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ORIGINAL ARTICLE **CME**

Intraoral Cone Radiotherapy for Cancer of the Oral Cavity

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ABSTRACT

Objective: *To evaluate treatment results of intraoral cone therapy with or without external radiotherapy as primary treatment in patients with carcinoma of oral cavity.*

Methods: *Between the years 1997 and 2011, 14 patients were identified for retrospective review. Statistical analysis by the Kaplan Meier method was performed for local disease–free survival, disease-free survival, and overall survival.*

Results: *The median patient age was 68 (range, 45-83) years; they all had squamous cell carcinoma and 12 (86%) were male. The tongue was the commonest primary site (n = 9). In all, nine (64%) has significant co-morbidities; five (36%) were not fit for surgery, four (29%) refused surgery, and five (36%) aimed for organ preservation. Eleven (79%) were T1 or T2, three (21%) were T3 or T4. Two (14%) patients received intraoral cone therapy alone, and 12 (86%) both intraoral cone and external radiotherapy. Two (14%) received concurrent chemotherapy and radiotherapy. The most commonly used regimen was 3 Gy/fr for 7 to 8 fractions (ranging from 2-3 Gy/fr for 3-19 fractions). The dose of locoregional external radiotherapy ranged from 50 to 66 Gy (median, 50 Gy). The median follow-up time was 55 (range, 2-157) months. The 2-year and 5-year disease-free survival were 91% and 80%, and 2-year and 5-year overall survival were 71% and 54%, respectively. Three patients (21%) developed local recurrence and all have salvage surgery done. Five-year local control rate was 83%. Three patients (21%) developed grade-3/4 mucositis, one patient (7%) developed radionecrosis, one patient (7%) developed sarcoma.*

Conclusion: *Intraoral cone radiotherapy is an effective means for treating primary tumours in the oral cavity with organ preservation. It is a feasible therapeutic option if the patient refuses, is too old, or not fit for surgery or brachytherapy.*

Key Words: *Carcinoma, squamous cell; Mouth neoplasms; Radiotherapy dosage; Radiotherapy, high-energy; Tongue neoplams*

中文摘要

口腔內置聚束管放射治療腫瘤

王韶如、黃志成、梁道偉、羅文龍、吳雲英、李安誠、施永健、董煜

目的：評估利用口腔內置聚束管治療在有或無體外放射治療的情況下應用於口腔腫瘤治療的結果。

方法：回顧1997至2011年期間14名口腔腫瘤患者的病例報告。統計學分析用Kaplan Meier法計算原位無瘤生存率、無瘤生存率及總生存率。

結果：14名口腔腫瘤患者均為鱗狀細胞癌，他們年齡介乎45至83歲，中位數68歲。12人（86%）為男性 。9人的原發灶為舌癌。14名患者中，9人（64%）有嚴重共病、5人（36%）並不適合接

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受手術、4人（29%）拒絕接受手術、5人（36%）旨在保留器官。11人（79%）屬T1或T2期，3人（21%）屬T3或T4期。2人（14%）只接受口腔內置聚束管治療，另12人（86%）接受口腔內置聚束管及放射治療；2人（14%）同時接受化療及放射治療。最常用的劑量為7至8次，每次3 Gy；所用的劑量介乎3至19次，每次2至3 Gy。局部放射治療的劑量介乎50至66 Gy（中位數50 Gy）。隨訪期介乎2至157個月，中位數55個月。兩年無瘤生存率及總生存率分別為91%及71%；五年無瘤生存率及總生存率分別為80%及54%。3名患者（21%）原位復發，全部只接受挽救性手術。五年局部控制率為83%。3人（21%）出現III / IV期黏膜炎、1人（7%）有放射性壞死、1人（7%）出現肉瘤。

結論：口腔內置聚束管放射治療有效處理口腔內原發腫瘤，並且可以保留病人器官。如果病人年紀太大、拒絕或不適宜接受手術或近距離放射治療，口腔內置聚束管放射線治療可作為一個可行的治療方法。

INTRODUCTION

Treatment modalities for carcinoma of oral cavity include surgical resection, radiotherapy, chemotherapy, or a combination of these. The choice depends on the stage and size of tumour, treatment toxicity, functional loss, patient's performance status, co-morbidity and preferences.[1] For early-stage T1 and T2 disease, single modality treatment with either surgery or radiation is used. The control rates are generally the same. For more advanced lesions, combined modality treatment is preferred.[1] Early studies showed that the success rates including local control and local recurrence–free survival of radiotherapy were high for early oral cavity tumours treated by brachytherapy alone or in combination with external radiotherapy[2,3]; the range being approximately 70 to >95%, respectively.[4-7]

Intraoral cone radiotherapy (IOC), like interstitial brachytherapy, is a kind of localised radiation therapy used as a boost part or as a primary treatment for cancer of the oral cavity. With proper selection of lesions in the oral cavity, IOC combined with external beams have been found to achieve good local tumour control and excellent cosmetic and functional results with minimal radiation sequelae.[8] It is, however, not a popular form of radiotherapy, as it requires special equipment, specialised skills and a high degree of patient selection.

Our centre introduced the IOC technique in 1997. In this study, we report our experience using IOC as the primary treatment for patients with cancer of the oral cavity.

METHODS

Patient Selection

A total of 17 patients with carcinoma of oral cavity received IOC between 1997 and 2011. Three of them were excluded from this study — two of whom had received IOC as part of their postoperative adjuvant therapy, and another as a component of palliative treatment for metastasis. Patient demographics, tumour characteristics, treatment modalities, treatment complications, and follow-up record of the remaining 14 patients were collected retrospectively by reviewing outpatient and hospital computer records.

All 14 patients were selected for IOC because they had either inoperable disease, were medically unfit for surgery, declined surgery, or with the aim of organ preservation. All patients had to have had primary sites easily accessible by the selected cone, be cooperative enough, and not have trismus.

The pretreatment evaluation protocol included basic blood tests, a dental check-up, and an imaging work-up with chest X-ray and computed tomographic scan for the head and neck. Panendoscopy was used to rule out synchronous tumour. The staging was based on the AJCC (American Joint Committee on Cancer) Cancer Staging (6th edition).

Treatment Details

All patients were immobilised by plastic tape, together with a tailor-made bolus if necessary. Two sets of intraoral aluminum cones (Northwest Medical Physics Centre, Lynnwood [WA], US) were used for electron beam therapy with a Varian linear accelerator. The aluminum cones measured 32 mm or 38 mm in diameter. Each diameter consisted of thee cones with different face angles (beveled ends) of 0°,15°, or 30°. Different electron beam energies from 6 MeV to 12 MeV with different isodose curves were accordingly available for treatment. Combinations of different face angles and beam energies could cover different sizes of

tumour that would be even slightly larger than the cone size (Figures 1 and 2).

The size of each cone was chosen according to the tumour size. If the aperture of the mouth of a patient was too small to insert a proper cone, scarification of a few teeth was necessary. The electron beam energy was selected to cover the depth of invasion plus 1-cm margin. In some cases, immobilisation was achieved by asking the patients to pull out the tip of their tongues with their fingers during radiotherapy (Figure 3).

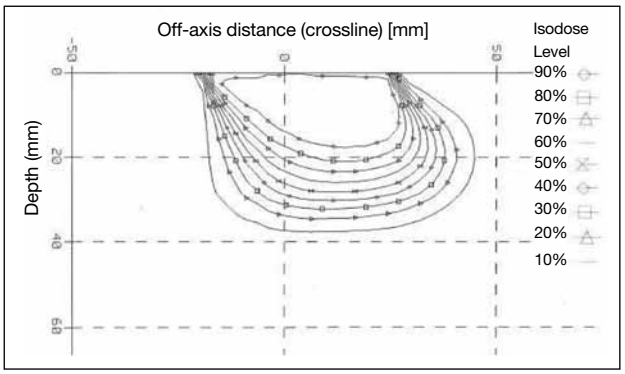

Figure 1. Isodose lines for 9 MeV electron, cone 38 mm, face angle 30°.

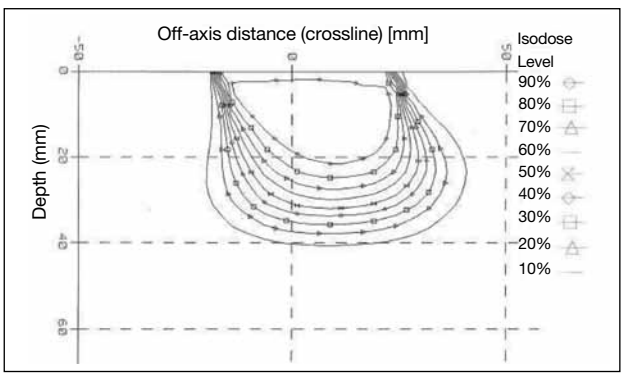

Figure 2. Isodose lines for 9 MeV electron, cone 38 mm, face angle 15°.

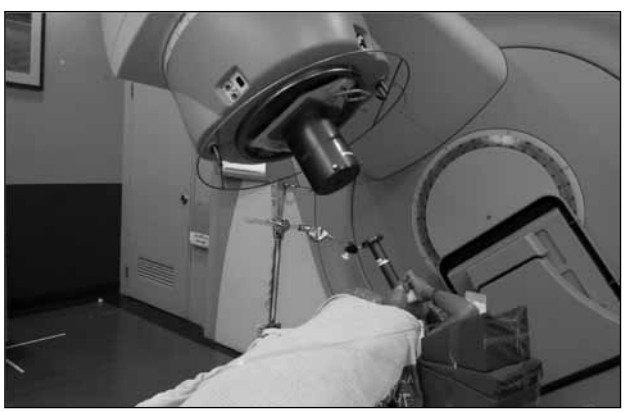

Figure 3. Set-up of intraoral cone therapy.

Treatment target area coverage was delineated visually through the selected cone. A collar for each cone size was provided, which fixed the cone onto an articulated arm assembly on the side rail of the couch. The alignment of the cone and collimator assembly was accomplished with an alignment rod that fitted into the proximal end of the cone. The gantry and couch were rotated to minimise the shadow cast by rod, which defined the axis of the cone or treatment. The rod was removed and the treatment area was reviewed again. Treatment would then begin after confirmation.

The set-up time for each IOC irradiation varied from 5 to 20 minutes, depending on the site and cooperation of the patient. The treatment time was about 5 minutes.

For treatment with a combination of external radiotherapy (ERT) and IOC, the former was delivered using a 6 MV photon linear accelerator. There was no treatment break between ERT and IOC. Concurrent chemotherapy was considered for high-risk patients, and consisted of cisplatin (100 mg/m^2 on day 1, every 3 weeks for 2 cycles) or cisplatin (100 mg/m^2 on day 1) plus 5-fluorouracil (1000 mg/m^2 on days 1 to 4, every 3 weeks for 1 cycle) given simultaneously with external radiotherapy.

Endpoints and Statistical Analysis

Complete remission (CR) was defined as no evidence of disease by clinical examination after the end of treatment and follow-up period.

Disease-free survival (DFS) was defined as the length of time after treatment with CR, achieved to the time of disease relapse with local recurrence, metastasis, or death related to treatment, whichever occurred first. Patients who were alive and disease-free or died of other causes were censored at the time of last assessment.

Overall survival (OS) was defined as the length of time after treatment till patient's death. Patients who were alive were censored at the time of last assessment.

Local failure-free survival was defined as the length of time after treatment with CR achieved to the time of disease relapse with local recurrence. Patients who had no evidence of disease after CR with regard to original

tumour site in the oral cavity were censored at the time of last assessment.

Adverse side-effects were retrospectively reviewed using NCI CTC (National Cancer Institute – Common Toxicity Criteria) grading system version 3.0. For statistical analysis, the Kaplan-Meier method was preformed for local disease–free survival, DFS, and OS.

Table 1. Patient characteristics (n = 14).

Characteristics	No. (%)
Age (years)	
<60	5 (36)
60-69	2 (14)
≥70	7 (50)
Sex	
Male	12 (86)
Female	2 (14)
Histology	
Squamous cell carcinoma	14 (100)
Site of involvement	
Tongue (one of them got double primary with Ca supraglottis)	9 (64)
Floor of mouth	2 (14)
Buccal mucosa	1 (7)
Hard palate	2 (14)
Indication of radiotherapy or intraoral cone therapy	
Not fit for operation	5 (36)
Refused operation	4 (29)
Organ preservation	5 (36)
T-stage	
T1	5 (36)
T2	6 (43)
T3	1 (7)*
T4	2 (14)†
N-stage	
N0	9 (64)
N1	3 (22)
N2	2 (14)

* With T2N0 Ca supraglottis simultaneously.
† Invade adjacent structure and ankyloglossia respectively.

Table 2. Summary of treatment regimens.

Treatment regimen	Data
Treatment modality	
IOC alone	2 (14%)
Both IOC and external RT	12 (86%)
Concurrent chemotherapy and RT	2 (14%)
Type of treatment first	
IOC first	11 (79%)
External RT first	3 (21%)
Dose of IOC	
Dose range per fraction (Gy)	2-3
Range of fractionation	3-19
Dose of external RT (Gy)	
Total external dose range	50-66
Median dose	50

Abbreviations: IOC = intraoral cone therapy; RT radiotherapy.

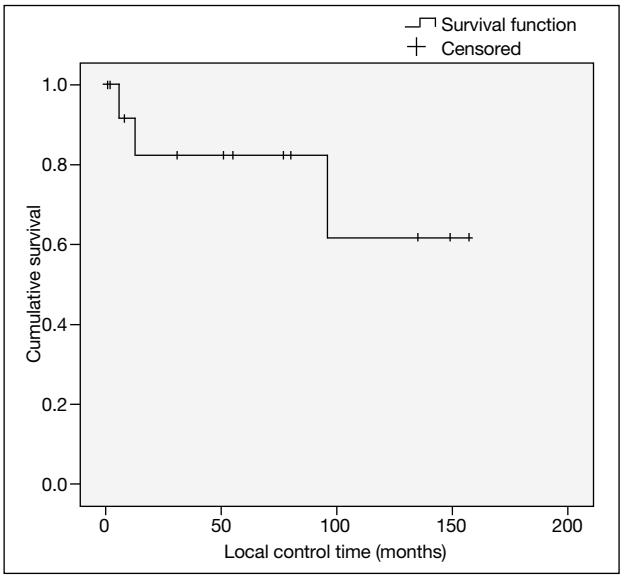

Figure 4. Probability of local control.

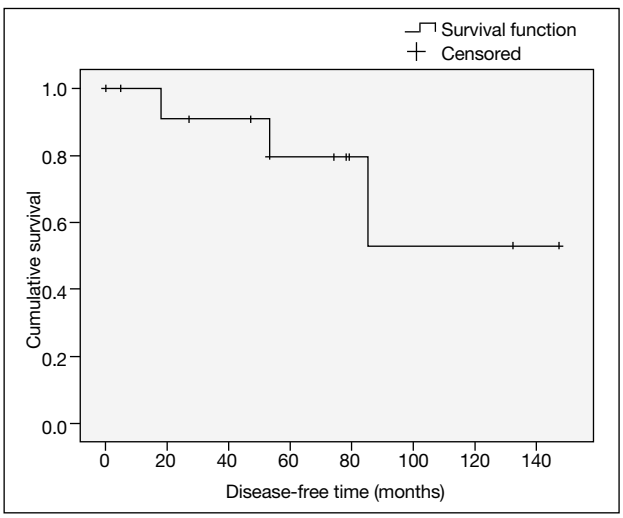

Figure 5. Probability of disease-free survival.

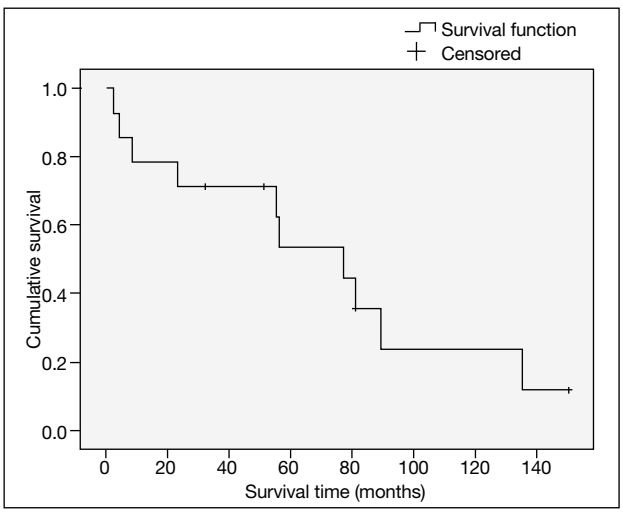

Figure 6. Probability of overall survival.

RESULTS

Patients and Tumour Characteristics

The median age of our cohort was 68 (range, 45-83) years. Twelve (86%) of the patients were male. The reasons for selecting these patients for IOC were as follows: five (36%) were not fit for surgery; four (29%) declined any operation, and five (36%) aimed for organ preservation. Nine (64%) of the patients had significant co-morbidity, including: diabetes mellitus, hypertension, liver cirrhosis, hepatic encephalopathy, cerebral atrophy, old tuberculosis, splenomegaly and oesophageal varices due to liver cirrhosis, chronic alcoholism, old cerebrovascular accident, end-stage renal failure, abdominal aortic aneurysm, carotid stenosis, and a history of carcinoma of the supraglottis six years before diagnosis of carcinoma of tongue.

The sites of primary involvement and the distribution of patients according to different T- and N- stages are summarised in Table 1. Among them, 21% and 36% had T3/4 disease and N1-2 diseases, respectively.

Regarding these 14 patients, two (14%) of them were treated with the IOC alone, while 12 (86%) patients with both IOC and ERT. Two patients received concomitant chemotherapy and radiotherapy (Table 2).

The most commonly used IOC regimen was 3 Gy/fr for 7 to 8 fractions (range, 2-3 Gy/fr for 3-19 fractions). The median dose of ERT was 50 Gy (range, 50-66 Gy) [Table 2]. The mean total biological effective dose (BED10) was 89.5 Gy.

Treatment Outcomes

The median follow-up time was 55 months (range, 2-157 months). All patients achieved local and regional CR after completion of radiotherapy. One (7%) of the patients developed a suprasternal metastasis during radiotherapy.

Three patients (21%) developed local relapse and all were treated with salvage operations. The five-year local control rate was 83% (Figure 4). Organ preservation was achieved in 79% of the patients. The two- and five-year DFS were 91% and 80%, respectively (Figure 5), while the two- and five-year OS were 71% and 54%, respectively (Figure 6). The median survival was 56 months (range, 4-162 months). The local- and distant-site failure pattern is shown in Tables 3 and 4, respectively.

Side-effects

Three patients (21%) developed grade 3/4 acute mucositis. Two patients (14%) developed grade 3/4 late

Table 3. Local-site failure patterns.

	Sex	Age (years)	Site	Stage	Modality	IOC dose	ERT dose	Time of LR (months)	Salvage operation
1	F	74	Tongue	T2N1	IOC then ERT	3 Gy x 8	2 Gy x 30	81	Partial glossectomy
2	M	82	Buccal mucosa	T1N0	IOC alone	3 Gy x 19	NA	12	Wide local excision
3	M	59	Tongue and supraglottis	T3N1 (tongue)	IOC then concurrent chemotherapy and radiotherapy	2 Gy x 3	2 Gy x 33	3	Hemiglossectomy and total laryngectomy with right radical neck dissection

Abbreviations: IOC = intraoral cone therapy; ERT external radiotherapy; LR = local relapse; NA = not applicable.

Table 4. Distant-site failure pattern.

	Sex	Age (years)	Site	Stage	Modality	IOC dose	ERT dose	Site failure
1	M	63	Tongue	T2N1	IOC then ERT	2 Gy x 8	2 Gy x 27	Bone metastasis

Abbreviations: IOC = intraoral cone therapy; ERT = external radiotherapy.

Table 5. Late toxicity.

	Sex	Age (years)	Site	Stage	Modality	IOC dose	ERT dose	Type of toxicity	Time to develop (years)*
1	M	51	Floor of mouth	T2N2	IOC then ERT	3 Gy x 7	1.2 Gy BD x 50	Radionecrosis	4
2	F	74	Tongue	T2N1	IOC then ERT	3 Gy x 8	2 Gy x 30	Sarcoma of local site	5.5

Abbreviations: IOC = intraoral cone therapy; ERT = external radiotherapy; BD = twice daily treatment.
* Period between completion of radiotherapy and occurrence of the toxicity.

toxicity. Among the latter, one developed radionecrosis and underwent hyperbaric oxygen therapy and one developed a sarcoma at the initial tumour site six years after the treatment, which was then treated with wide local excision (Table 5).

DISCUSSION

A study with 101 patients with early carcinoma of oral cavity, T1 and T2, treated by ERT and / or IOC achieved a two-year DFS rate (including surgical salvage) of 88% and local control rate of 85%.[9] Another study for early oral tongue cancer treated with interstitial brachytherapy showed a five-year local control rate of 82%.[10] In our series, both early and locally advanced disease were included. The five-year DFS was 80% and the five-year local control rate was 83%. Our result was comparable to historical results in terms of five-year control even though our patients had a higher proportion with advanced stage disease.

The frequency of radiation complications (soft tissue ulceration and / or radionecrosis) was 14% in a prior study[9] and in this study 7% endured radionecrosis. It was reported that floor of mouth (FOM) lesions were associated with the highest rate,[9] which was also observed in our study, as the only patient who developed radionecrosis also had carcinoma of FOM. Wang et al[9] postulated that the radiation tolerance of FOM may be lower than at other sites like the tongue, as the latter is a more vasculo-muscular organ.

One patient (7%) developed a sarcoma at the initial tumour site, diagnosed six years after radiotherapy; treatment was by wide local excision. The overall frequency of radiation-induced tumour ranged from 0.03 to 0.3%. In van der Laan et al's study,[11] for example, 0.7% of patients developed malignancy within the previously irradiated head and neck site. Sarcomas account for 12% of postradiation neoplasms.[12] Our study was too small to form any significant conclusions on the risk of radiotherapy-induced sarcoma by using IOC.

While interstitial brachytherapy is a more popular boost technique, IOC offers several advantages over the former including shorter operating time, shorter treatment time, decreased general anaesthesia risk and bleeding risk. It is potentially better tolerated and patient can have a better quality of life during treatment. Besides, it affords better radiation protection compared to preloaded interstitial brachytherapy. The modality of treatment depends on feasibility and the patient's choice. However, the highly selected site and size of tumour, the patient's cooperation and preference, and specialist and instrument availability limit wider use of IOC.

In conclusion, IOC is a well-tolerated treatment option, achieving local control rates as well as organ preservation comparable to interstitial brachytherapy. Moreover, it is suitable for those refusing surgery or are medically unfit for the operation.

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