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Practice guidelines

ESTRO ACROP guidelines for positioning, immobilisation and position verification of head and neck patients for radiation therapists



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ABSTRACT

Background and purpose: Over the last decade, the management of locally advanced head and neck cancers (HNCs) has seen a substantial increase in the use of chemoradiation. These guidelines have been developed to assist Radiation Therapists (RTTs) in positioning, immobilisation and position verification for head and neck cancer patients.

Materials and methods: A critical review of the literature was undertaken by the writing committee.

Materials and methods: Based on the literature review, a survey was developed to ascertain the current positioning, immobilisation and position verification methods for head and neck radiation therapy across Europe. The survey was translated into Italian, German, Greek, Portuguese, Russian, Croatian, French and Spanish.

Materials and methods: Guidelines were subsequently developed by the writing committee.

Results: Results from the survey indicated that a wide variety of treatment practices and treatment verification protocols are in operation for head and neck cancer patients across Europe currently.

Results: The guidelines developed are based on the experience and expertise of the writing committee, remaining cognisant of the variations in imaging and immobilisation techniques used currently in Europe.

Conclusions: These guidelines have been developed to provide RTTs with guidance on positioning, immobilisation and position verification of HNC patients. The guidelines will also provide RTTs with the means to critically reflect on their own daily clinical practice with this patient group.

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Introduction

These guidelines have been developed to assist Radiation Therapists (RTTs) in positioning, immobilisation, position verification and treatment for head and neck cancer (HNC) patients presenting for radiation therapy.

In the full guideline document available on the ESTRO website¹, the management of head and neck cancers and likely anticipated toxicities as well as reports of current practice throughout Europe, both from a European survey and specific vignettes from RTTs across

Europe are given. This practice is then discussed in accordance with the literature. The guidelines that follow are based on the experience and expertise of the writing committee, remaining cognisant of the variations in imaging and immobilisation techniques used currently in Europe. These are to assist RTTs in critical analysis of their own practice in positioning, immobilisation, position verification and treatment practices of this patient group in their own radiation therapy departments.

Material and methods

Literature review

A critical review of the literature was undertaken by the authors, searching relevant databases including PubMed, Embase

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¹ <http://estro.org/about-us/governance-organisation/committees-activities/rtt-committee-activity-professional-issues>.

and Google Scholar. Search terms used included combinations of and Boolean operations of 'head and neck cancer', 'radiation therapy', 'radiotherapy', 'positioning', 'immobilisation', 'verification', 'cone beam CT', and 'electronic portal imaging'. Studies in English, French, Portuguese, Italian and German were included. An overview of this literature is given in Table 1 of the [supplementary material](#).

Survey development and distribution

Based on the literature review, a survey was developed to ascertain the current positioning, immobilisation and position verification methods for head and neck radiation therapy across Europe. The survey consisted of 40 questions, divided into 5 sections. The sections contained both open and closed questions on: Demographics, Patient Positioning, Immobilisation devices, CT/Simulation Practice, Position Verification as well as elements of quality assurance (QA) in relation to positioning and immobilisation.

The survey was piloted on 5 RTTs whose first language was English and the suggested minor phrasing changes were implemented. The survey was then translated into the following languages: Italian, German, Greek, Portuguese, Russian, Croatian, French and Spanish. All surveys, together with instructions for completion, were subsequently uploaded into an online survey distributor, SurveyMonkey™.

Contact details for RTTs in each European country were acquired through the ESTRO membership database as well as through the National Societies. An invitation email, both outlining its purpose and providing a link to the survey was sent to these contact persons in their own language, where possible. The contact RTT was asked to distribute the link to all departments nationally. In many cases, the survey was made available on National Society websites.

Data analysis

Data analysis was performed using SPSS Statistics version 20.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.). Descriptive statistics were calculated and appropriate figures and tables constructed. Cross tabulations were performed where appropriate to maximise data analysis.

Vignettes of practice

To further expand on the current practice across Europe, a number of RTTs were asked to provide a vignette of their departmental practice. For comparability purposes, RTTs were asked specifically to describe the practice in their departments for locally advanced oropharyngeal patients undergoing definitive chemoradiation, as this was deemed to be a site commonly observed in the majority of radiation therapy departments where head and neck cancers are treated.

Guidelines

The guidelines were developed based on the literature while remaining cognisant of the variation in treatment delivery and verification imaging capacities of radiation therapy departments across Europe.

Results

Results from the European-wide survey indicated that a wide variety of treatment practices and treatment verification protocols are in operation for head and neck cancer patients across Europe

currently. These ranged from 3DCRT to VMAT and from daily online CBCT imaging to offline correction protocols using kV EPIs or in some cases, MV portal imaging.

In terms of immobilisation, the majority of respondents use thermoplastic masks in their immobilisation of head and neck patients, with some variance in how shoulder position is maintained. The full results from this survey are available in the complete guideline document, available on the ESTRO website.

Guidelines for positioning, immobilisation and position verification of head and neck patients for RTTs.

1. Positioning prior to thermoplastic mask construction

The aim of positioning and immobilisation should be to maximise patient comfort, while ensuring a high reproducibility, and hence treatment accuracy throughout the course of treatment. Head and neck cancer patients may be positioned and immobilised in dedicated mould rooms or more frequently, in the CT room. In either instance, it is a pre-requisite that the same laser alignment system and couch top are present as at the simulator, CT, MRI, PET and linear accelerator.

- 1.1. Following departmental patient identification procedures, the patient should be brought to a designated patient information area.
- 1.2. A full and detailed explanation of the procedure should be given to the patient by an RTT.
- 1.3. During the consultation, the importance of remaining still and breathing normally throughout the procedure should be stressed.
- 1.4. Other aspects related to both the safety and efficacy of the procedure should be discussed with the patient including the likely mask temperature, and how the patient can alert the RTTs if they are having difficulty during the procedure.
- 1.5. The patient should be asked to remove all clothing from the waist up. Any dentures, hearing aids, toupees, earrings and all kinds of piercings in the treated area including tongue piercings must also be removed. Shoes should be removed and any wallets in back pocket of trousers of male patients. Female patients should remove makeup. If possible, the patient should be provided with a gown, which can be removed, as the procedure commences.
- 1.6. The patient should be positioned on the treatment couch, in the prescribed treatment position as comfortably and reproducibly as possible. The sagittal laser should be used to ensure straightness, checking that it bisects the nasal septum, sternal notch, xiphisternum and symphysis pubis as much as is possible. This aids in the minimisation of rotations.
- 1.7. All immobilisation devices must be indexed and fixed to the couch, to minimise rotational and translational errors. Neck rests should provide adequate support for the head and neck and gaps should not be present underneath the head of the patient nor at the top of the neck rest.
- 1.8. In the case of inadequate support of the head and neck by conventional neck rests, the position can be adapted by adding 'wedges' or using individual, customised neck rests, or a combination of both. Selection of 'wedges' underneath the neck rest should be based on the required position of the neck for treatment. The RTT should be aware of the diagnosis of the patient and the likely beam arrangement when selecting the most appropriate neck position, which is usually neutral or extended in head and neck cases. Care should be taken to ensure that selected neck rests are of good quality and fit for purpose as differences in neck rests can result in discrepancies in positioning from pre-treatment to treatment areas (Fig. 1).

- 1.9. Any additional supports required for the procedure, such as knee rests or shoulder retractors should be indexed to the couch (Fig. 2).
 - 1.10. Depending on the site to be treated in the head and neck, the patient may require a mouth bite or customised stent. These may be constructed either in the radiotherapy department or by a specialist dental centre. If required, the mouth bite or stent should be in situ prior to construction of the thermoplastic mask. It is preferable for patients to be given time to grow accustomed to the mouth bite or stent, if possible, prior to making the mask.
 - 1.11. Documentation of the fixed positions of all immobilisation devices should be performed by one RTT and checked by a second. Careful documentation of specific devices for the patient should be made, for example, unambiguous annotation of mouth bites or stents.
 - 1.12. The mask selection should be made according to the institution protocol for that specific sub site. According to the treatment site and disease extension, masks should be of 3 or more fixation points. If treating the low neck, a 5-point mask is recommended. If a 3-point mask is used, a device to maintain shoulder position, such as a retractor, is mandatory.
 - 1.13. It may be necessary to cover the hair with cotton-type material and to ensure that the patient's airway is not compromised during the procedure. This may necessitate enlarging the gap for the nasal and mouth areas slightly. For post-operative patients with tracheostomies in situ, care should be taken to avoid airway obstruction. This will necessitate placing petroleum-based gauze over the stoma, which will not obstruct breathing, as well as making an appropriate sized gap in the material to clear the tracheostomy site.
- Note: From our survey results, a combination of standard and customised neck rests are currently used throughout Europe with standard neck rests most commonly used for 3DCRT techniques and a combination of standard and customised for modulated techniques such as IMRT and VMAT.*

2. Construction of thermoplastic mask

- 2.1. The patient should be positioned as outlined in 1.6 prior to commencing the construction of the mask.
- 2.2. If using a water bath, the manufacturer's guidelines on water bath temperature should be adhered to, as should the length of time required for hardening of the mask. It should be noted that this is due to both the type of thermoplastic and perforation size, which varies from one manufacturer to the next and will impact on the shrinkage of the mask.
- 2.3. The material should be placed in the water bath for the stated period of time, removed from the water bath and excess moisture should be drained. The temperature of the material must be checked before placing on the patient's skin to avoid burns.
- 2.4. If using an 'oven' to heat the material, it should be heated to the appropriate temperature and the material checked before being placed on the patient's skin.
- 2.5. The material should be draped over the head and neck of the patient. For correct construction of a four or five point thermoplastic mask, three RTTs should be involved in the process. One RTT should be at the superior aspect of the patient and one on either side. If constructing a 3-point mask, two RTTs are preferable.
- 2.6. RTTs must work quickly and accurately to mould the material closely to the patient's skin, ensuring that there are no gaps and that the neck position remains as required throughout the moulding procedure. This must be completed within 1–2 min, as the hardening process will then commence.



Fig. 1. Quality assurance of neck rests



Fig. 2. Non-indexed supports should be avoided.

- 2.7. Specific attention should be given to the forehead, bridge of nose, chin and shoulders to ensure that the mask will provide adequate immobilisation of the patient. It is the responsibility of the staff member at the superior aspect of the patient to ensure that the head is held still in position, to minimise rotations, ideally with the help of the sagittal laser.
- 2.8. The material should be allowed to harden for the specified length of time as per the manufacturer's recommendations. This can be anything from 5–15 min, depending on material type. You can reduce the cooling time with towels from the fridge, cold gel pads or using cold air.

- 2.9. The patient should be supported and reassured by the RTTs during this time period. Motivating and supporting patients to use abdominal breathing will help them to relax during the whole procedure.
- 2.10. It is recommended that the mask be removed and refitted prior to commencement of CT scanning to ensure that the fit is correct and that the immobilisation provided by the mask is adequate. Specific attention should be paid to the most stable bony landmarks: forehead, bridge of nose, chin and good contact with the chest and shoulder area should be evident (Figs. 3 and 4). This also allows the patient the opportunity to take a short break prior to the commencement of image acquisition, which is advisable.
- 2.11. The procedure and patient position should be clearly documented by RTTs in the patient chart. For safety reasons, the patient name, type of neck rest and wedges used should always be documented on the patient mask, preferably using a method that can identify the mask in the oncology information system.
- 2.12. 'Cutting out' the mask should be avoided except to facilitate bite blocks or respiratory devices, such as tracheostomies.

3. CT procedure

- 3.1. All departmental procedures in relation to patient informed consent and identification should be adhered to prior to commencing the CT scanning procedure.
- 3.2. The patient diagnosis, prescription and required scanning margins should be known to the RTTs before commencing CT, so as to adhere to the ALARA principle. Scanning margins as per local standard operating procedures (SOPs) should be adhered to.
- 3.3. If contrast is to be used, the RTTs must screen the patient for potential anaphylaxis as per departmental protocol, document this screening procedure and ensure that the emergency trolley is prepared and fully stocked. It is necessary to check the patient creatinine clearance prior to intra-

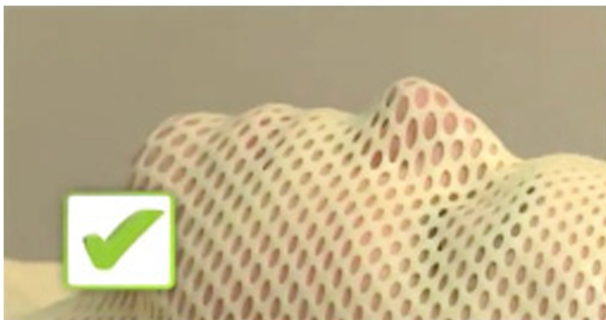


Fig. 3. Good immobilisation of forehead, nose and chin.



Fig. 4. Poor immobilisation of the shoulder and upper thorax.

venous contrast administration. The RTT must ensure that the contrast is heated to 37 °C to match the patient body temperature. According to national and local departmental policies, a radiation oncologist or other nominated clinician may need to be present during the cannulation and contrast administration procedures.

- 3.4. If marking of any nodal regions or post-operative surgical scars is required, this should be performed prior to patient immobilisation.
- 3.5. The patient should be (re)-positioned accurately on the treatment couch with the thermoplastic mask in situ. In cases where the mask has been constructed in the CT room, the patient will already be correctly positioned.
- 3.6. If bolus is planned for the patient's treatment, this should be in situ prior to CT scanning so as to account for the actual bolus to be used at treatment in the dose calculations. This is preferable and more dosimetrically accurate than adding bolus during the treatment planning process and constructing it after the plan has been created. For head and neck cases, individual, customised bolus should be constructed.
- 3.7. Care should be taken to ensure that the treatment couch is set at an appropriate height so as to ensure that the immobilisation device is within the field of view (FOV). This is important, as the immobilisation device must be contoured, along with the targets and organs at risk, prior to beam modelling.
- 3.8. The correct scanning protocol or localisation procedure for the head and neck should be selected as per departmental protocol.
- 3.9. The RTTs must ensure that both patient orientation and the orientation of the topogram or pilot scan are correctly entered at the CT console.
- 3.10. The RTTs should use the topogram or pilot scan to confirm the scanning borders that are required for the head and neck case. It is advisable to check orthogonal topograms and a single axial slice prior to the full scan to check for rotations.
- 3.11. It is recommended to use axial slice thickness of 3 mm or less for head and neck cases. This is to ensure sufficient anatomic detail for target and organ at risk delineation, minimising the partial volume effect, as well as adequate anatomic details on digitally reconstructed radiographs (DRRs) from the treatment planning system (TPS), which will be used in treatment verification procedures.
- 3.12. The dose length product (DLP), number of axial slices and scan length should be documented in the patient chart. This is in line with the European Commission directive 97/43 (Euratom) on the recording of dose reference levels for imaging using ionising radiation.
- 3.13. Following the CT procedure, scan data can be exported to the TPS or virtual simulation software for delineation.
- 3.14. The patient can be removed from the scanner and the thermoplastic mask removed. If needed, a photograph of the patient position can be taken and added to the patient chart. If contrast has been administered, the departmental protocol in relation to observation should be adhered to prior to the patient leaving the department. As a minimum requirement, the patient must remain in the department for a further fifteen minutes.

4. Treatment verification and delivery

General principles

- 4.1. The quality of positioning and immobilisation should be verified on a daily basis by visual inspection of positioning and immobilisation devices. Careful daily positioning of the patient on the neck rest, prior to placing and fixing the immobilisation device is strongly recommended.

- 4.2. The patient weight should be monitored on a weekly basis as significant weight loss or gain may ultimately necessitate a re-plan.
- 4.3. If the mask appears too loose or too tight, the RTT should evaluate the positioning and immobilisation devices, patient weight and volumes through portal imaging (2D) or cone beam CT (3D), as appropriate.
- 4.4. In the absence of 3D volumetric imaging capabilities, it is advisable to perform a new CT scan either between treatment phases or after a pre-defined number of fractions for simultaneous integrated boost techniques, as a check point for target volumes, OARs and external contour variations.
- There are many imaging modalities currently in use throughout Europe and in many instances the choice of modality is resource-dependent. Mindful of this, the following are guidelines as to the method and frequency of image verification.
- 4.5. Orthogonal Planar MV Imaging: 109 respondents in our survey use MV EPs or MV portal films in head and neck verification. When using MV planar imaging, orthogonal images should be acquired to verify the isocentre position. The aperture must be sufficiently large to capture relevant match structures. Image quality using orthogonal planar MV imaging is sufficient for head and neck matching. Images should be acquired with the lowest energy possible for improved contrast. The monitor units used for image acquisition should be kept as low as possible (2–5 monitor units), but

should ensure adequate image quality for the matching procedure.

Orthogonal Planar kV Imaging

- 4.6. Orthogonal kV imaging has the added advantage of a large field of view and improved contrast, compared to orthogonal planar MV imaging

kV Cone Beam CT (CBCT)

- 4.7. Dose presets should be always as low reasonably achievable to obtain sufficient information on volumes and external contour, being mindful that image quality can be degraded due to scatter, noise, artefact or patient size.
- 4.8. 3D imaging capacity brings with it additional information for the RTT about tumour and nodal shrinkage, oedema and the potential impact of weight loss on target and OAR location (Fig. 5).
- #### MVCT (MegaVoltage Computed Tomography)
- 4.9. The selected couch speed and imaged volume should always be as low reasonably achievable to obtain sufficient information on volumes and external contour, being mindful that image quality can be degraded due to scatter, noise, artefact or patient size (Fig. 6).
- 4.10. Although kVCT systems outperform MVCT in terms of low contrast visibility, MVCT images do allow for the visualisation of tumour and nodal shrinkage, oedema and the potential impact of weight loss on target and OAR location.

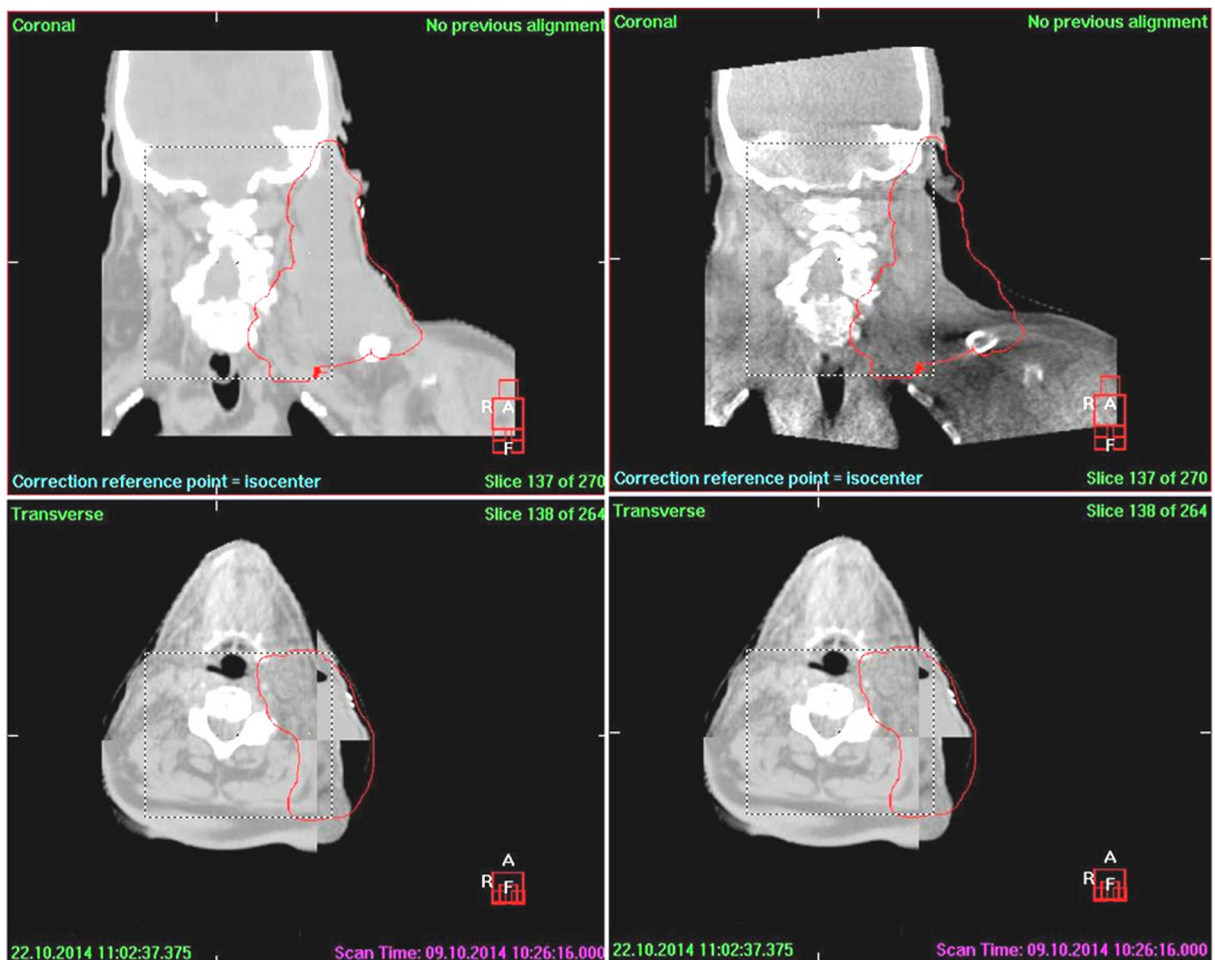


Fig. 5. Tumour shrinkage as observed with kVCBCT.

Furthermore, there are no artefacts due to teeth fillings or implants.

Match structures for image verification

- 4.11. Bony match structures/regions of interest (ROIs) for image verification should be a surrogate for the target and, depending on the tumour location, may include nasal septum, vertebral bodies and processes, maxilla, angle of mandible, base of skull, head of clavicle.
- 4.12. It may be prudent to define *primary* and *secondary* match structures at planning for use during image verification. *Primary* match structures are those whose anatomy are in close proximity to the target and are therefore most useful for position comparison and, for 3D volumetric imaging using CBCT, will determine the position of the clipbox. *Secondary* match structures are structures whose presence are useful for guidance purposes only.

Correction protocols

Selection of online or offline correction protocol for the verification of head and neck radiotherapy patients is multifactorial and department dependent. Resources, equipment, education of staff and required patient throughput are all factors, which will be considered by individual departments when preparing such a protocol. However, it is strongly recommended that some basic principles be adhered to, irrespective of this.

- 4.13. Of primary concern is the reduction of the systematic error. Systematic errors are those that are generally introduced in the treatment preparation stage and hence their non-correction will result in a shift of the cumulative dose distribution. This would likely compromise both tumour control probability and normal tissue complication probability.
- 4.14. Offline correction strategies, such as the no-action level (NAL), extended no-action level (e-NAL) and shrinking action level (SAL) are all proven strategies to reduce the systematic error [1,2]. Sourcing and correcting for the systematic error early in the course of treatment is to be recommended.
- 4.15. The essence of all offline correction strategies is the imaging of the patient on sequential fractions (e.g. $n = 3$) to quantify the correction that should be applied to subsequent fractions. Images should be acquired on sequential fractions to ascertain if the error is systematic or random.
- 4.16. Random errors are those that generally arise in the treatment delivery phase. They are day-to-day discrepancies and result in a blurring of the cumulative dose distribution. Random errors can only be minimised using online correction strategies, that is, daily image guidance.
- 4.17. It is advisable that individual departments quantify their own population- based errors in order to reliably inform their choice of CTV-PTV margins for subsets of head and neck patients and to ensure that their margins are sufficient.

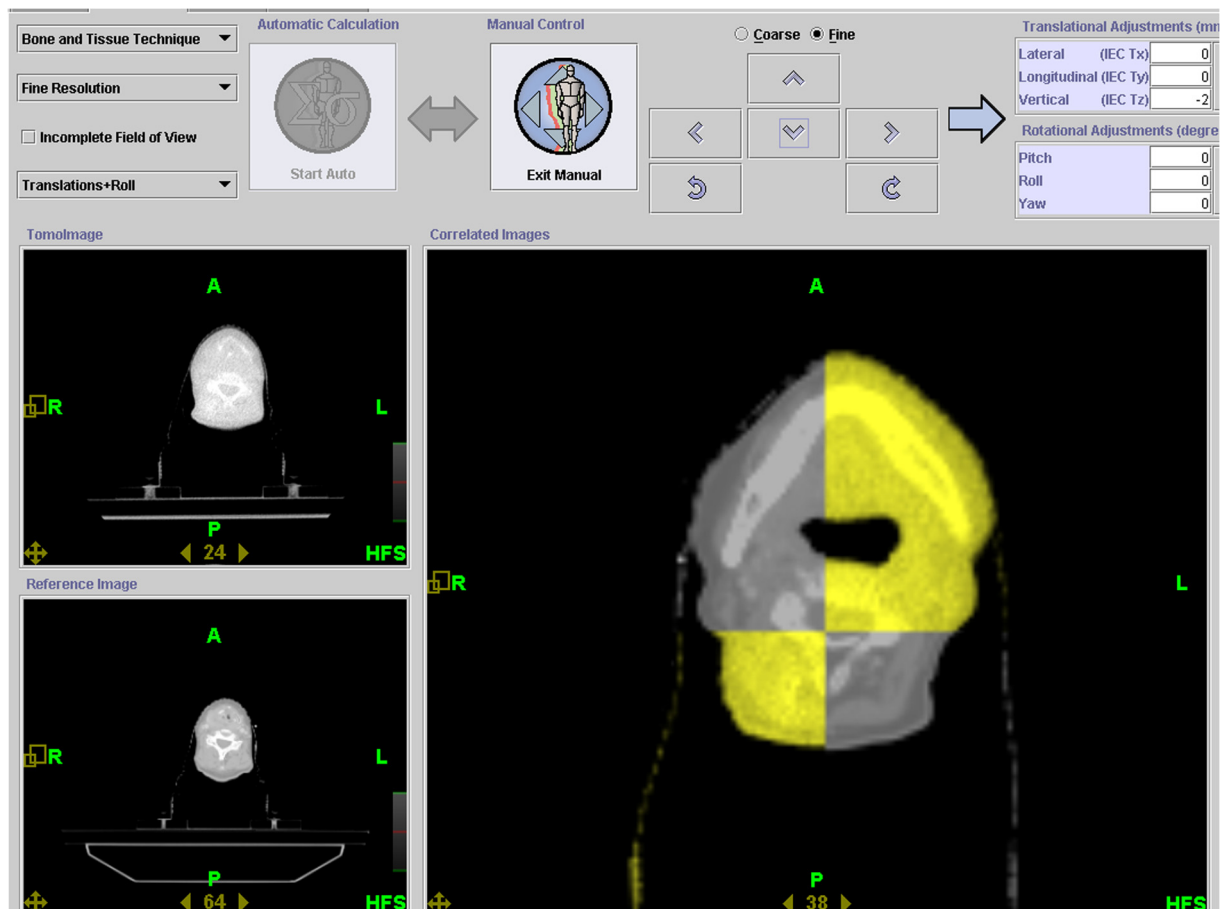


Fig. 6. MVCT imaging and co-registration.

The mechanism for this has previously been clearly outlined by others [3,4] and it is recommended that this be adhered to.

Discussion

The preparation of this guideline document has demonstrated that although there have been substantial changes in the set-up, positioning, immobilisation and verification of head and neck cancer patients over the last number of years across Europe, significant variations still exist. These variations can be attributed to differences in resource type and quality, institutional protocols as well as considerable differences in education level of radiation therapy professionals across Europe [5].

RTTs must be aware of the potential dosimetric impact of poor positioning and immobilisation and/or position verification procedures as well as their influence on required margins for HNC radiation therapy [6–9].

These guidelines have been developed to provide RTTs with guidance on positioning, immobilisation and position verification of HNC patients. The guidelines will also provide RTTs with the means to critically reflect on their own daily clinical practice with this patient group.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tipsro.2016.12.001>.

References

- [1] De Boer HC, Heijmen B. A protocol for the reduction of systematic patient setup errors with minimal portal imaging workload. *Int J Radiat Oncol Biol Phys* 2001;50(5):1350–65.
- [2] De Boer HC, Heijmen B. ENAL: an extension of the NAL setup correction protocol for effective use of weekly follow-up measurements. *Int J Radiat Oncol Biol Phys* 2007;67(5):1586–95.
- [3] The Royal College of Radiologists, Society and College of Radiographers, Institute of Physics in Engineering and Medicine. *On target: ensuring geometric accuracy in radiotherapy*. London: The Royal College of Radiologists; 2008.
- [4] Van Herk M. Errors and margins in radiotherapy. *Semin Radiat Oncol* 2004;14(4):322–5.
- [5] Eriksen J, Beavis A, Coffey M, Leer JW, Magrini S, Benstead K, et al. The updated ESTRO core curricula 2011 for clinicians, medical physicists and RTTs in radiotherapy/radiation oncology. *Radiother Oncol* 2012;103(1):103–8.
- [6] Neubauer E, Dong L, Followill DS, Garden AS, Court LE, Allen White R, et al. Assessment of shoulder position variation and its impact on IMRT and VMAT doses for head and neck cancer. *Radiat Oncol* 2012;7:19. doi: <http://dx.doi.org/10.1186/1748-717X-7-19>.
- [7] Siebers JV, Keall PJ, Wu Q, Williamson JF, Schmidt-Ullrich RK. Effect of patient set-up errors on simultaneously integrated boost head and neck IMRT treatment plans. *Int J Radiat Oncol Biol Phys* 2005;63(2):422–33.
- [8] Yu Y, Michaud AL, Sreeraman R, Liu T, Purdy JA, Chen AM. Comparison of daily versus non-daily image-guided radiotherapy protocols for patients treated by intensity-modulated radiotherapy for head and neck cancer. *Head Neck* 2014;36(7):992–7.
- [9] Kapanen M, Laaksomaa M, Tulijok T, Peltola S, Wigren T, Hyodynmaa S, et al. Estimation of adequate setup margins and threshold for position errors requiring immediate attention in head and neck cancer radiotherapy based on 2D image guidance. *Radiat Oncol* 2013;8:212. doi: <http://dx.doi.org/10.1186/1748-717X-8-212>.