16%; $P = 0.32$) in nimorazole-treated patients. The benefit was observed for T2 as well as higher stage disease. The treatment was well tolerated with no severe or persistent side-effects. However, the median radiotherapy overall treatment times in both placebo and nimorazole arms were 50 days, compared with a planned 45 days. The NIMRAD trial will evaluate synchronous nimorazole with contemporary advanced radiotherapy techniques and practices. It has the potential to improve the outcomes of older patients, those who are unfit for standard combined modality treatments as well as selected patients with high-risk T2 tumours who currently receive radiotherapy alone. There are no data suggesting that patients unsuitable for cisplatin or cetuximab might not benefit from nimorazole: the DAHANCA-5 trial recruited patients up to 84 years old in both randomisation arms; there was no difference in locoregional control for patients above and below the median age of 60 years; and nimorazole is part of standard treatment in Denmark in HNSCC patients irrespective of patient age.

There is recognised heterogeneity in tumour hypoxia and resultant variable effectiveness of hypoxia modification therapies [10,12]. There are a number of approaches to measuring hypoxia, but none is routinely used in clinical practice. The NIMRAD trial will allow prospective validation of a gene signature that has been derived and tested in multiple datasets [13], is set up to good clinical practice conditions, has undergone assay development and is ready for biomarker qualification stage 1 [14]. In addition, a predictive hypoxia gene signature developed by the DAHANCA group will be further evaluated [12]. The aim is to qualify prospectively a gene signature that can be used in clinical practice to personalise treatment and select appropriate patients for hypoxia modifying treatment.

Definition of Head and Neck Squamous Cell Carcinoma Intensity-modulated Radiotherapy Treatment Volumes

There is marked variation in the definition of head and neck IMRT treatment volumes [15]. The standardisation of volume delineation is important to ensure quality, consistency and allow meaningful comparisons between treatments. At the inception of IMRT, an anatomical approach to volume delineation was adopted, which closely related to conventional treatment volumes [16]. This approach was/is being used in the UK PARSPORT, ART-DECO and De-ESCALaTE HNSCC trials [17–19]. However, with improved diagnostic imaging and the advent of highly conformal radiotherapy techniques, recent co-operative group trials have used a geometric expansion to define smaller treatment volumes [20]. This aims to lessen toxicity and potentially allows radiation dose escalation to the tumour. The NIMRAD trial uses a hybrid outlining approach, with a geometric expansion to define the high dose treatment volume. This approach has also been incorporated in the modified outlining guidelines of the De-ESCALaTE trial.

In the NIMRAD trial, either two dose or three dose levels may be used. This will be a stratification factor and each centre must stipulate the dose level they wish to use. Patients will be treated once daily for 30 fractions over 6 weeks and depending on the number of dose levels, the prescribed doses to the respective planning target volumes (PTVs) are: PTV1, 65Gy; PTV2, 60Gy or 54Gy; PTV3, 54Gy.

The approaches to volume delineation are illustrated in Figure 1. For a two dose volume approach, the clinical target volume (CTV) CTV1_65 includes the gross primary or nodal disease (gross tumour volume) with a 1 cm isotropic margin and the whole of involved nodal level(s). CTV2_54 includes the remainder of the involved subsite and uninvolved nodal levels at risk of microscopic disease. For a three dose volume approach, CTV1_65 includes the gross primary or nodal disease with a 1 cm isotropic margin. CTV2_60 includes the remainder of the involved subsite and nodal level(s). CTV3_54 includes uninvolved nodal levels at risk of microscopic disease. After neck dissection, CTV1_65 (for two dose levels) or CTV2_60 (for three dose levels) includes the whole of pathologically involved nodal levels; CTV2_54 includes pathologically uninvolved nodal levels at risk of microscopic disease. For well-lateralised oropharyngeal cancers, ipsilateral subsite and neck treatments should be adopted. These are defined in NIMRAD as confined to the tonsillar fossa or lateral pharyngeal wall with <1 cm medial disease extension and >1 cm clearance from midline and node negative or N1 disease only.

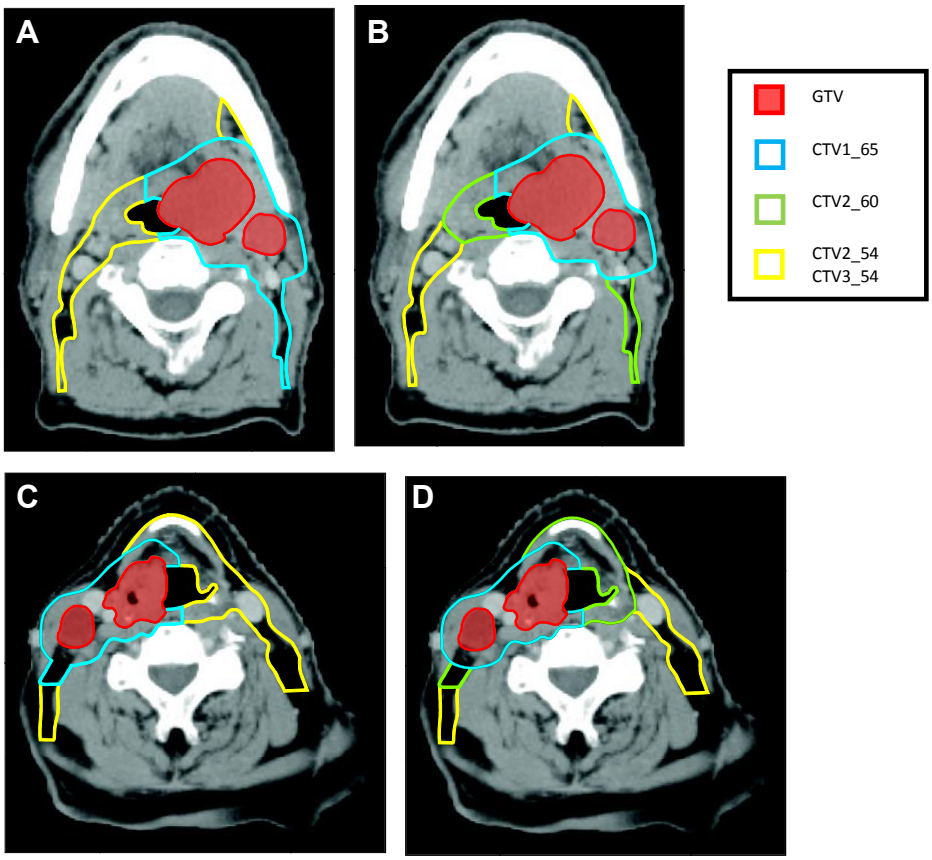

Fig 1. Approach to volume definition. A locally advanced tonsil cancer delineated with 2 (A) or 3 (B) dose levels; a locally advanced supraglottic cancer delineated with 2 (C) or 3 (D) dose levels.

Table 1
Elective nodal irradiation defined by subsite and neck nodal status

Subsite	Node-negative side of neck	Node-positive side of neck*
Oropharynx	II–IVa	Ib,II,III,IVa,Va,Vb ipsilateral VIIa (RP)
Larynx	II–IVa	Ib,II,III,IVa,Va,Vb
Hypopharynx	II–IVa, ipsilateral VIIa (RP)	Ib,II,III,IVa,Va,Vb ipsilateral VIIa (RP)

* Level II involved – CTV2 should include level VIIb (retrostyloid nodal level).
* Level IVa/Vb involved – CTV2 should include IVb/Vc (medial and lateral supraclavicular fossa nodal levels).
RP, retropharyngeal nodal level.

The anatomical definition of lymph node levels are described by the 2013 DAHANCA, EORTC, HKNPCSG, NCIC, CTG, NCRI, RTOG and TROG endorsed consensus guidelines [21]. The selection of electively treated nodal levels by subsite and neck nodal status is defined in Table 1.

Radiotherapy Quality Assurance and Streamlining

In the TROG 02.02 trial, poor radiotherapy was responsible for a 20% decrease in 2 year overall survival [22]. This underscores the critical importance of radiotherapy volume delineation and treatment planning quality assurance. For NIMRAD this builds on the rigorous quality assurance programme that has been developed and implemented by the National Cancer Research Institute Radiotherapy Trials Quality Assurance Groups group for the IMRT credentialing of multicentre head and neck trials in the UK, including PARSPORT, COSTAR, ART-DECO and De-ESCALaTE [17–19,23]. The process was designed to minimise quality assurance repetition while maintaining the high quality of treatment delivery. Centres may be eligible for quality assurance streamlining based on prior participation in the ART-DECO and/or De-ESCALATE IMRT trials [18,19].

Acknowledgement

NIMRAD is sponsored by The Christie NHS Foundation Trust (protocol code number: CFTSp032). The trial is funded by Cancer Research UK.

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