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Research article

A review of Image Guided Radiation Therapy in head and neck cancer from 2009–201 – Best Practice Recommendations for RTTs in the Clinic



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ABSTRACT

Radiation therapy (RT) is beneficial in Head and Neck Cancer (HNC) in both the definitive and adjuvant setting. Highly complex and conformal planning techniques are becoming standard practice in delivering increased doses in HNC. A sharp falloff in dose outside the high dose area is characteristic of highly complex techniques and geometric uncertainties must be minimised to prevent under dosage of the target volume and possible over dosage of surrounding critical structures. CTV-PTV margins are employed to account for geometric uncertainties such as set up errors and both interfraction and intrafraction motion. Robust immobilisation and Image Guided Radiation Therapy (IGRT) is also essential in this group of patients to minimise discrepancies in patient position during the treatment course. IGRT has evolved with increased 2-Dimensional (2D) and 3-Dimensional (3D) IGRT modalities available for geometric verification. 2D and 3D IGRT modalities are both beneficial in geometric verification while 3D imaging is a valuable tool in assessing volumetric changes that may have dosimetric consequences for this group of patients. IGRT if executed effectively and efficiently provides clinicians with confidence to reduce CTV-PTV margins thus limiting treatment related toxicities in patients. Accumulated exposure dose from IGRT vary considerably and may be incorporated into the treatment plan to avoid excess dose. However, there are considerable variations in the application of IGRT in RT practice. This paper aims to summarise the advances in IGRT in HNC treatment and provide clinics with recommendations for an IGRT strategy for HNC in the clinic.

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Introduction

The global prevalence of head and neck cancer (HNC) is 550,000 cases per year [1]. 90% of HNC are squamous cell carcinomas arising in the epithelial lining of the oral cavity, nasopharynx oropharynx, larynx and hypopharynx [2] Treatment approaches vary depending on tumour stage, location and patient characteristics with concurrent chemo-radiation an established standard of care in both early stage and locally advanced disease [3,4]. Prognosis is favourable for early stage disease while survival rates for locally advanced disease have been rising steadily over the past decade [5].

A cumulative radiation therapy (RT) dose of 70 Gray (Gy) is frequently delivered with curative intent in 1.8–2.0 Gy daily fractions. Altered fractionation schedules such as hyper-fractionation, accelerated fractionation, hypo-fractionation and a combination of these are becoming common with the role of radiobiology in local control an important consideration for this group of patients [6].

In Europe 97% of patients are treated using highly complex and conformal planning techniques such as 3-Dimensional Conformal RT (3DCRT) and Intensity Modulated RT (IMRT) [7]. Unlike 3DCRT and conventional RT, a rapid fall off in dose is characteristic of IMRT planning – permitting delivery of a highly conformal dose to the Planning Target Volume (PTV) and improved sparing of surrounding Organs at Risk (OARs) [8,9]. Robust immobilisation and Image Guided Radiation Therapy (IGRT) are essential to minimise geometric uncertainties and the risk of undertreating the target volume (TV) and overtreating adjacent OARs [10–13].

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The application of IGRT strategies in RT practice has grown exponentially in the past decade but internationally large variation has been reported in the availability and utilisation of IGRT in clinical practice [14–16]. Furthermore, IGRT modalities are both underused due to concerns regarding accumulated imaging dose [17] and potential time consuming nature of its execution [18].

This scoping review summarises the evidence for IGRT in HNC and provides recommendations for the implementation of an IGRT strategy for HNC cancer in the clinic.

Materials and methods

Study identification

EMBASE, MEDLINE, Web of Science and Cochrane electronic databases were searched for publications using the following terms in the title or abstract: (IGRT OR “image guided radiation therapy” OR “image guided radiotherapy”) AND (“Head and neck” OR Ear OR face OR head OR jaw OR lip OR mouth OR neck OR eye OR nose OR nasal OR pharynx OR tongue OR salivary OR sinus OR nasopharynx*) NEAR (cancer* OR tumo?r* OR carcinoma* OR neoplasm*) to retrieve all HNC studies reporting IGRT information published between 2009 and 2019. After duplicates were removed 727 papers were identified and screened for eligibility.

Study eligibility criteria

Eligible studies were identified using the Preferred Reporting Items for Systematic Reviews guidelines (Fig. 1) [PRISMA 2015]. Studies not reporting IGRT data for HNC were excluded. Reviews, case studies, non-human studies and surveys were also excluded. All studies reporting any data relating to IGRT in HNC were included. Following screening for eligibility there were 144 studies reporting IGRT data for HNC.

Data extraction

Each regime reported in these 144 studies were categorised according to IGRT modality – 2 dimensional (2D) / planar imaging, 3 dimensional (3D)/volumetric imaging e.g. Megavoltage cone beam CT (MVCBCT), Kilovoltage cone beam CT (KVCBCT) and CT on rails; imaging frequency (daily, weekly, extended No Action Level (eNAL), etc; and key messages from paper (e.g. set up errors and volumetric changes reported, correlation between 2D and 3D imaging, CTV-PTV margins used). The following variables were also noted: author, year, country of first author, type of study and number of participants. All key messages were analysed and categorised for discussion.

Results and discussion

Immobilisation

Thermoplastic masks provide rigid immobilisation minimising set up uncertainties with Head and Neck immobilisation studies consistently reporting average systematic interfraction motion of 2–5 mm with similar average values observed in mediolateral (ML), craniocaudal (CC) and anteroposterior (AP) directions [19,20]. However, some immobilisation studies have reported translational shifts of up to 6 mm [19,21]. Pitch, yaw and roll of 1° have been consistently reported in studies investigating rotational displacements [12,19].

Five-point fixation is recommended with fixation at head, neck and shoulders as standard to minimise sub regional variations in set up errors in the lower neck and shoulders [22–24]. Open face

masks are growing in popularity as they can minimise distress in claustrophobic patients [25,26]. The literature lacks set up data relating to interfraction motion associated with open face masks but mean intrafraction motion of 0.6–1.3 mm has been reported [25–27] – comparable to 0.5–1.8 mm observed with conventional masks [28–30].

CTV-PTV margins, set up errors & imaging frequency

ICRU 50 defines the Planning Target Volume (PTV) as ‘taking into consideration the net effect of all possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV’ [31]. The Gross Tumour Volume (GTV) is delineated based on demonstrable disease while the Clinical Target Volume(s) (CTV) encompass tissue at risk of containing subclinical disease both locally and within regional lymphatics [4]. A PTV margin is added to CTV volumes to compensate for possible daily geometric uncertainties such as set up discrepancies, bed sag and internal organ motion [32]. This CTV-PTV margin should avoid being too liberal – thus unnecessarily irradiating surrounding OARs, or too tight – increasing risk of the CTV falling outside the high dose area. Formulas including those reported by van Herk [33] and Stroom [34] have been used to calculate CTV-PTV margins based on systematic and random errors reported by individual institutions. Mzenda et al. [35] states the importance of using reported institutional set up errors to define CTV-PTV margins. Using a formula to expand margins has been questioned in some studies as set up errors are rarely consistent in their direction and magnitude over a course of head and neck IMRT [36,37]. 5 mm CTV-PTV margins were standard in early IMRT planning [38,39] and these margins have been reported as adequate to account for systematic and random errors in many HNC IGRT studies [40–47].

3–5 mm margins have been reported as appropriate only where daily IGRT [45,48], or alternating day IGRT [49,43] is routine practice. Where daily IGRT is not practiced studies recommended CTV-PTV margins of greater than 5 mm due to potential sub region set up variabilities in mandible, nasal septum and neck [50–53,24,54,55] and unstable set ups in patients with a high Body Mass Index (BMI) [50]. Random errors of up to 2–5 mm have been reported which could result in geometric miss if not imaged and corrected online where standard CTV-PTV margins are used [13,56,57].

Where daily IGRT is routine clinical practice 40–80% reductions in margin sizes are possible [11,13,28,29,58–60]. Widespread use of IGRT has given clinicians confidence to reduce CTV-PTV margins to 3 mm reporting reduced patient toxicities with no reduction in local control [61,62]. Van Kranen et al. reported total OAR doses reductions of approximately 1 Gy per mm reduction in CTV-PTV margin, with no compromise in CTV dose delivery where 3 mm CTV-PTV margins were used [62]. This was also supported in a recent study where a reduction in margins from 5 to 3 mm verified with daily CBCT showed reduced severity, frequency and duration of toxicity whilst maintaining disease-related outcomes [63]. Trans-Tasman Radiation Oncology Group (TROG) Guidelines extensively discuss the variability in CTV-PTV margins for head and neck cancers but typically suggest a 3–5 mm margin [64] and discourage a CTV-PTV below 2 mm regardless of IGRT practices [65]. This is to account for other possible sources of geometric uncertainty such as TV delineation [66] and intrafraction motion [30].

Where institutions wish to avoid daily imaging publications have recommended adopting an eNAL IGRT protocol – imaging day 1–3 and applying a systematic shift depending on departmental action level protocol (2–3 mm generally observed) [67]. However, use of an eNAL protocol may not always be adequate to

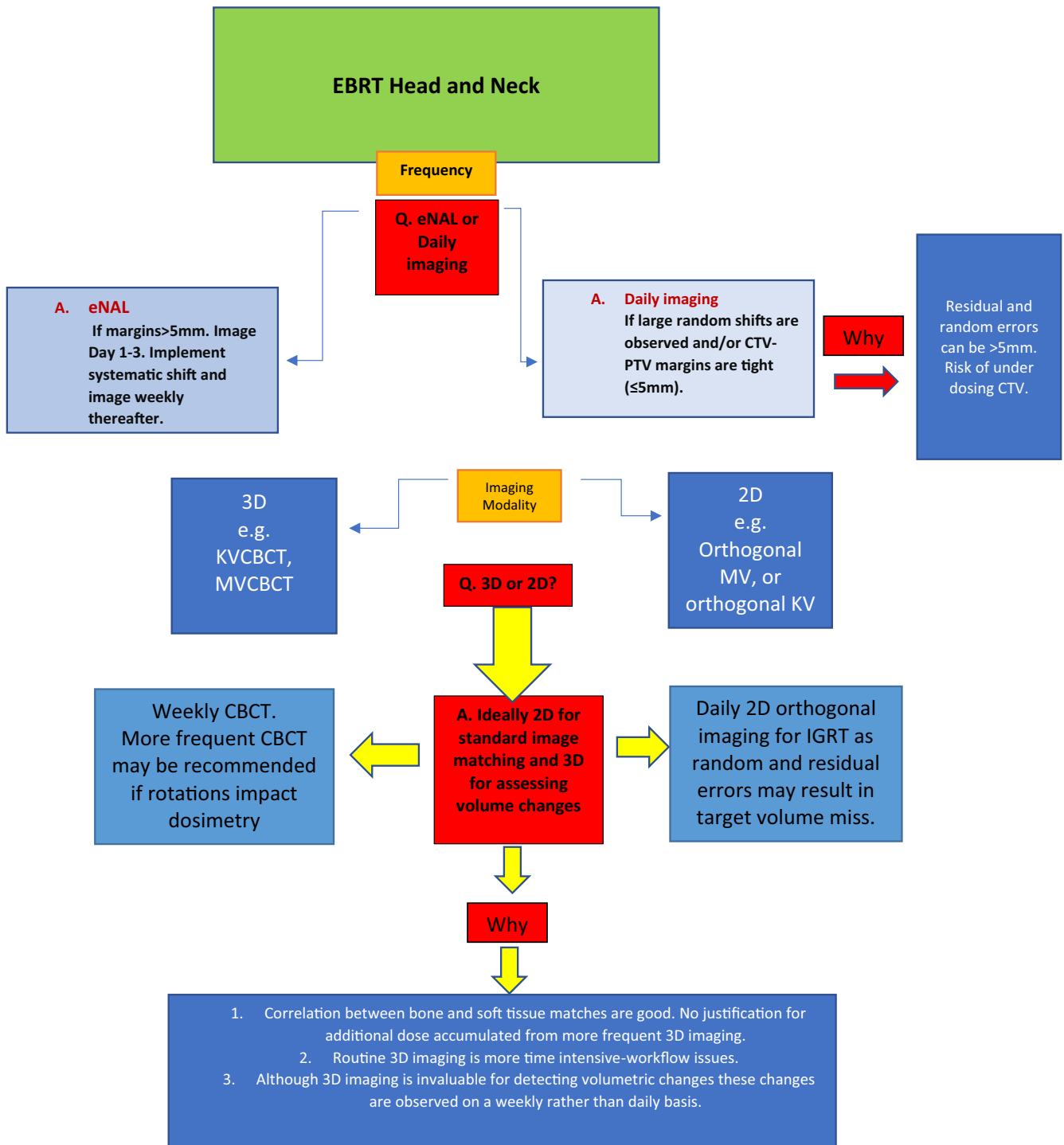


Fig. 1. Flow chart of recommendations.

account for random errors even when 5 mm margins are used [44,48,56].

Imaging frequency is a local, departmental decision but daily online imaging applying all translational shifts is recommended where 3–5 mm margins is clinical practice. Evaluation of setup accuracy at a department level and collaboration between clinicians, planning and treatment staff is strongly advised to validate margins that are utilised, or intend to be utilised, locally which will underpin the IGRT strategy in the clinic.

IGRT modalities and imaging frequency

2D imaging

IGRT modalities have evolved exponentially regarding in room availability and use. 2D and 3D images can be acquired using MV and KV exposures. An orthogonal set composed of a direct anterior/posterior and a direct lateral view should be acquired as a bare minimum to quantify shifts in ML, CC and AP directions [67]. Studies have reported user variability and a lack of consistency in shifts quantified where oblique images are acquired e.g. stereoscopic images [68–70]. KV imaging is the optimum choice for bone match-

ing but in the absence of KV imaging facilities, orthogonal MV images produce enough bone detail for matching purposes [71].

3D imaging

3D Volumetric imaging such as KV CBCT and MV CBCT are extensively used for geometric verification – in conjunction with 2D images or as the solo imaging modality [17,72]. Consensus on its frequency in IGRT strategies is lacking [73] with suggestions that it is often over used in IGRT [15]. HNC image registrations have reported good correlation in translational shifts between 2D and 3D image matches [74–76]. Shifts from 3D bony matched images have reported similar results to those from 2D images [47,77] and standard planning margins provide adequate soft tissue coverage in HNC patients where IGRT matches are based on bone [78]. Bone based matches in HNC produce similar dosimetric outcomes to implanted fiducial matching [79].

Unlike 2D imaging, 3D imaging quantifies both translational and rotational displacements [75]. Robust immobilisation should produce rotations of less than 0.5 ° in pitch, yaw and roll planes [80,19]. Lack of robotic couches in the clinic means rotational shifts were often quantified but can only be corrected by resetting up the patient [81]. Where significant rotations are observed global bony anatomy matching may still result in some treated sub-regions misaligned by >5 mm [82]. Improvements in the relative agreement of HNC anatomical sub regions (particularly the inferior neck) has been observed where rotational corrections were applied [83]. The dosimetric effect of rotations on PTV and OAR dose is multifaceted and depends on the size, shape and proximity of PTV and OARS, degree of dose grade steepness and margin sizes [84]. The reported dosimetric impact of HNC rotations is inconsistent with rotations of up to 3 degrees reporting no compromise to dose coverage [85] and rotations as small as one degree having a significant dosimetric impact [86].

In conclusion, as CBCT acquisition can increase the overall treatment session by three minutes [28] 3D imaging should be scheduled efficiently where the limitations of 2D imaging may compromise the integrity of the treatment plan. Departments that have real concerns regarding rotations and their potential impact on adjacent dose volume constraints (DVCs) should consider acquiring 3D imaging regularly to quantify and correct rotations.

3D IGRT, volume changes and Adaptive Radiation Therapy (ART)

Changes such as tumour shrinkage, weight loss and oedema during a course of RT leads to anatomical and positional variations that can be identified using 3D IGRT such as KVCBCT and MVCBCT [87,88]. Average weight loss of 6–10% over a H&N RT course has been reported [89,87,90] while parotid glands can shrink by up to 30% [91–93,62,94]. Mean TV reductions reported vary – Liu reported a 1.5–1.8% reductions in CTV and GTV [93] while Berwouts et al. reported a 72% and 46.3% reduction in GTV and PTV volumes, respectively, over an entire treatment course [95]. PTV reduction of 50% was also reported by Bujold [66]. Due to the steep fall off associated with modern complex planning techniques, volumetric changes may require modification of original plan to avoid discrepancies in planned and delivered dose [96]. Weight loss can cause over dosage, under dosage and dose inhomogeneity in TVs [97].

Volumetric changes can result in a significantly increased dose to OARS if not corrected for – the parotid glands are especially susceptible to increased mean doses due to the medial migration of the shrinking parotids into high dose areas [98]. Castelli et al. reported a 1.1 Gy increase in mean dose delivered to ipsilateral parotid gland with changes in parotid glands in first 2 weeks indicative of an increased risk of acute xerostomia [98]. Worryingly the contralateral parotid gland which is considered the spared par-

otid gland reports significant increases (11.7–29%) in mean parotid dose [99,100] exceeding DVC thresholds when volumetric changes are not addressed with a replan [101]. Total spinal cord doses can increase by 10 Gy [20] and in one study the maximum dose to the brain stem increased from 49.9 Gy to 52.6 Gy exceeding DVC for this organ [102].

Traditional RT practice accounted for anticipated volumetric changes by rescanning and replanning H&N patients at a fixed point in the treatment course or when triggered by significant weight loss.

21–65% of patients may benefit from plan revision as a result of dosimetric changes [94]. Adjuvant treated patients [103], HPV+ patients [104] and proton based plans [105] have been suggested as some categories of patients where a replan is likely to be beneficial during the treatment course. CBCT scans can produce safe and accurate dose distributions identifying where tumour shrinkage or other anatomical changes might compromise planned dose distributions [106]. This may be a more efficient provisional measure to assess the dosimetric consequences of observed volumetric changes and whether a replan is merited.

Adaptive Radiation Therapy is becoming more prevalent in RT practice, and is inherently reliant upon departmental IGRT protocols. A comprehensive discussion of ART is beyond the scope of this paper but has been well-covered by recent reviews [107,108]. The growing body of ART literature does however provide an insight into when volumetric changes are likely to be detected that merit replanning during the treatment course. Significant volumetric changes have been reported in the second week of treatment [109] with fraction 10 suggested as an optimal ART intervention point by van Kranen et al. [62]. Other studies have suggested week 4–5 of a 7 week course as the most common period where significant volumetric changes are evident [110,111]. Algorithms to identify patients (based on pre-treatment factors) who may benefit from ART have been developed but are still being validated [96].

While 2D and 3D imaging report similar levels of accuracy in daily IGRT, 3D facilities are valuable tools in detecting and calculating dosimetric consequences as a result of volume changes. As volumetric changes are a gradual process, weekly 3D imaging should be sufficient in a RT course to detect volumetric changes of dosimetric consequence.

In contrast to traditional ‘offline’ ART strategies that involve replanning between fractions, ‘online’ ART enables plan adaption in response to daily volumetric changes while the patient remains on the treatment couch prior to treatment delivery [112]. Though still an emerging technology with limited clinical data available, online ART is commercially available with both MR- and CBCT-based treatment platforms [107]. Such systems represent a paradigm shift from linear workflow of conventional RT for RTTs at the treatment console, merging treatment planning with established practices in online IGRT [107,108]. As such, the technological and clinical requirements for online ART are likely to supersede traditional considerations of IGRT protocol development calling for increased education and training and clear protocols in adaptive and on-line approaches and thresholds [113]. The introduction of an MRI based platform in RT requires an MRI compatible immobilisation solution and a comprehensive commissioning process to ensure geometric accuracy of the MRI data set [114] and provision of a reliable MR-IGRT option [115].

Imaging dose

While non-ionising radiation based IGRT systems such as MRI are likely to grow in the next decade this technology is in its infancy and radiation based IGRT systems largely remain the gold standard in routine clinical practice. In diagnostic imaging, Ionising Radiation (Medical Exposure) Regulations (IR(ME)R recommends

establishing dose reference levels locally and monitoring these doses over time [116]. There are currently no similar recommendations for imaging dose in IGRT, likely due to the relatively low consequence of imaging dose when compared with prescribed treatment dose. The AAPM TG180 report provides broad guidance that imaging dose should not exceed 5% of the treated therapeutic dose [117].

Depending on IGRT modality and frequency of use, dose can vary considerably. Accumulated dose from daily orthogonal MV imaging over a standard 35 fraction H&N treatment can deliver approximately 1 Gy to the parotid gland and spinal cord [118] while daily MVCBCT can contribute the equivalent dose of one extra treatment fraction and increase toxicity based on NTCP modelling [119]. kVCBCT imaging typically contributes <0.5c Gy per session to structures within the head and neck region, though this can vary depending on the region measured and imaging system utilised [120,121]. Accounting for KV dose in treatment plan is not standardly possible, but MV imaging doses can be modelled and incorporated into dose distribution at the planning stage [118,122]. Variability in vendor specific customised exposure settings and imaging modality and frequency is an issue in establishing dose reference levels for IGRT protocols [123].

Incorporating MV imaging dose into the treatment plan and avoiding daily MVCBCT imaging is advised to reduce excess dose [124]. Other dose limiting recommendations include: use of a posterior CBCT acquisition angle (90–290 degrees) to reduce eye dose [125], utilising topogram feature to move field of view caudally

[126] and using the lowest numbers of monitor units possible to acquire MV images [124].

At the commissioning and acceptance phase IGRT parameters could be optimised to minimise accumulated, incidental doses from IGRT. All RTTs should be educated on the potential risks associated with accumulated imaging dose and follow the principles of ALARA in IGRT practices.

Conclusion and recommendations

IGRT is now an integral part of RT delivery for HNC patients. Planning margins and techniques should be the strongest indicator when designing departmental IGRT strategies. Intradepartmental collaboration between RT disciplines is advised to ensure the IGRT strategy is appropriate to accurately deliver the treatment plan. As attention turns to the latent effects of RT treatment, RTTs should be mindful of ALARA principles in minimising excessive imaging dose in their daily practice and be prepared for an MR guided future in IGRT.

2D and 3D modalities both have their own unique advantages in HNC IGRT. RTTs must maximise available IGRT systems in an efficient manner by identifying optimum modality and frequency of 2D and 3D IGRT facilities in an HNC treatment course. All RTTs should be competent in image acquisition, registration and interpretation to maximise the benefits of available IGRT facilities with minimum impact on treatment session times providing high qual-

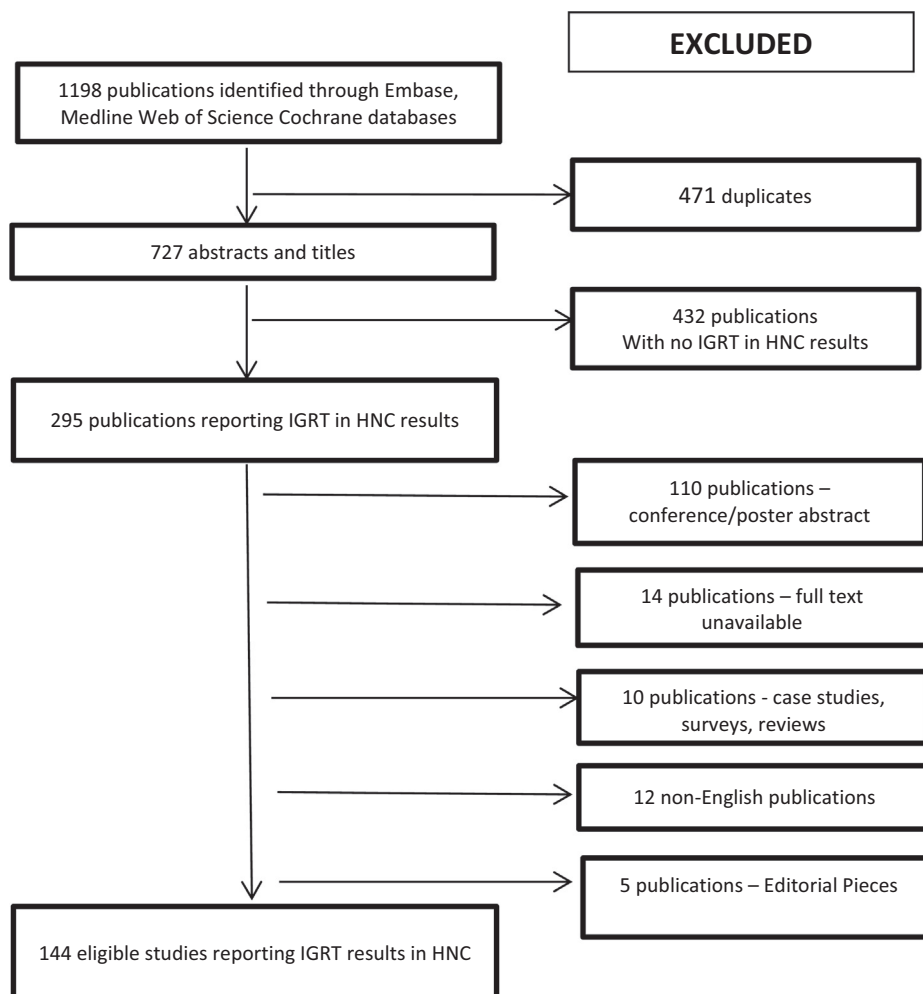


Fig. 2. The process of study identification for the review.

ity treatment to all HNC patients. This should provide a solid knowledge base to facilitate the growing implementation of ART into routine clinical practice where the role of RTTs in its safe and effective implementation cannot be underestimated.

Appendix

See Fig. 2.

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