GAMMA KNIFE RADIOSURGERY FOR RECURRENT NASOPHARYNGEAL CANCER

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Purpose : To report the results of salvage treatment of recurrent nasopharyngeal cancers (NPC) using Gamma Knife radiosurgery (GK) alone or combined with conventional radiotherapy.

Materials and methods : From 1993 to 1997, eleven patients (6 males and 5 females) were diagnosed to have recurrent tumors over the primary site of nasopharynx and/or skull base at our hospital after initial radiotherapy. The time interval between the primary radiotherapy and salvage GK was 1 to 12 years (median = 2.0 years). All patients received single fraction of Gamma Knife radiosurgery was performed with peripheral doses of 12.5 to 20 Gy (median = 15 Gy) to cover the recurrent tumor as conformal as possible. The tumor volumes (TV) were less than 1 to 33 cc (median = 11cc) whereas radiation volumes (RV) were 6 to 48 cc (median = 20.9 cc). Retrospectively the patients were divided into two groups according to their treatment. Four patients received GK without further radiotherapy (Group A). The other 7 patients received hyperfractionated external beam radiotherapy of 30 to 47 Gy (median = 38 Gy) and concurrent chemotherapy (cisplatin, 5-FU, mitomycin C) for further boost of the tumor (Group B).

Result : All patients tolerated GK well without significant acute toxicity. The first MRI after GK showed tumor regression for eight out of nine patients receiving this examination. One patient died of sepsis induced by concurrent chemotherapy, not receiving fractionated RT. For the other 3 patients receiving GK without combined RT (group A), 2 tumors recurred 7 and 15 months later and one patient lost to image follow-up and expired within 6 months after GK. Five out of seven patients of group B remained local control at the last image follow-up (6 to 62 months after GK). However, three patients of this group of had prominent brain damage shown by MRI and PET scan after salvage irradiation. The median survival of all our patients is 48.8 months. The five-year survival rate is 36.4%.

Conclusion : Combined fractionated RT, GK radiosurgery and concurrent chemotherapy seem to achieve better local control for intracranially recurrent NPC than GK alone. It is not recommended to use single-fraction radiosurgery to salvage a newly diagnosed skull base recurrent NPC. Bilateral opposing fields in fractionated RT should be avoided to lower the incidence of late complications.

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INTRODUCTION

Fractionated external-beam radiotherapy (RT) represents an important primary treatment modality in the management of patients with nasopharyngeal cancer. However, in spite of the satisfactory local tumor control that can be achieved by RT, primary tumor relapse does occur at a frequency of 10 to 56% [2,6], depending on different initial stages. Recurrent NPC over the primary site after full-dose RT is a challenge for radiation oncologists because of the high incidence of late complications associated with re-irradiation. Previously reported treatment for this problem included brachytherapy, chemotherapy, surgery and/or re-irradiation with conventional RT [1,4,5,12]. However, for intracranial or skull base recurrence it is difficult to treat the tumors successfully with either surgery or brachytherapy. Salvation with conventional RT for the intracranial lesions after previous full-dose irradiation carries a high risk of late sequela. Radiosurgery is another alternative modality of treatment for these recurrences. Re-irradiation with Gamma Knife (GK) or linac-based radiosurgery can obtain conformal dose distribution with multi- isocenter technique. In treating patients with GK, each shot or isocenter of GK have 201 beams from 201 Co-60 sources. Therefore it spares the surrounding normal tissues and gives high dose to the tumor bed at the same time. Previous reports showed that radiosurgery alone or combined with external beam RT could obtain at least palliative effect for the recurrent NPC over the primary site or intracranial region [3,8,9]. In this article we retrospectively review our series of patients with recurrent NPC treated either with GK radiosurgery alone or combined GK with external beam RT.

MATERIALS AND METHODS

From 1993 to 1997, 12 patients (7 males & 5 females) with recurrent nasopharyngeal cancer post definitive RT were irradiated by Gamma Knife radiosurgery as an important part of their salvage treatment. One patient was excluded from this review because the patient had open surgery for debulking the main tumor over the sphenoid sinus before GK. The size of this tumor was too large to be treated with the Gamma Knife without surgery. The general data of our patients under analysis are listed in Table 1. Patient number was assigned in the order of GK date. According to the radiation treatment they received, they were retrospectively classified as group A (GK alone, 4 patients) or group B (GK plus fractionated RT, 7 patients).

For each patient, a stereotactic frame (Leksell Model B from Elekta Instruments, Atlanta, GA) was applied under local anesthesia by our neurosurgeons before image study. Magnetic resonance imaging (MRI) was performed with and without gadolinium injection to define the tumor location and shape. The neuroradiologists and radiation oncologists did target delineation. Treatment planning system for GK: KULA for 7 patients, Leksell Gamma Plan (version 4.0) for four. A 201-source Cobalt 60 gamma unit (Model B, Elekta Instruments, Atlanta, GA) was used for radiosurgery. The patient's head was rigidly fixed by the frame and attached the GK collimator helmet according to the pre-set coordinates. Precise radiation dose was then given.

For GK treatment planning, radiation volumes for GK were 6.4 to 48.1 cc (median = 20.9 cc). Shot number for GK: 2 to 19 (median = 12). Usually multiple shots were used to make the dose distribution as conformal as possible. Tumor doses given by GK: 12.5 to 20 Gy at 50 to 60% isodose volumes in single fraction (median = 15 Gy).

For fractionated external beam RT, the fraction size is 1.05 Gy to 1.2 Gy/fraction, bid, total 30 to 47 Gy (median = 38 Gy). Two patients (Case 5 and 7) received RT before GK,

Table 1. General data of patients

Patient	Treatment Group*	Age	Sex	Previous RT (Gy) before GK	Last RT - GK Interval	Recurrent sites
1	A	55	M	70	4 y	NP
6	A	54	M	70	3 y	CS
8	A	48	M	70 + 50***	1 y	NP & CS
9	A	37	F	70 + 70 + Brachytherapy***	2 y	CS & clivus
2	B	39	F	70	10 m	CS
3	B	43	F	70	1 y	CS
4	B	45	F	59.5 **	12 y	SS & CS
5	B	66	F	70	2 y	NP, OF, CS
7	B	28	M	80	6 m	CS
10	B	68	M	70	4 y	NP & CS
11	B	49	M	70	10 m	CS

CS- cavernous sinus, Fx- fraction, NP- nasopharynx, OF- orbital fossa, SS- sphenoid sinus
* See text for grouping ** Fraction size is 17 fractions
*** The treatment after the initial 70 Gy was used for salvage treatment for the recurrence.

Table 2. GK and fractionated external beam RT parameters

Patient	Group	Planning System	Volume (ml) RV	TV	Dose (Gy) Prescribed	Max	IDL %	# of shots	FEBRT Dose (Gy)	FEBRT Fx	FEBRT technique
1	A	KULA	6.4	0.0*	20.0	40	50	2	-	-	-
6	A	KULA	10.1	7.9	15.0	30	50	10	-	-	
8	A	LGP	48.1	33.0	13.5	27	50	17	-	-	
9	A	LGP	35.5	25.6	14.0	28	50	18	-	-	
2	B	KULA	20.9	11.0	15.0	30	50	12	31.2	26	BLO
3	B	KULA	21.1	12.3	12.5	25	50	12	36	30	BLO
4	B	KULA	9.9	4.9	15.0	30	50	10	30	25	BLO
5	B	KULA	17.2	8.3	15.0	30	50	12	36	26	BLO
7	B	KULA	10.1	6.2	15.0	30	50	12	47	45	O3F
10	B	LGP	38.1	30.5	14.0	28	50	19	40.8	34	3DC
11	B	LGP	18.0	13.2	14.4	24	60	16	40.8	34	3DC

FEBRT - fractionated external beam RT, BLO - bilateral opposing fields, LGP - Leksell Gamma Plan, O3F - oblique 3 fields, 3DC - 3 Dimensional Conformal (Render Plan) IDL—isodose line.
* < 5 mm in diameter, too small to be measured.

and the other 5 patients received GK before RT. Within the combined GK plus RT group, all patients except the last two cases received opposing fields with custom-made blocks for the recurrent tumors. The last two cases received 3-D conformal radiotherapy (3 and 4 fields respectively) planned with Render Plan. The GK and fractionated external beam RT parameters are summarized in Table 2.

Five patients receiving GK without additional conventional RT because of: (1) very small tumor size (patient 1) or (2) previous two courses of high-dose conventional RT (patient 8,9), or (3) the patient refused (patient 6).

Chemotherapy (C/T) composed of cisplatin (20 to 60 mg/ m^2 on D1, single dose) + 5-FU (700 mg/ m^2 on D1-4, 24 hour continuous infusion) + or - mitomycin-C (4 to 6 mg/ m^2 on D1, single dose), given concurrently with GK and/or conventional RT as radiosensitizers for most of the patients of the two groups.

Most of our patients were regularly followed up at our OPD and received MRI for tumor and side effect evaluation at intervals of three to six months. Survival data was analyzed by computer software (Stata, version 6.0)

RESULTS

Follow-up data

The treatment outcome for group A and B were listed in Table 3.

Acute toxicity

All but one patient tolerated GK and combined treatment well without severe acute toxicity. One patient died of sepsis, which was induced by concurrent chemotherapy within 2 weeks after GK radiosurgery.

Local control

Nine patients had image follow-up with MRI. For the other two cases (belonging to group A) the local control could not be evaluated and they both expired within 7 months after GK. Five out of seven patients of group B remained local control at the last image follow-up (6 to 62 months after GK). However, two patients of group A were found to have local failure 7 to 15 months after GK. The MRI pictures of some of the recurrent tumors before and after combined treatment are shown in Figure 1.

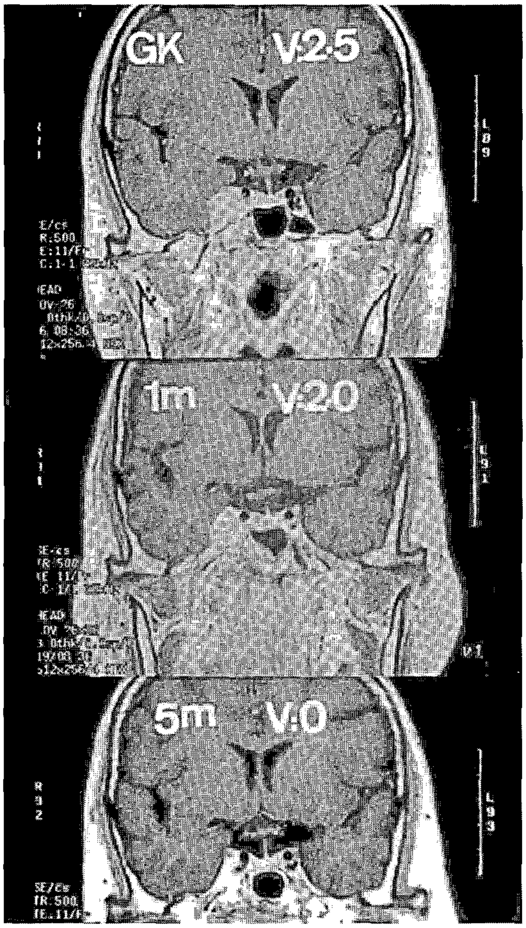

Fig 1. The MRI pictures of patient No. 2 (coronal view) before and after combined GK and fractionated RT treatment.

Table 3. Follow-up data

Patient	Group	Image FU in months	Tumor Status	Survival in months	Alive / Dead	Complication(s)	Further Salvage Treatment
1	A	16	LF in NP	51	D	MNB	Op x3, RT x1
6	A	—	No image follow-up	7	D	?	—
8	A	—	No image follow-up	0.4	D	Sepsis	—
9	A	7	LF	12	D	—	RT 50Gy/41 Fx
2	B	39	CR of CS, relapse in NP	110	D	TLN	—
3	B	53	LC	69	A	TLN	Op for TLN
4	B	46	LC	49	D	TLN, MNB	—
5	B	3	Residual	4	D	?	—
7	B	31	LC, R/O SF	34	D	—	—
10	B	6	LC	8	D	MNB	—
11	B	62	LC	62	A	TLN	—

CR - complete response, CS - cavernous sinus, LC - local control, LF - local failure, TLN- temporal lobe necrosis, MNB - massive nasal bleeding, SF-systemic failure, Sepsis- chemotherapy induced

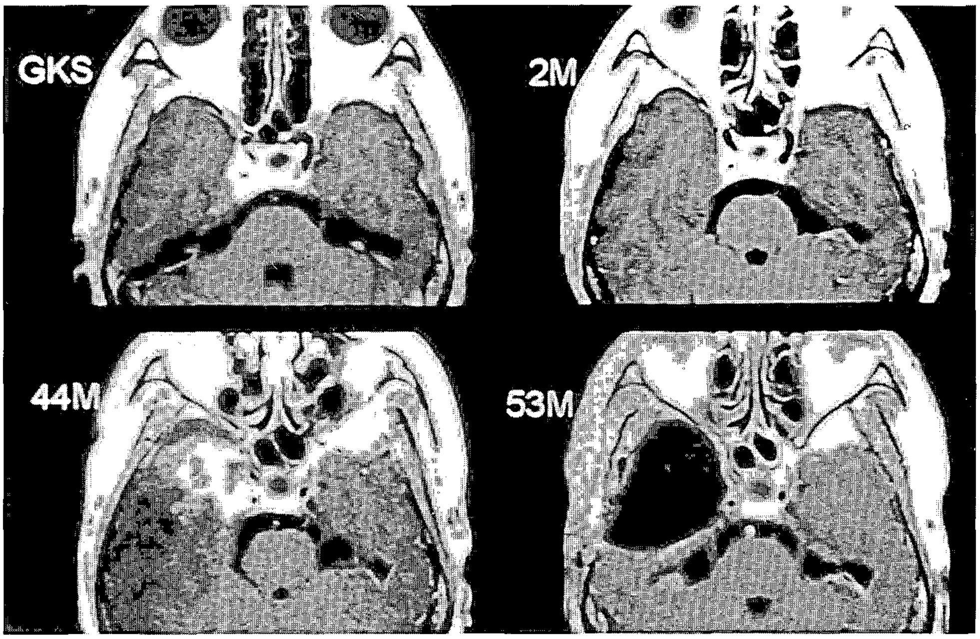

Fig 2. Long-term MRI follow-up of patient No. 3 (axial view). She had temporal lobectomy after right temporal lobe necrosis.

Late complications

Unfortunately patient 2 had brain necrosis of the temporal lobe detected by MRI 2 years after treatment. The other patient (patient 3) also developed symptomatic brain necrosis 2 years after GK revealed by MRI but her recurrent tumor remained controlled (Fig. 2). Our last patient (patient 11) also developed temporal lobe necrosis 3 years after GK but had good local control of his disease.

Survival

The median survival of all our patients is 48.8 months. The five-year survival rate is 36.4%. The overall survival curve after salvage irradiation of all our patients is shown in Fig. 3 .The separate survival curves of group A and group B are shown in Fig. 4. Group B seemed to have better survival than group A (logrank test, $p = 0.0710$).

DISCUSSION

From literature review, the use of conventional radiotherapy for recurrent primary NPC post full-dose irradiation can obtain a local control rate of around 26 to 40% and the incidence of sequela was 20% or higher [9,10,13]. Temporal lobe necrosis, brain stem damage, cranial neuropathy, and endocrine dysfunction are common complications because a significant volume of the normal brain tissue usually received accumulated high dose. The complication rate is hard to evaluate because many of these patients die soon after re-irradiation and do not have enough time to develop a significant complication. The 5-year survival rate after re-treatment was from 15 to 33% [9,11,13]. Besides external beam RT, surgery and brachytherapy have been used for salvage treatment. However, for patients who had tumor recurring above the skull base or intracranially, the treatment option will be more limited because the disease extent is beyond the scope in which surgery or brachytherapy can be successful. These patients are candidates for conformal irradiation with GK radiosurgery because previously irradiated normal brain tissue will be spared better and a large dose can be accurately directed toward the lesion site as a

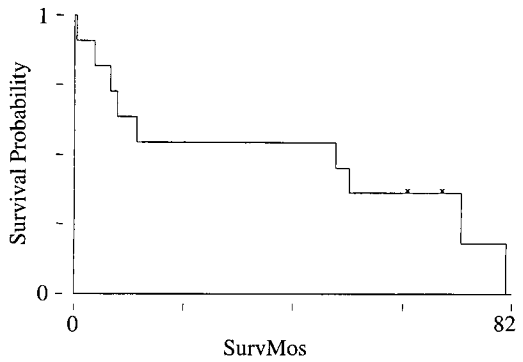

Fig 3. The Kaplan-Meier survival curve of all of our patients.

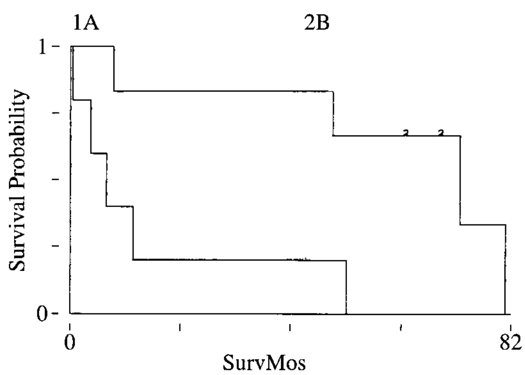

Fig 4. The Kaplan-Meier survival curves of the two different treatment group. Group B (combined GK and fractionated RT) had better survival than Group A (GK only).

part of salvage RT (boost) or used alone as palliative treatment.

Initially, we treated the first case with GK radiosurgery alone because the recurrent lesion is very small. However, for the following much larger recurrent tumors, GK and conventional RT plus concurrent chemotherapy were combined in order to obtain a durable period of tumor control. That goal was reached in most of our patients. The longest tumor control period is longer than 9 years. For the four patients receiving GK without additional conventional RT, all of them failed with two recurring within 15 months of GK.

We believe that GK radiosurgery alone is not adequate for long-term control of recurrent NPC for the following reasons: 1) from the viewpoint of radiobiology, fractionated irradiation has the advantage of re-oxygenation and redistribution and makes it possible to accumulate enough dose to obtain higher cure rate without severe complications. But what dose from a single fraction of GK can eradicate all malignant cells is still not known. 2) The dose gradient of each shot given by GK at the tumor margin is not adequate for microscopic disease infiltrating beyond the gross tumor volume (GTV). Fractionated external beam irradiation will complement this drawback by covering a safe margin around the visible tumor (CTV). Hyperfractionated radiotherapy may also reduce the tumor size and increase oxygen supply and indirectly increase the effectiveness of radiosurgery. Therefore, combination of fractionated RT is necessary to improve local control rate whenever possible.

In reviewing the dose of the two groups, we found that GK doses for group A (no further RT) are 13.5 to 20 Gy (median = 15 Gy). GK doses for group B (with further RT) are 12.5 to 15 Gy (median = 14.5 Gy). Though the patient number of each group is small, patients of group B seemed to have longer tumor control (and perhaps better survival) than group A, mainly due to extra dose from conventional RT.

The fractionated RT technique we used still left room for improvement. Before we had a 3-D treatment planning system, we used bilateral opposing fields for all but the last two patients. Therefore, the temporal lobe would receive the same dose as the tumor during external beam irradiation. We tried to decrease the late complication rate by using hyperfractionation (1.05 to 1.2 Gy per fraction, bid). Also, up to now the optimal dose for the best tumor control and the least complication is unknown. Gamma Knife radiosurgery plus fractionated radiotherapy seemed to have more durable tumor control than GK alone because of higher total dose in the former group. However, the risk of late brain damage still exists even after hyperfractionated external beam radiotherapy and we did see a significant number of late brain damage in the combined irradiation group (group B). To answer the question of optimal dosage, an investigation involving more patients is needed. Before the answer is available, we suggest planning the external beam with 3-D conformal technique or even IMRT using multiple fields to spare as much normal brain tissue as possible in order to decrease the incidence of late complications. Merely opposing fields should be avoided.

CONCLUSION

Combined fractionated external beam RT, GK radiosurgery and concurrent chemotherapy seem to achieve more durable local control for intracranially recurrent NPC. However, with the bilateral opposing fields, late complications of the brain may still occur in spite of hyperfractionated external beam RT. For the fractionated external beam RT, bilateral opposing fields should be replaced with 3D-conformal RT or IMRT consisting of multiple fields. The optimal combination of GK and conformal RT requires further investigation.

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以加馬刀治療復發鼻咽癌

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目的：探討以加馬刀治療放療後復發之鼻咽癌的結果。
材料與方法：自 1993 至 1997 年，共有十一位（六男五女）放療後復發的鼻咽癌病患接受加馬刀放射手術治療，首次放療與加馬刀的間隔時間是一至十二年（中位值二年）。加馬刀的治療劑量是 12.5 至 20 Gy（中位值 15 Gy），腫瘤體積是從小於 1 至 33 cc（中位值 11 cc），放療所照體積（Radiation Volume）是 6 至 48 cc（中位值 20.9 cc）經由回溯研究這些病人根據治療種類的不同而分為兩組：有四位病人僅接受加馬刀而無接受傳統放療（A 組）。另七名病人除加馬刀外接受傳統的分次體外放療（劑量 30 至 47 Gy ，中位值 38 Gy），及同步化療（Cisplatin ， 5FU 及 Mitomycin C），是為 B 組。
結果：所有病人都能完成加馬刀治療而無明顯之急性副作用。在九位有做 MRI 檢查的病人中有八位都看到腫瘤縮小。在 A 組病人中只有一位病人死於同步化療引起之敗血症，一位在六個月內死亡，另兩位病人在十五個月內復發。在 B 組病人中，有五位病人腫瘤長期控制良好。但這其中有三位病人在治療後 MRI 上發現有明顯的腦部損傷。所有病人的中位存活期為 48.8 個月，五年存活率為 36.4% 。
結論：加馬刀合併分次放療及同步化療對復發鼻咽癌似乎可以比單獨加馬刀達到較好的療效。分次放療宜避免用兩側對照的照野以免腦部損傷。
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關鍵詞：鼻咽癌、復發、放射手術、合併療法