RESEARCH ARTICLE

Treatment Outcome with Brachytherapy for Recurrent Nasopharyngeal Carcinoma

Soon Keat Cheah[1], Fen Nee Lau[1], Mastura Md Yusof[2], Vincent Chee Ee Phua[2]*

Abstract

Background: To evaluate the treatment outcome and major late complications of all patients with recurrent nasopharyngeal carcinoma (NPC) treated with intracavitary brachytherapy (ICBT) in Hospital Kuala Lumpur. Materials and Methods: This retrospective study was conducted at the Department of Radiotherapy and Oncology, Hospital Kuala Lumpur, Malaysia. All patients with histologically confirmed recurrent NPC in the absence of distant metastasis treated in the period 1997-2010 were included in this study. These patients were treated with ICBT alone or in combination with external beam radiotherapy (EBRT). Treatment outcomes measured were local recurrence free survival (LRFS), disease free survival (DFS) and overall survival (OS). Results: Thirty three patients were eligible for this study. The median age at recurrence was 56 years with a median time to initial local recurrence of 27 months. Majority of patients were staged as rT1-2 (94%) or rN0 (82%). The proportion of patients categorised as stage III-IV at first local recurrence was only 9%. Twenty one patients received a combination of ICBT and external beam radiotherapy while 12 patients were treated with ICBT alone. Median interval of recurrence post re-irradiation was 32 months (range: 4-110 months). The median LRFS, DFS and OS were 30 months, 29 months and 36 months respectively. The 5 year LRFS, DFS and OS were 44.7%, 38.8% and 28.1% respectively. The N stage at recurrence was found to be a significant prognostic factor for LRFS and DFS after multivariate analysis. Major late complications occurred in 34.9% of our patients. Conclusions: Our study shows ICBT was associated with a reasonable long term outcome in salvaging recurrent NPC although major complications remained a significant problem. The N stage at recurrence was a significant prognostic factor for both LRFS and DFS.

Keywords: Nasopharyngeal cancer - recurrence - brachytherapy - outcome - Malaysia

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Introduction

Nasopharyngeal carcinoma (NPC) is one of the leading neoplasms diagnosed annually in Southern China, Southeast Asia, Northern Africa and Alaska. In China, it is one of the most common cancers and is considered an endemic disease (Chan et al., 2002). The 2005 Malaysian National Cancer Registry (NCR) reported NPC as the 3rd most common malignancy among Peninsular Malaysian males after large bowel and lung cancer. In spite of aggressive treatment, 10 year local recurrence free rates are only about 15-20% (Zhang et al., 1989; Lee et al., 2005).

Patients with early stage recurrent NPC can be considered for surgery but this constitutes only a small percentage of patients with recurrent NPC. Most patients should be considered for re-irradiation and this can be done with ICBT with or without EBRT.

Brachytherapy offers the possibility of high dose irradiation with rapid dose fall off beyond the target volume, therefore permitting sparing of surrounding critical structures. The frequency of treatment is less and overall treatment duration is slightly shorter compared to EBRT. Numerous publications have consistently shown the categorical benefit of brachytherapy in achieving good long term local control (LC) and improved survival outcome. A recent study employing ICBT using HDR afterloading technique in treating recurrent NPC patients reported median overall recurrence free survival (RFS) of 26 months with 3 and 5-year disease free survival (DFS) rate of 50% and 25% respectively. A higher normalized total dose was associated with a higher chance of LC (Terlikiewicz et al., 2005). One study investigating 91 patients with non-metastatic locally recurrent NPC treated with EBRT with or without ICBT reported 5 year DFS and OS of 33% and 33% respectively (Leung et al., 2000). Although there was a significantly better LC with a total dose of more than 60Gy, this was associated with a high incidence of major late complications. A total of 57% of patients from this series experienced one or more major complications with recurrent T stage predictive of major complications. A recent study analysed the outcome of treatment employing modern RT techniques with or without ICBT on 29 recurrent NPC patients.

*[1]Department of Oncology and Radiotherapy, Kuala Lumpur General Hospital, [2]Clinical Oncology Unit, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia *For correspondence: vince_phua@yahoo.com*

There were an almost equal number of patients in Stages I-II and III-IV. Approximately 83% of patients received IMRT while 45% received combined modality treatment (CMT) with ICBT. The 5-year LC and OS were 52% and 60%, respectively. Although there were no differences in outcome between groups treated with CMT versus EBRT, grade 3 complications were significantly lower in the CMT group (Koutcher et al., 2010).

Materials and Methods

This is a retrospective study conducted at the Department of Radiotherapy and Oncology, Hospital Kuala Lumpur. The aim is to evaluate the LRFS, DFS, OS and major late complications of all patients with recurrent NPC treated with ICBT between the periods 1997 to 2010 at this centre. All patients with histologically confirmed recurrent NPC in the absence of distant metastasis were included in this study. These patients were treated with ICBT alone or in combination with EBRT. The total brachytherapy dose was normalised according to the linear quadratic formula (without a time factor correction) for a biologically equivalent effect to conventional 2 Gy per fraction treatment. An α/β value of 10 Gy was used for tumour effect while an α/β value of 3 Gy was used for late organ effect Several endpoints were defined in our study as below. *Initial time to local recurrence:* Time interval from primary diagnosis of NPC until histopathological recurrence. *Local recurrence free survival (LRFS)*: Time interval from histopathological recurrence until local recurrence post brachytherapy. Patients with no local recurrence were censored at death, date of analysis (15 December 2011) or last follow-up date. *Disease free survival (DFS)*: Time interval from histopathological recurrence until either locoregional recurrence or distant metastases post brachytherapy or death. Patients with no recurrence were censored at date of analysis or last follow-up date. *Overall survival (OS)*: Time interval from histopathological recurrence until mortality of any cause. Surviving patients were censored at date of analysis. We obtained the mortality data from the National Registry Department (NRD). All data analysis was performed using SPSS version 16.0. Kaplan Meier method was used for survival analysis.

Brachytherapy technique

In HKL the commonest fractionation regime used in ICBT alone was 30Gy in 5 or 6 fractions. The ICBT fractionation most commonly used in combination therapy with EBRT was 10-12Gy in 2 fractions. Each fraction is given 3-7 days apart to allow for normal tissue recovery. The total EBRT dose ranges between 40-50Gy. Neoadjuvant chemotherapy was used selectively to downstage locally advanced tumour prior to re-irradiation. Although this approach remains controversial, some patients may benefit from tumour down-staging that leads to a smaller radiation volume and less radiation toxicity. ICBT with the microSelectron® stepping source HDR technique using Iridium-192 as the radiation source was first introduced in 1997 at HKL. Our centre uses a set of Nucleotron® HDR nasopharyngeal balloon applicators which consist of 2 sets of nasopharyngeal catheters and dummy seeds. The planning target volume (PTV) is drawn on both orthogonal films by the oncologist based on the extent of the disease from the diagnostic images. The physicist counter-checks the films and digitizes the images. Both dose points and organs at risk are marked by the oncologist. The dose points are prescribed to either 1.0 or 1.5 cm from the central axis of the catheters. Organs at risk such as the brainstem, spinal cord, pituitary and optic chiasm are marked at the midline plane. The pituitary is marked at the centre of the pituitary fossa. The brainstem is marked 0.5 cm behind the inferior clivus. Three dose points are chosen to define the spinal cord. The initial two dose points are marked at the posterior vertebral body of C1 and C2 while the third dose point is marked between these two points at the posterior vertebral body. All cases in our study involve 2D computerised planning using the PLATO® planning system.

Results

A total of 61 patients were treated with ICBT between 1997 and 2010. However, only 33 patients were eligible for this study analysis after obtaining full medical records from both the radiotherapy department and the Archives Unit of HKL. The clinical characteristics are listed in table 1. The median age at recurrence was 56 years (range: 36-82 years). Median time to initial local recurrence was 27 months (range: 4-188 months). Fifteen patients recurred less than 24 months, out of which only three patients recurred within 12 months after primary treatment for NPC. Majority of patients were staged as rT1-2 (94%) or rN0 (82%). The proportion of patients categorised as stage III-IV at first local recurrence was only 9% in this patient population. Out of the five patients with rT2, four of them have parapharyngeal involvement (rT2b). A total of 32 patients were treated for local recurrence while one patient was treated for persistent local disease. Out of 32 patients, 29 were treated as first local recurrence while the remaining three patients received treatment for second local recurrence. The secondMedian time interval from first local recurrence to initiation of salvage treatment was 2.5 months (range: 0.6-7.1 months). Salvage treatment may vary from neoadjuvant chemotherapy, EBRT, ICBT or combined modality treatment (CMT). Twenty one patients received CMT while 12 patients were treated with ICBT alone. All but two patients completed their treatment. One of these two patients did not achieve satisfactory target volume coverage despite computerised optimisation. He received three brachytherapy insertions

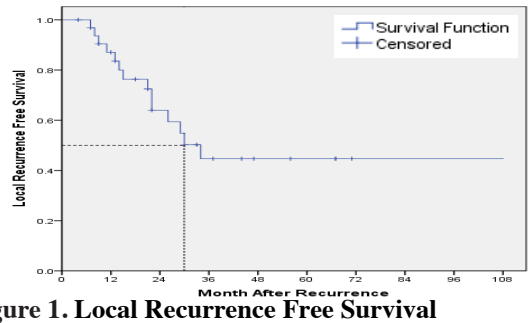

Figure 1. Local Recurrence Free Survival

Table 1. Clinical Characteristics

Characteristic		n=33 (%)
Age at recurrence	≤50 or less	16 (48.5)
	≥50	17 (51.5)
Gender	Male	27 (81.8)
	Female	6 (18.2)
Ethnicity	Malay	9 (27.3)
	Chinese	23 (69.7)
	Eurasian	1 (3.0)
T stage at recurrence	T1	26 (78.8)
	T2	5 (15.2)
	T3	1 (3.0)
	T4	1 (3.0)
N stage at recurrence	N0	27 (81.8)
	N1	4 (12.1)
	N2	2 (6.1)
AJCC stage at recurrence	I	22 (66.7)
	II	8 (24.2)
	III	1 (3.0)
	IV	1 (3.0)
Modality of radiation		
Brachytherapy alone		12 (36.4)
Brachytherapy and external beam		21 (63.6)
Completion of brachytherapy	Yes	31 (93.9)
	No	2 (6.1)
Normalised total dose, Gy	≤50	13 (39.4)
	>50	20 (60.6)
Median: 56.0 (range:13.0-74.0)		
Normalised total brachytherapy dose, Gy	<10.0	2 (6.1)
	10.0<20.0	21 (63.6)
	20.0<30.0	4 (12.1)
	>30.0	6 (18.2)
Neoadjuvant chemotherapy	Yes	6 (18.2)
	No	27 (81.8)

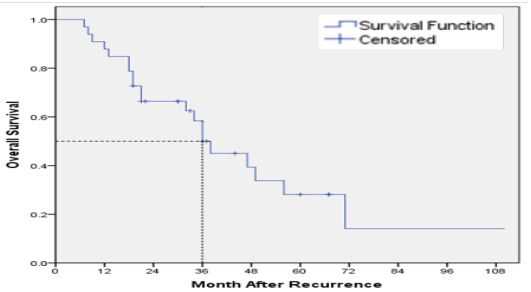

Figure 2. Overall Survival

before conversion to EBRT. The other patient developed soft palate oedema after one insertion procedure. Attempts at further insertions failed despite intervention from the head and neck surgeon who tried to release the synechiae. This patient subsequently received EBRT alone. Median total dose received was 56Gy (range: 13-74Gy). A total of 20 patients received more than 50Gy. Combination therapy was given to 21 patients with a median dose of 58.8Gy (49.9-74.0Gy). Twelve patients were treated with brachytherapy alone with median dose of 16Gy (range: 9.3-37.5Gy). All patients who received EBRT before or after ICBT received EBRT doses ranging between 39.6-50.4Gy. Six patients received neoadjuvant chemotherapy. The most common regime was 5-day cisplatin/5-fluorouracil regime. This regime was used in all patients except one patient who was given ifosfamide based regime. Treatment characteristics are summarised in Table 1.

Only 27 patients were evaluable for treatment response by direct nasopharyngoscopy and available imaging. Six patients did not have nasopharyngoscopy as planned.

Table 2. Treatment Results

Characteristic	n=33 (%)	
Response at first nasopharyngoscopy		
Complete response	23 (69.7)	
Partial response	3 (9.1)	
No response	1 (3.0)	
Unknown	6 (18.1)	
Overall status		
Alive and well	8 (24.3)	
Alive with recurrence	3 (9.1)	
Alive with unknown recurrence status	1 (3.0)	
Death	21 (63.6)	
Recurrence after brachytherapy		
Yes	17 (51.5)	
No	10 (30.3)	
Unknown	6 (18.2)	
Type of recurrence		
Local alone	7 (21.2)	
Local and regional	1 (3.0)	
Local and metastatic	4 (12.1)	
Local, regional and metastatic	3 (9.1)	
Regional alone	1 (3.0)	
Regional and metastatic	1 (3.0)	
Site of distant metastases		
Lung	4 (12.1)	
Liver	4 (12.1)	
Distant nodal metastases	3 (9.1)	
Bone	1 (3.0)	
Further treatment after brachytherapy		
Surgery	2 (6.1)	
Palliative chemotherapy	8 (24.2)	
Cause of death		
Advanced NPC	15 (45.5)	
Septicaemia (aspergillosis)	1 (3.0)	
Neutropaenic sepsis	1 (3.0)	
Cardiac failure	1 (3.0)	
Aspiration pneumonia	1 (3.0)	
Temporal lobe necrosis	1 (3.0)	
Carotid blowout	1 (3.0)	
Major Complications	Dose (Gy)	
Moderate to severe trismus	7(21.2)	37.5-62.5
Temporal lobe necrosis/sclerosis	3 (9.1)	62.5
Palatal fistula	1 (3.0)	62.5
Orocervical fistula	1 (3.0)	74.0
Right optic neuropathy	1 (3.0)	37.5
Carotid blowout	1 (3.0)	60.0

Four were completely lost to follow up while two patients passed away within six months of brachytherapy. The 27 evaluable patients had a median nasopharyngoscopy assessment at 3 months (range: 1-9 months). Treatment outcome is summarised in Table 2. The median LRFS, DFS and OS were 30 months (range: 4-108 months), 29 months (range: 4-108 months) and 36 months (range: 7-110 months) respectively. Median time to local failure, time to progression and time to distant metastases was 32 months (range: 16-108 months), 27 months (range: 4-108 months) and 14 months (range: 8-35 months) respectively. The 5 year LRFS, DFS and OS were 44.7%, 38.8% and 28.1% respectively. Survival curves for both LRFS (Figure 1) and OS (Figure 2) are shown below.

Ten patients who developed progressive disease after brachytherapy received further salvage treatment. One patient underwent nasopharyngectomy while another underwent right neck node dissection. Eight patients underwent palliative chemotherapy at progression. Both patients who underwent surgery are still alive, one of them with local and metastatic disease. All eight patients who underwent palliative chemotherapy have died. Eight

Table 3. Multivariate Analysis for Local Recurrence Free Survival

Characteristic		Hazard ratio	95% CI	p value
N stage at recurrence				
	0	1		
	1-2	5.07	1.15-22.47	0.032
Neoadjuvant chemotherapy				
	Yes	1.33	0.37-4.87	0.66
	No	1		
Modality of radiation				
	Brachytherapy alone	1		
	Combination	1.53	0.17-13.89	0.7
Total dose, Gy	≤50	1		
	>50	0.24	0.03-2.53	0.25

patients (24%) subsequently developed distant metastases. Median time to death from distant metastases was 8 months (range: 1-38 months). The causes of death are listed in Table 2.

About 35% patients developed major complications. Neurological complications occurred in 12.1% of patients. The patient who developed right optic neuropathy received 66Gy of CCRT and was retreated 32 months later with ICBT alone with a normalised total dose of 37.5Gy. She received a cumulative dose of 1.9Gy to the optic chiasm from ICBT. She had no other predisposing co-morbidity. As the dose contributed by the ICBT to the optic chiasm was low, we believe that this complication may be attributed to the late effect of the primary CCRT. Three patients with temporal lobe necrosis/sclerosis were treated with 70Gy of CCRT and re-irradiated with 50Gy of EBRT and ICBT with a normalised total dose of 62.50Gy. Unfortunately, all three did not have documentation of their brainstem dose from ICBT. All of them were retreated within 16-21 months after completion of CCRT. We compile a list of major non-

Among patients with trismus, 71.4% occurred in the CMT group whereas only two patients or 28.6% occurred in the ICBT alone group. A fatal carotid blowout occurred in one patient who was irradiated twice to the neck. He received 60Gy and 10Gy boost to the neck initially before re-irradiation with 60Gy electron beam therapy. The treatment gap between primary RT to re-irradiation was 15 months. Both patients with fistula received primary EBRT of 70Gy without chemotherapy and were re-irradiated with CMT. The patient with palatal fistula had local disease extending to the palate prior to reirradiation. The major complications and the total dose received during re-irradiation are summarised in Table 2.

Discussion

Our 5 year LRFS, DFS and OS of 44.7%, 38.8% and 28.1% respectively were similar with those reported in the literature for reirradiation after ICBT. The 5 years OS of other studies in recurrent NPC range between 6-60% (Yang et al., 1996; Leung et al., 2000; Law et al., 2002). In the study employing the mould technique, the 5 year LC rate of 63% (for first local recurrence) was attributed to improved dose conformity (Kwong et al., 2001). The IMRT technique with a mean GTV dose of 70Gy achieved a 5-year LRFS and DFS of 86% and 45% probably due to dose escalation (Han et al., 2012). Our median total dose was 56Gy but there was a wide range of doses from 13-74Gy. Better dose conformity and dose escalation may contribute to improved survival.

A longer time interval to initial local recurrence was associated with improved outcome among patients with recurrent NPC in some studies. The time interval to initial local recurrence was 27 months in this study. A large retrospective review involving 847 patients with recurrent NPC found that patients with longer latency period achieved a significantly higher disease specific survival and distant failure free survival (Lee et al., 1999). Long latency period reflects a different pathological behaviour yet to be determined although several possibilities were discussed including tumour recurrence, new second primary either de novo or secondary to radiation or re-infection with different Epstein-Barr viral genome.

In our study, almost all our patients were staged rT1-2 stage disease. Only two patients were staged rT3-4. In a larger study, rT stage was found to be a statistically significant factor for LC but not disease specific survival or OS (Law et al., 2002). Conversely, rT stage was found to be statistically significant for OS but not overall RFS (Terlikiewicz et al., 2005). The type of recurrence was shown to be a significant prognostic factor for LC from other studies. Patients with persistent disease tend to do better with long-term LC rate of 85-87% compared with a lower LC rate between 45-63% among those with locally recurrent disease. Patients with second local recurrence do worse with 5-year LC rate of 23% (Kwong et al., 2001). This study had only one patient with locally persistent disease and this patient was disease free for more than 5 years.

Various publications have stressed the importance of re-irradiation dose as an independent prognostic factor for OS and LC. However, re-irradiation using mainly EBRT techniques to more than 60Gy failed to achieve long term LC instead was associated with significant neurological complications (Teo et al., 1998). Re-irradiation doses between 50-60Gy were able to obtain 100% LC rate for recurrent T1-3 lesions using IMRT techniques (Han et al., 2012). Other studies show retreatment total dose between 50-60Gy was associated with improved LRFS or OS (Chang et al., 2000; Leung et al., 2000). However, normalised total brachytherapy dose was not demonstrated to have a statistically significant effect on OS. Only the total dose from the EBRT was shown to be associated with a significant effect on OS (Terlikiewicz et al., 2005).

Combined modality treatment has also been shown to improve LRFS and DFS (Leung et al., 2000). In addition, combination therapy was associated with significantly less complications even in the era of IMRT (Koutcher et al., 2010; Leung et al., 2000). A combination of EBRT dose of 40Gy and normalised total dose of 10-20Gy with brachytherapy may achieve an adequate tumouricidal dose with acceptable risk of complications.

About 20% of our study population subsequently developed distant metastases. Median time to distant metastases was 14 months (range: 8-35 months). Three patients were diagnosed with distant metastases within a year. The most common sites of distant metastases were

the liver and lung. All patients who developed distant metastases had evidence of loco-regional recurrence. In comparison, a large retrospective study in an endemic area with recurrent NPC only found distant metastatic rate of 6%. Bone metastases were the commonest and the earliest site of metastases which accounted for about 40% of cases (Yang et al., 1996; Liu et al., 2008).

The rate of complications in our study may not reflect the actual incidence of complications secondary to salvage RT due to under-reporting. Another important factor to bear in mind in interpreting our complication results was the difficulty in differentiating between primary RT and salvage RT as the primary factor to the development of complications. Based on available data, major complications occurred in 34.9% of our patients. Comparatively, about 57% of patients in a large retrospective review developed major complications after salvage radiation in locally recurrent NPC (Teo et al., 1998). The most common major complication encountered in our study was moderate to severe trismus involving approximately 20% of the patients. A retrospective review comparing outcome among EBRT, CMT and ICBT alone as salvage for recurrent NPC found a higher percentage of patients in the EBRT arm alone that experienced trismus (37%) as compared to CMT (24%) or brachytherapy alone (13%) (Teo et al., 1998). This finding is consistent with our study although an even higher percentage (70%) of our patients who received combination treatment developed moderate to severe trismus. Central nervous system (CNS) complications occurred in approximately 12% of our patients. There were three patients with temporal lobe necrosis or sclerosis. All of them were staged rT1. All three patients received primary CCRT and were retreated within 14-21 months. The normalized total dose received was 62.5Gy (EBRT: 50Gy). We speculate that this may be due to inadequate neural tissue recovery as the time interval was short and may be compounded by the concurrent usage of chemotherapy during the initial treatment. A lower dose of EBRT combined with a higher ICBT component may reduce this neurological complication.

In conclusion, our study shows ICBT was associated with a reasonable long term outcome in salvaging recurrent NPC and should be considered as an option in reirradiation alone or in combination with EBRT.

References

Chan ATC, Teo PML, Ngan RK, et al (2002). Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol*, **20**, 2038-44.

Chang JTC, See LC, Liao CT, et al (2000). Locally recurrent nasopharyngeal carcinoma. *Radiotherapy and Oncol,* **54**, 135-42.

Chong VFH, Khoo JBK, Chan LL, et al (2002). Neurological changes following radiation therapy for head and neck tumours. *Eur J Radiol*, **44**, 120-9

Chua DTT, Sham JST, Au GKH (2005). Induction chemotherapy with cisplatin and gemcitabine followed by reirradiation for locally recurrent nasopharyngeal carcinoma. *Am J Clin Oncol*, **28**, 464-71.

Chua DTT, Sham JST, Kwong DLW, et al (1998). Locally recurrent nasopharyngeal carcinoma: treatment results for patients with computed tomography assessment. *Int J Radiation Oncol Biol Phys*, **41** 379-86.

Chua DTT, Wu SX, Lee V, et al (2009). Comparison of single versus fractionated dose of stereotactic radiotherapy for salvaging local failures of nasopharyngeal carcinoma: a matched-cohort analysis. *Head and Neck Oncol*, **1**, 13.

Emami B, Lyman J, Brown A, et al (1991). Tolerance of normal tissue to therapeutic irradiation. *Int J Radiation Oncol Biol Phys*, **21**, 109-22.

Han F, Zhao C, Huang SM, et al (2012). Long-term outcomes and prognostic factors of re-irradiation for locally recurrent nasopharyngeal carcinoma using intensity-modulated radiotherapy. *Clin Oncol*, **24**, 569-76.

Law SCK, Lam WK, Ng MF, et al (2002). Reirradiation of nasopharyngeal carcinoma with intracavitary mould brachytherapy: an effective means of local salvage. *Int J Radiation Oncol Biol Phys*, **54**, 1095-113.

Lee AWM, Foo W, Law SCK, et al (1999). Recurrent nasopharyngeal carcinoma: the puzzles of long latency. *Int J Radiation Oncol Biol Phys*, **44**, 149-56.

Lee AWM, Kwong DLW, Leung SF, et al. (2002). Factors affecting risk of symptomatic temporal lobe necrosis: significance of fractional dose and treatment time. *Int J Radiation Oncol Biol Phys*, **53**, 75-85.

Lee AWM, Poon YF, Foo W, et al (1992). Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. *Int J Radiation Oncol Biol Phy*, **23**, 261-70.

Lee AWM, Sze WM, Au JSK, et al (2005). Treatment results for nasopharyngeal carcinoma in the modern era: The Hong Kong experience. *Int J Radiation Oncol Biol Phys*, **61**, 1107-16.

Lee AWM, Yau T (1997). Complications of radiotherapy in nasopharyngeal carcinoma. Chong VFH and Tsao S.Y (eds). 1st ed. Armour Publishing Singapore, 114-127.

Leung TW, Tung SY, Sze WK, et al (2000). Salvage brachytherapy for recurrent nasopharyngeal carcinoma. *Int J Radiation Oncol Biol Phys*, **48**, 1331-38.

Liu MZ, Tang LL, Zong JF, et al (2008). Evaluation of sixth edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement. *Int J Radiation Oncol Biol Phys*, **70**, 1115-23.

Marks LB, Yorke ED, Jackson A, et al (2010). Normal tissue complication probability models in the clinic. *Int J Radiation Oncol Biol Phys*, **76**, 10-9.

Koutcher L, Lee N, Zelefsky M, et al (2010). Reirradiation of locally recurrent nasopharynx cancer with external beam radiotherapy with or without brachytherapy. *Int J Radiation Oncol Biol Phys*, **76**, 130-7.

Kwong DLW, Wei WI, Cheng ACK, et al (2001). Long term results of radioactive gold grain implantation for the treatment of persistent and recurrent nasopharyngeal carcinoma. *Cancer*, **91**, 1105-13.

McDonald MW, Moore MG, Johnstone PAS (2012). Risk of carotid blowout after reirradiation of the head and neck: a systematic review. *Int J Radiation Oncol Biol Phys*, **82**, 1083-9.

Poon D, Yap SP, Wong ZW, et al (2004). Concurrent chemoradiotherapy in locoregionally recurrent nasopharyngeal carcinoma. *Int J Radiation Oncol Biol Phys*, **59**, 1312-8.

Sham JST, Kwong PWK, Hung K, et al (2003). Linear accelerator-based stereotactic radiosurgery for limited, locally persistent, and recurrent nasopharyngeal carcinoma: efficacy and complications. *Int J Radiation Oncol Biol Phys*,

56, 177-83.

Suntharalingam N, Podgorsak EB, Tolli H (2005). Brachytherapy: physical and clinical aspects in radiation oncology physics: a handbook for teachers and students. Podgorsak EB (ed.). 1st ed. International Atomic Energy Agency. Vienna. Austria: 451-83.

Syed NAM, Puthawala AA, Damore SJ, et al (2000). Brachytherapy for primary and recurrent nasopharyngeal carcinoma: 20 years' experience at long beach memorial. *Int J Radiation Oncol Biol Phys*, **47**, 1311-21

Teo PML, Kwan WH, Chan ATC, et al (1998). How successful is high-dose (>60Gy) reirradiation using mainly external beams in salvaging local failures of nasopharyngeal carcinoma. *Int J Radiation Oncol Biol Phys*, **40**, 897-913

Terlikiewicz J, Makarewicz R, Lebioda A, et al (2005). An analysis of outcomes after re-irradiation by HDR (High-Dose-Rate) brachytherapy among patients with locally recurrent nasopharyngeal carcinoma (NPC). *Rep Pract Oncol Radiother*, **10**, 193-201

Yang TS, Wang HM, Liaw CC (1996). Prognostic factors of locoregionally recurrent nasopharyngeal carcinoma-A retrospective review of 182 cases. *Am J Clin Oncol*, **19**, 337-43.

Zhang EP, Lian PG, Cai YF, et al. (1989). Radiation therapy of nasopharyngeal carcinoma: prognostic factors based on a 10 year follow-up of 1302 patients. *Int J Radiation Oncol Biol Phys*, **16**, 301-5.

Zheng XK, Ma J, Chen LH, et al. (2005). Dosimetric and clinical results of three-dimensional conformal radiotherapy for locally recurrent nasopharyngeal carcinoma. *Radiotherapy and Oncology*, **75**, 197-203.