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Review Article

Postoperative Intensity Modulated Radiation Therapy in Oral Cavity Cancer

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Abstract.

Intensity-modulated radiation therapy (IMRT) has been widely accepted for treatment of head-and-neck cancers (HNC). The higher conformality of dose distribution produced by IMRT allows tight dose gradients around the target and sharp fall-off near the boundaries. Thus, we can deliver higher dose to the tumor or risky target without increase, or even with decrease, in dose distributed to normal tissues. This may result in improvement of local control as well as reduction of normal tissue damage. However, most published studies of IMRT have focused on treating diseases with gross tumor, resulting in a lack of consensus regarding use of postoperative IMRT for HNC. This unmet need for HNC is of great importance for oral cavity cancers because surgery remains the mainstay treatment. This article reviews the issues in target selection and delineation, dose specification, and the patterns of failure from published reports for postoperative IMRT in oral cavity cancers. We have attempted to provide more and detailed information as a reference for daily practice of treating physicians.

Keywords **:** Oral cavity cancer, IMRT, Postoperative radiotherapy

綜合評論

術後強度調控式放射線治療於口腔癌之應用

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中文摘要

主題：強度調控式放射線治療於頭頸部癌症的治療已被廣泛的使用。由於強度調控式放射線治療可以提高劑量分布的順形性，使得腫瘤體積內得到充足的放射線劑量並進而減少因放射線治療所引起的毒性反應，所以可達到提高腫瘤控制率和降低正常組織併發症的目的。目前強度調控式放射線治療多應用在沒有切除的頭頸部癌症上；反之，在手術後輔助性治療的運用則較少被探討。口腔癌病患多先接受手術切除，放射線治療的角色則以術後輔助性的型態較多。此篇文章回顧了近年來於口腔癌病患接受術後強度調控式放射線治療的應用，包括治療區域的擬定、劑量的給予、及治療後局部復發的形式，以期能幫助臨床上更多運用。

關鍵字: 強度調控式放射線治療、口腔癌、手術後放射線治療

INTRODUCTION

The prevalence of oral cavity cancer (OCC) remains high and keeps increasing in Taiwan. According to registration data from the National Department of Health in Taiwan [1], OCC was the sixth most common cancer in 2006 and accounted for the fourth largest number of cancer deaths in males. Compared to the United States and Western Europe, the mortality rate among males is relatively higher in our country (Table 1), which might be related to the high prevalence of betel nut chewing [2-4]. Clearly, clinical and basic research focusing on OCC remains important.

The main treatment of OCC is wide excision with or without neck dissection. Except for those very-early-stage or inoperable tumors, adjuvant radiotherapy remains a crucial component of the modern multidisciplinary treatment [5-7]. Among various radiotherapy techniques, intensity-modulated radiotherapy (IMRT) has been widely accepted for the treatment of head and neck cancers (HNC). IMRT employs a powerful and advanced computer program that plans a precise radiation dose distribution in three dimensions based on individual tumor size, shape and location. Remarkably, it allows for higher radiation doses than traditional radiotherapy methods and, at the same time, spares more surrounding healthy tissues. HNC are ideal sites for IMRT application because the tumors often occur in close proximity to multiple critical normal tissues such as brainstem, optic chiasm, optic nerves, and the spinal cord. In addition, because there is a lack of organ motion in the head-and-neck region, daily patient setups can be reproduced accurately by using adequate immobilization. Furthermore, because head-and-neck cancer often presents at a locally advanced stage, the dose escalation to primary tumor using IMRT may result in an improvement in local control without increase in toxicities [8-11]. For example, a superior loco-regional outcome following IMRT has been reported for nasopharyngeal [12-14] and oropharyngeal tumors [15-17]. It is also noted that a tendency towards better outcome has been described in hypopharyngeal cancer patients received IMRT [18]. However, the majority of clinical IMRT investigations were focused on treating disease with gross tumor, leaving a lack of consensuses regarding use of post-operative IMRT for HNC. This unmet need for HNC is of great importance for OCC because surgery remains mainstay treatment and the rate of high risk patients is still high.

Concerning the clinical application of IMRT in treatment of OCC, several crucial issues should be addressed. First, the anatomical alteration is usually great after radical surgery, making tissue boundary ambiguous. Second, a significant inconsistency in target volume delineation and nodal basin selection exists even between physicians in the same single department. Third, no available data of long-term outcome for OCC treated by IMRT that can be used as a guide for adequate target delineation and nodal basin selection. Last, unlike the other HNC, the guideline for OCC IMRT is lacking, especially that for post-operative setting.

Inadequate coverage of risky regions when depicting target volumes could easily compromise the clinical impact of the ideal dose distributions and may result in local recurrence. Among the target volumes, the clinical target volumes (CTV) are the most important ones due to intended coverage of tumor bed and preoperative tumor volume. Unfortunately, vigorous distortion of the normal head-and-neck anatomy usually happens, making appropriate target delineation a big challenge to radiation oncologists. This obstacle is of critical importance in OCC because these patients have poorer locoregional control compared to cancer in other head-neck-neck regions [19,20]. To improve

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Table 1. Worldwide mortality rates in patients treated for carcinoma of the oral cavity; age-adjusted death rates per 100,000 population

Death rate	Taiwan (2006)	Japan (2003)	HK (1999)	Korea (2001)	U.S.A. (2000)	Canada (2000)	U.K. (2002)	France (2000)
M	17.7	6.5	12.8	2.4	3.6	3.9	4.4	13.7
F	1.4	2.5	3.4	0.7	1.8	2.0	2.3	2.7

treatment outcome, we should make more effort to find out both failure patterns and prognostic factors of OCC following treatment with IMRT. Toward this end, this paper reviews the target delineation, selection, dose specification, and comparison of failure patterns of published postoperative IMRT studies for OCC.

TARGET DELINEATION FOR POSTOPERATIVE OCC

Delineation of the Primary Tumor CTV

The surgery for OCC consists of composite excision of the primary tumor area with or without modified/selective neck node dissection. After radical removal of tumor, various new reconstructive procedures using loco-regional or free flaps are applied to facilitate earlier functional restoration. All these procedures cause extensive changes in normal anatomy over the operated area and lead to difficulty in delineating the CTV. It is of concern that both overextension and underestimation for coverage of CTV would mitigate the clinical benefit of IMRT. Thus, optimal coverage by CTV remains an important but uncertain issue.

From literature reviews, various descriptions for determination of pos-operative CTV in OCC are listed in Table 2. For example, Laura et al. included the tumor resection bed, the surgical neck node dissection bed, and the surgical scars for CTV [21]. Lee et al. defined CTV as the preoperative gross tumor volume and the potential direct routes of microscopic spread [22]. Yao et al. reported 55 patients with OCC treated with IMRT. They defined CTV1 as tumor bed which included 5-10 mm margin for preoperative tumor volume determined from preoperative images, surgical and pathologic findings, as well as surgical defects and postoperative changes [23]. In a recent study by Studer et al., 10-15 mm margin for preoperative gross tumor volume was used to generate high-dose CTV [24]. Taken together, there are still numerous questions in delineating CTV around the operative bed in the daily practice of treating physicians. The most difficult part is to define the optimal margin around these anatomy-altered sites to ensure the possible routes for microscopic spread. Furthermore, we do not have convincing evidence to make us comfortable while putting additional margins for high-risk pathologic features such as close/positive margin, extracapsular extension and soft tissue invasion. To answer these questions, we do need more clinical trials addressing these issues, which may cost a lot of medical resources but only be of interest to radiation oncologists.

Delineation of the Lymphatic CTV

There are several guidelines developed for nodal classification [25-27]. In 2003, a consensus was proposed and adopted by the major international cooperative groups to determine the lymph node levels and related CTVs in the node-negative neck [28]. Level Ia corresponds to the old-style term “submental nodes”. These lymph nodes are located in a triangular region limited anteriorly by the platysma muscle and the symphysis menti, posteriorly by the body of the hyoid bone, cranially by the geniohyoid muscle or a plane tangent to the basilar edge of the mandible, caudally

Table 2. Publications on target delineation and dose specification in postoperative IMRT for oral cavity cancer

Author	Delineation for CTV1	Dose to operative bed(Gy)	Dose to subclinical disease(Gy)
Dawson et al. [21]	Resected tumor bed + surgical neck node dissection bed + surgical scar	61.2 Gy (57.6-64)	50.4 Gy (46-54)
Lee et al. [22]	Preoperative gross tumor volume + potential routes of microscopic spread + margin for setup errors	66 Gy	Upper neck : 60 Gy Lower neck & SCF : 50-54 Gy
Chao et al. [37]	Surgical bed or nodal region, include positive/close margin and ECE (+) sites	68.53 +/- 4.71Gy	60.96 +/- 5.33 Gy 50.4 Gy for lower neck
Eisbruch et al. [20]	Not mentioned	61.2 Gy (57.6-64)	50.4 Gy (46-45)
Yao et al. [23]	5-10 mm margin for preoperative tumor volume determined from preoperative image, surgical and pathologic findings, surgical defects and postoperative change	60-66 Gy	60 Gy for PTV2 50-54 Gy for PTV3
Studer et al. [24]	10-15mm margin for preoperative gross tumor volume	66 Gy (60-70Gy)	46-54 Gy

by the hyoid bone, and laterally by the medial edge of the anterior belly of the digastric muscle. Level Ib corresponds to the submandibular nodes. It is located within the boundaries of the digastric muscle, platysma and the body of the mandible. The entire submandibular glands are included. Level II corresponds to the upper jugular nodes. It extends from the skull base to the bottom of hyoid, posterior to the submandibular gland, the anterior edge of the carotid artery and the posterior belly of the digastric muscle, anterior to the posterior edge of the sternocleidomastoid (SCM) muscle, medial to the medial edge of the carotid artery and the paraspinal muscles, and lateral to the SCM and the platysma. Level III corresponds to the midjugular nodes. It extends from the hyoid to the bottom of the cricoid cartilage, contains internal carotid artery and is confined to area in between SCM and paraspinal muscles. Level IV corresponds to the lower jugular nodes. It extends from the bottom of the cricoid cartilage to 2 cm above the sternoclavicular joint. The anterior, posterior, lateral and medial borders are the same as level III. Level V corresponds to the posterior triangle nodes. It lies posterior to the back of the SCM muscle and anterior to the anterior edge of the trapezius muscle. Finally, Level VI corresponds to the paratracheal and pretracheal nodes from the bottom of the hyoid and the top of the manubrium.

In addition, Grégoire et al. proposed several principles for depicting primary and nodal CTVs in the node-positive and post-operative neck [28], They announced that the entire surgical bed should be encompassed, especially in cases of extracapsular extension (ECE). If pathologic involvement of level II is found, extend the upper border to include the retrostyloid space up to the base of skull. In case of involvement of level IV or Vb, extend the lower border to include the supraclavicular fossa (SCF). When an involved lymph node abuts a muscle, include this muscle at least for the entire invaded level and at least add a 1-cm margin in all directions. In addition, when an involved lymph node is located at the boundary with another level, it is recommended to extend the

Table 3. Published locoregional failure analysis of postoperative IMRT for oral cavity cancer

Author	Number of OCC	Failure No. of OCC	Median time to locoregional failure (month)	Pattern of failure		
				Primary site	Ipsilateral neck	Contralateral neck
Dawson et al. [21]	13	6	4.5 (3-8)	3	Level II 2 RP 2	Level Ib 1[a] III 1 IV 1[b]
Chao et al. [37]	15	5	7 (0-12)	2	level Ia 1 III 2 IV 1	0
Yao et al. [23]	55	9	4.1 (3-12.1)	5	Level I 1	Level Ib 2 III 1[b]

[a]Marginal recurrence ; [b]Out-field failure

CTV to include this adjacent level.

However, in the post-operative setting, there is still ongoing debate whether the full operative bed should receive a prophylactic dose only to the pathological node-positive levels or a full dose to the entire neck. Similar to that for primary tumor CTV, neck dissection usually disrupts some anatomical landmarks and borders between each level, making contouring nodal levels an uncertain task. Therefore, establishment of guidance for adequate delineation of the lymph node regions is crucial to improve the inconsistency of IMRT treatment.

SELECTION OF THE LYMPHATIC CTV

In general, the coverage for the CTV of the neck depends on the primary disease site as well as the extent of the tumor. Lindberg et al.[30] recorded 2044 head and neck cancer patients in the M.D. Anderson Cancer and found that ipsilateral submandibular and subdigestric nodes were most frequently involved in oral tongue, floor of mouth, and retromolar trigone cancers. Mid-jugular nodes were the next commonly affected. Similar pattern of nodal metastasis was reported by Byers et al. [31] and Shah [32] after performing elective neck dissection to detect microscopic metastasis for cancers of the lower gum and buccal mucosa. Grigoire et al. [33] further analyzed distribution of metastatic lymph nodes with unilateral prophylactic and therapeutic radical neck dissection (RND) and found that level I and II were the most commonly affected in both procedures. Moreover, the percentage of level III node involvement in prophylactic RND arm was only slightly elevated in oral tongue cancer but significantly higher at all sites in therapeutic RND arm. Level IV node was rarely metastasized in clinically negative neck, but the incidence was more than 15% in clinically positive neck [31-33]. Level V node involvement was infrequent at all subsites of cancer in the OCC despite varying clinical neck status [31,34]. Furthermore, contralateral neck metastasis in OCC was obvious in oral tongue or floor of mouth cancers, advanced primary T staging, or tumors across the midline [35-37]. It is also suggested that the surgical specimens could provide helpful information in determining the neck node levels at risk. Collectively, we proposed that for patients without nodal involvement, ipsilateral level I to III should be enrolled in lymphatic CTV. For those with nodal metastasis, ipsilateral level I to IV with or

without level V and SCF should be included in lymphatic CTV, with different dose specifications. Elective nodal irradiation to contralateral neck should be considered in advanced T stage, pathologically positive neck nodes, and tumors at oral tongue, floor of mouth, or adjacent to midline.

DOSE PRESCRIPTION AND SPECIFICATION

Conventional radiation therapy usually consists of initial and several cone-down plans to achieve dose gradients to areas with varying degree of risk. In the era of IMRT, we can achieve the same, or even more complicated, dose gradients by using a single planning throughout the entire treatment course by "simultaneously integrated boost" technique [38]. In this sense, there are two common options for dose prescription: First, one can use daily fraction size at 2 Gy to the high-dose region and a smaller daily fraction size to the low-risk area simultaneously. The total dose of low-risk target volumes should be escalated according to estimation of biologically effective dose. One way or another, one can keep the dose prescription to the low-risk area at conventional fraction size (1.8-2 Gy) and increase daily fraction size to the high-risk region. For example, accelerated fractionation schedule using very high daily dose (2.4Gy) to the high-risk target to shorten the overall treatment time has been reported [39]. Since critical normal tissues such as nerves, normal mucosa, bone, etc. are often embedded or near the target, greater dose heterogeneity inside the target volume with larger hot spot are usually noted in IMRT plans. This implies that delivery of large-fraction doses to the target should be carefully evaluated especially in postoperative setting. The dose specification from the published postoperative IMRT trials is listed in Table 2. It is our understanding that the most common prescribed dose is 60-66 Gy to the operative bed and 50-60 Gy to the subclinical areas.

PATTERNS OF FAILURE

The reports of the patterns of recurrences are summarized in Table 3. By Dawson et al., almost all recurrence occurred inside IMRT fields, and marginal recurrence was found in one patient at contralateral level Ib neck. Out-field failure was noted at contralateral level IV neck by Dawson et al. and at contralateral level III by Yao et al. Because most common patterns of failure are in-field, we can reasonably assume some approaches to improve the locoregional control of IMRT, such as increase in radiation dose to the high-risk regions, administration of concurrent chemotherapy or target therapy agents.

CONCLUSIONS

Compared to conventional radiotherapy, IMRT shows significant improvement in sparing uninvolved organs and in conformity for target irradiation in treatment of OCC. However, several challenging clinical issues should be addressed and overcome before it can be universally accepted. Of these, accurate delineation of the clinical target volumes as well as optimization of dose and fractionation remains the most critical issues to be determined.

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