Interdisciplinary and Regional Cooperation Towards Head and Neck Cancer Interventional Radiotherapy (Brachytherapy) Implementation in Southeast Asia

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INTRODUCTION

The overall incidence of head and neck cancer (HNC) is rising globally with a 30% projected increase annually by 2030. In 2020, HNC accounted for 16.5% of all new cases of cancer in Southeast Asia (SEA).[1] The incidence of oral cavity cancer in the region was particularly high and ranked fourth

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for incidence and fifth for mortality. This challenge requires close collaboration among different medical disciplines to improve healthcare outcomes in this patient population.

HNC treatment decisions often require balancing tumor control with toxicity and functional preservation. Brachytherapy (BRT), which entails the placement of radioactive sources directly or close to the tumor allows for high doses to be limited to the tumor itself while limiting irradiation of the surrounding tissues to very low, if not negligible doses, thereby minimizing the probability of normal tissue complications. Hence it is a particularly useful tool in HNC management.

In the primary setting, BRT can be used alone (eg, in the treatment of lip or nasal vestibule cancers), with local control reported to be greater than 90% at 5 years in early-stage disease.[2] It can also be used for radiotherapy dose escalation in combination with external beam radiotherapy (EBRT) and/or chemotherapy (eg, in advanced oral cavity tumors) for more advanced tumors, with published local control rates of up to 84%.[3] In the salvage setting, BRT can be used in previously irradiated cancers or second primary cancers arising in a previously irradiated field. For re-irradiation of recurrent lymph node metastases of HNC, local control rates of 60–70% have been reported.[4]

Better outcomes have been reported in modern studies that report on recent advancements, leading to the adoption of the term interventional radiotherapy (IRT). Despite this, several factors limit the widespread use of IRT within SEA and most of the Asia-Pacific region. Firstly, there is a lack of comprehensive training and education for qualified multidisciplinary teams to perform these complex procedures. The integration of IRT would require collaborative and interdisciplinary approach among specialties. Secondly, there is increasing preference for more advanced EBRT procedures, such as proton therapy or stereotactic body radiotherapy (SBRT), thus diluting interest and enthusiasm for IRT. These techniques do not require surgical interventions as in IRT, which entail steep learning curves. Therefore, implementation and evidence generation are relatively easier and quicker. Currently, the availability of proton therapy in SEA remains limited due to high capital costs; the evidence and indications for SBRT in head and neck cancers remain limited to palliative treatment.[5] IRT can potentially provide even greater conformity than these techniques and would require lower capital costs. Thirdly, there is great variability in literature and guidelines on dosages and techniques, and in particular cumulative dose constraints and dose-volume data are scarce in the salvage setting. Comprehensive data collection and research are required to provide more uniform treatment recommendations.

We review the evolution of BRT to IRT and its current and potential roles in HNC management, and the requirements and challenges towards its effective and sustainable implementation in SEA.

From brachytherapy to interventional radiotherapy

The concept of radioactive substances was discovered in 1896 by Becquerel, and their potential for halting cancer tissue growth was observed in the early 1900s by Alexander Graham Bell, Pierre and Marie Curie. This discovery was assimilated with advanced medical technology leading to radiation therapy. At first, it was only delivered using external beam sources called teletherapy (*tele-*, long distance), or external beam radiotherapy. Subsequently, a novel technique was developed that entailed direct or close application of these sources into body surfaces or cavities or implantation into tumor, called brachytherapy (*brachy-*, short distance). The first clinical application was documented in 1903, when the technique successfully treated an inoperable cervical cancer. In 1920, the therapeutic implantation of radium was pronounced by the Curie Foundation. Other terms came into use, including curie therapy, highlighting the role of The Curies in the discovery and development of the clinical use of radioactivity, and plesiotherapy (*plesio-*, near) to refer specifically to the application to external body surfaces or skin.[6,7] The newer term *interventional radiotherapy* (IRT) mainly highlights the use of cross-sectional imaging, volume-based dosimetry and an increasingly interdisciplinary approach to implantation[8,9] that is associated with more modern techniques and recent publications.

For the succeeding sections, we will use the term *brachytherapy* to refer to the era roughly before

2017, when two-dimensional, point-based dosimetry was employed, and *interventional radiotherapy*, to refer to the era starting 2017, with the greater adoption of three-dimensional, intensity-modulated, volume-based dosimetry and other advancements.

Interventional radiotherapy for head-and-neck cancers

The main role of traditional BRT in HNC has been in early and accessible disease, such as in the lip, oral cavity, oropharynx, nasopharynx and superficial (skin and mucosal) cancers, where sufficient doses could be given for long-term tumor control while allowing for anatomic and functional organ preservation.[10,11]

Previously, the evidence for effectiveness and safety of BRT for HNC came largely from rich, decades-long experience with the use of temporary low-dose-rate wire implants in high-volume centers and a few, small clinical trials (Table 1). In 2009, the Head and Neck Working Group of the European Brachytherapy Group [Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO)] published a consensus guideline to guide and harmonize clinical practice and outcomes reporting.[12]

In 2017, an update to this guideline was published, highlighting the emergence of newer technologies such as the *stepping-source technique* that required robotic manipulation and temporary high-dose-rate seed source loading, and *image-guided brachytherapy*, that entailed the use of cross-sectional imaging for volume-based dosimetry.[13] Unlike the radioactive wires that were associated with more rigid geometry that limited dosimetric optimization, the use of radioactive seeds allowed for more flexible geometry and thus greater dosimetric optimization. Compared to point-based dosimetry, volume-based dosimetry better guided tumor dose coverage and organ sparing. These advancements have led to improved tumor control, reduced side effects and extended applications beyond traditional indications to other head-and-neck subsites and treatment settings.

After the 2017 GEC-ESTRO update, the HNC IRT has become an effective cosmesis-preserving alternative to surgery such as for nasal vestibule cancers,[14] and as a viable alternative to salvage EBRT in the setting of re-irradiation.[15] Recent publications support its effectiveness and safety in emerging applications such as in paranasal sinus and parotid cancers, by incorporating advanced technologies such neuronavigational and stereotactic systems, and a revival of the use of low-dose-rate sources in the form of permanent seed implants.[16,17]

More clinical trials have been published that provided better-quality evidence for the effectiveness and safety of the procedure, particularly with the incorporation of the above advancements that are now more commonly associated with IRT (Table 1). Nevertheless, head-to-head comparison between treatment options (surgery, EBRT, or IRT) for certain head and neck subgroups and Asian studies are lacking. Information from the latter is vital to better guide the integration of IRT into clinical guidelines, especially if health economics are to be considered.[18] India serves as an example in which the country has published its own guidelines after sustained research, publications and clinical implementation.[19] A recent randomized trial from India comparing intensity-modulated radiotherapy (IMRT) alone versus combining IMRT with BRT showed statistically significant reduction in xerostomia with the addition of BRT.[20]

For most other low- to middle-income countries (LMICs), implementing IRT for HNCs might be a challenge.[18,21,22] In many healthcare facilities, adequately equipped radiotherapy facilities and skilled radiation oncologists and radiotherapy and nursing personnel are lacking – strategic organizational planning and professional training will be critical.[18,21,23] The evidence base for IRT, while growing, remains limited. Furthermore, local and regional studies are scarce. This scarcity is even more glaring in resource-limited settings, where treatments must meet an incremental cost-effectiveness ratio to be better justified.[18] Finally, the awareness among radiation oncologists and other specialists regarding the recent evolution of IRT and associated improvement in clinical outcomes also remain limited, as evidenced by the common omission of brachytherapy lectures or discussions in recent multi-specialty head-and-neck oncology conferences.[24] This would be instrumental as cancer management

Table 1. Modern Studies on Brachytherapy or Interventional Radiotherapy in Head and Neck Cancers

Authors, year	Location	Study design	Population (n, site or setting)	Intervention	Outcome
Publications before 2017					
Inoue, et al. (2001)[3]	Japan	RCT	59, early oral tongue cancer	HDR versus LDR BRT	LDR versus HDR 5y LC: 84%, 87% 5y nodal control: 77%, 76%
Rudžianskas, et al. (2014) [27]	Lithuania	RCT	64, various recurrent HNC	HDR BRT versus 3D-CRT EBRT	HDR versus 3D-CRT 2y OS: 67%, 32% 2y LC: 63%, 25% Lower late toxicity with HDR ($p = 0.001$).
Rosenblatt, et al. (2014)[28]	Austria	RCT	274, nasopharyngeal carcinoma non-metastatic (grade WHO I-III)	Neoadjuvant chemotherapy + concurrent chemoradiation ± BRT boost	No significant difference in DFS ($p = 0,496$) and OS ($p = 0.742$)
Teudt, et al. (2016)[29]	Germany	RET	9, various HNC (squamous cell carcinoma)	HDR BRT	Best outcome with exclusive interstitial IRT where satisfaction could not be achieved with surgical reconstruction. 2y relapse free-rate of 82%. Mild skin irritation post BRT: 4/9
Publications 2017 onwards					
Budrukkar, et al.(2017)[30]	India	PRO	35, superficial HNC (T1/2, N0)	Surface-mold BRT	5y LC 82% 5y DFS 69% Local recurrence: 5/35
Bussu, et al. (2019)[15]	Italy	NCT	58, various HNC	Definitive or perioperative IRT	2y DFS 89% 2y RFS 82%
Khan, et al. (2019)[31]	United states	RET	51, recurrent HNC	Salvage surgery, followed by interstitial BRT	5y and 10y OS: 56%, 46% Post-procedural AE: 21/51, of which, 8 were severe. No perioperative death or carotid hemorrhage.
Tagliaferri, et al.(2020)[32]	Italy	NCT	20, primary nasal vestibule cancers	IRT versus surgery	Comparable functional and cosmetic outcomes. Less AE with IRT
Xiang & Wu (2020)[33]	China	NCT	58, various HNC	HDR BRT ± IMRT	3y OS: 82.3%, with biologically effective doses of 78.5 Gy (73-90)
Soror, et al. (2023)[34]	Germany	RET	60, recurrent HNC	HDR IRT	5y local RFS: 37.3%, AE: 28/60, of which 21 were severe
Budrukkar, et al. (2023)[20]	India	RCT	90, early-stage oropharyngeal cancers	IMRT alone vs IMRT + BRT	Xerostomia using salivary scintigraphy 44% IMRT arm vs 14% IMRT + BRT arm ($p = 0.008$)

Abbreviations: 3D-CRT, *three-dimensional conformal radiotherapy*; AE, adverse event; BRT, *brachytherapy*; DFS, *disease-free survival*; EBRT, *external beam radiation therapy*; HDR, *high-dose-rate*; HNC, *head-and-neck cancer*; IRT, *interventional radiotherapy*; LC, local control; NCT, *non-randomized clinical trial*; OS, *overall survival*; PRO, *prospective cohort*; RCT, *randomized clinical trial*; RET, *retrospective cohort*; RFS, *relapse-free survival.*

in general has become multidisciplinary and IRT has become increasingly interdisciplinary. Strong collaboration among healthcare stakeholders – policy makers, hospital administrators, clinicians and patients will be key to develop and sustain comprehensive IRT care facilities.[21,22]

Towards implementation of head and neck interventional radiotherapy in Southeast Asia

IRT HNC has become an effective and invaluable modality in HNC management in Europe, as well as some Asian countries such as India, Japan and China. In SEA, the potential of IRT could be realized and expansion to other indications be allowed if two complementary conditions are met – that the practice and uptake of IRT is increased and that this increase in clinical activity is able to generate scientific evidence to support the technique, or to guide further research towards its development or refinement. We discuss how this might be achieved in Southeast Asia.

Hub-and-spoke partnerships. When initiating a HNC IRT program, the caseload in a single center may be initially limited, slowing progress along the learning curve. From a broader and pragmatic perspective, it would perhaps be most effective and efficient to identify institutes that could be developed into referral centers or *hubs* for HNC IRT. Centers that have adequate experience in image-based and interstitial IRT techniques for cervical, endometrial, or prostate cancers, which are the most common applications, are the best suited to expand their applications to head-and-neck cancers. Administrative support, good interdisciplinary culture and working relationships would greatly help in expansion; a functional head-and-neck multidisciplinary tumor board may be a good indicator. A healthy in-house census or a strong referral network, the presence of training programs in radiation oncology, head-and-neck surgery, medical oncology, medical physics, oncology nursing as well as good research capability and culture, all indicate opportunities for sustainability, in terms of clinical, training and research activities.

In HNC, IRT applications vary in complexity and therefore the required expertise, depending on the site and setting (Table 2). Centers that are yet beginning to gain experience in head-and-neck IRT could start with low-complexity applications and then move towards more complex cases. Virtual inter-hospital hub-and-spoke tumor boards could facilitate sharing knowledge and skills in patient selection, implant planning, quality assurance, troubleshooting and other areas. When potential hubs have been identified in a region or country, these future

Table 2. IRT Applications, Complexity and Interdisciplinary Requirements

Sites	Complexity	Interdisciplinary Technical Input	Interdisciplinary Techniques
Surface			
Skin	Low	Optional	
Intra-oral (palate, alveolar)	Low	Preferred	Personalized applicator design and fabrication
Intracavitary			
Nasopharynx	Moderate	Optional	
Interstitial			
Lip	Moderate	Optional	
Nasal vestibule	Moderate	Optional	
Eyelid	Moderate	Preferred	
Oral cavity (oral tongue, buccal mucosa)	Moderate	Optional	
Oropharynx	High	Mandatory	Tracheostomy
Nasopharynx	High	Mandatory	Endoscopic guidance
Perioperative			
Oral cavity (oral tongue)	High	Mandatory	Surgical
Paranasal sinus	High	Mandatory	Surgical
Neck	High	Mandatory	Surgical

hubs could be the *spokes* in an international hub-and-spoke IRT tumor board. In this framework, an international hub could provide guidance to the spokes, who could also learn from each other's cases and experiences. This approach has been shown effective for other diseases and settings.[25]

Interdisciplinary collaboration. While a multidisciplinary approach entails collaboration among different disciplines, the specialists stay within their boundaries and approach the problem from the perspective of their own discipline. Interdisciplinary entails integration of knowledge and methods from different disciplines to arrive at a common understanding and derive a solution.

Ideally, interdisciplinary decision-making should guide patient selection and validation of indication for IRT. Interdisciplinary inputs during implantation planning may be necessary for certain low- or moderate-complexity cases, where inputs may be important in the design of a personalized applicator, or a specialist evaluation with regard to clinical tumor extent may be critical. Highly complex cases require interdisciplinary collaboration in implant planning and execution, such as when endoscopic guidance or a surgical intervention is necessary to carry out the procedure safely, or when IRT is planned as a perioperative procedure. Perioperative IRT entails implantation after tumor resection and during the same operation. A center that is unable to develop an interdisciplinary culture will be unable to implement highly complex head-and-neck IRT applications.

National and regional collaboration. Interdisciplinary collaboration within each center is critical in achieving optimal patient outcomes and advancing clinical practice; across centers, it will facilitate multicenter research and lobbying for health policy changes.

Harmonization of surgical approaches and radiotherapeutic protocols to certain extents across centers would allow comparability of outcomes and transferability of skills and technical innovations. Harmonization of collected clinical data into a collaborative registry would allow for more effective and efficient generation of scientific information to support current practice or guide its development.[26] It may also serve in identifying areas of improvement or expansion of indications of IRT. This harmonization at the clinical and research levels could facilitate the establishment of a national training and referral consortium. National consortia could then establish similar cooperation in training and research at the regional level.

Lobbying for professional awareness and health policy support. Finally, awareness of the technique's evolution should extend beyond the radiation oncology community and IRT team. In published literature, the term *brachytherapy* would be associated with older techniques and suboptimal outcomes. Rebranding to IRT could facilitate recognition of the technical and technological evolution and the resulting improvement in clinical outcomes, especially among professions outside the field of radiation oncology. Conversely, this may add to the confusion due to multiple terminologies used.

Dissemination of these advances in professional societies could also increase awareness and inclusion of the technique in relevant discourses that shape clinical guidelines and health policies. This could then shape a more responsive and conducive health system and public funding.

CONCLUSION

Interventional radiotherapy has improved clinical outcomes compared to traditional brachytherapy and has extended its applications in HNC. Multidisciplinary collaboration is essential for effective clinical implementation. Multisectoral discussion among all stakeholders is essential for efficient resource allocation and referral systems, and therefore sustainability. Strategic cooperation in the national, even regional levels will be instrumental in evidence generation and capacity building.

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