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POSTER

Impact of observer delineation variation on target coverage and dose to organs at risk in nasopharyngeal cancer patients

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Purpose: To provide a qualitative and quantitative correlation between inter-observer variation and dose coverage of targets and organs at risk (OAR) in Nasopharynx Patients (NPC).

Materials & Method: Ten nasopharyngeal patients' were included in this study. Ten Head & Neck radiation specialists delineated the Clinical target volumes (CTV) on CT with MRI and specific delineation instructions available. A median CTV was determined for each patient and accounted as the reference target volume. A 3D margin of 5 mm was applied to generate the planning target volume (PTV). The optical chiasm, brainstem, spinal cord and cerebellum were delineated for evaluation. The inverse planning module of ADAC Pinnacle³™ was used to generate an IMRT plan for each CTV, resulting in eleven different dose distributions per patient.

In-house software package (Uncert[®]) simulating random and systematic errors was used to calculate the dose to the median CTV and organs at risk (OAR) for each dose distribution, delineation and patient. The 95% and 90% dose volume to the median CTV was used to calculate the delineation effect on the CTV. The maximum dose was used to determine the impact of the inter-observer variation on dose to the OARs.

Results: a) The 95% dose coverage of the median CTV was 95.7% (sd 4.9). For the same volume, the 95% dose coverage dropped to 84.8% (sd 8.10) when the treatment plans designed for the individual observer PTVs were applied ($p < 0.05$). b) There was a direct impact of inter-observer variation on the maximum dose to the OARs. For the chiasm, brainstem, spinal cord and cerebellum, the percentage of patients unable to fulfill both the pre-set PTV and OAR dose levels due to difference in observer PTV volumes, was 50%, 70%, 10% and 70% respectively.

Conclusion: Inter-observer delineation variation has a quantifiable direct impact on target dose coverage and influences dose to the OARs. Interobserver variation leads to underdosage or avoidance of designated tumor volumes and/or unnecessary radiation dose to normal tissues. Delineation variation has to be addressed and minimized for accurate and objective target delineation and ultimately for highly conformal radiation treatments.

Keywords: Delineation Effect, IMRT, Inter-observer Variation, Nasopharynx, Radiotherapy;

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Impact of induction chemotherapy on treatment outcome in patients with early stage nasopharyngeal carcinoma

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Background: Prospective phase III studies failed to show any impact on survival with the addition of induction chemotherapy in patients with nasopharyngeal carcinoma (NPC). In order to evaluate the role of induction chemotherapy on survival and failure patterns in different patient subgroups according to T and N stage, we performed subgroup analysis of two phase III trials.

Materials and Methods: The pooled data from two phase III trials comparing induction chemotherapy (cisplatin/epirubicin or cisplatin/bleomycin/5-fluorouracil) followed by radiotherapy (CRT) with radiotherapy alone (RT) in NPC were reviewed and analyzed according to the following 4 subgroups based on T and N stage (1997 AJCC stage classification system): Group 1 with early T and N stage (T1-2N1), Group 2 with advanced N stage (T1-2N2-3), Group 3 with advanced T stage (T3-4N0-1) and Group 4 with advanced T and N stage (T3-4N2-3). A total of 784 patients were included for analysis based on intent-to-treat. Median follow-up for surviving patients was 67 months.

Results: No significant differences in survival, loco-regional control and distant metastases-free rates were observed between CRT arm and RT arm in Group 2, 3 and 4. On the contrary, significant differences in survival and distant metastases-free rates were observed in Group 1 favoring CRT arm.

Conclusion: Our pooled data analysis showed that patients with early stage NPC (T1-2N1 or stage IIb) treated by radiotherapy alone had a relatively poor long term survival due to distant metastases which could be

improved by induction chemotherapy. Further studies to evaluate the role of adjunctive chemotherapy in early stage NPC are warranted.

	Group 1 (T1-2N1) n = 208	Group 2 (T1-2N2-3) n = 181	Group 3 (T3-4N0-1) n = 241	Group 4 (T3-4N2-3) n = 154
5-year survival rates				
CRT:	79%	55%	62%	44%
RT:	67%	60%	57%	43%
p:	0.048	0.98	0.16	0.51
5-year local relapse-free rates				
CRT:	86%	78%	65%	68%
RT:	83%	77%	56%	58%
p:	0.62	0.88	0.054	0.56
5-year nodal relapse-free rates				
CRT:	89%	77%	91%	74%
RT:	88%	73%	88%	70%
p:	0.81	0.96	0.58	0.80
5-year distant metastases-free rates				
CRT:	86%	61%	81%	55%
RT:	74%	70%	79%	49%
p:	0.0053	0.63	0.93	0.34

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Preliminary report of randomized phase II clinical study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma (NPC)

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Background: A prospective randomized phase II study was performed to evaluate the feasibility and efficacy of concurrent weekly oxaliplatin with radiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma (NPC).

Material and methods: From Jan. 2001 to Jan. 2003, 115 locoregionally advanced nasopharyngeal carcinoma were randomized, to either radiotherapy alone (RT arm, 56 patients) or to concurrent chemo-radiotherapy (CCRT arm, 59 patients). All patients' characteristics were well balanced in both arms. Concurrent chemotherapy with oxaliplatin 70 mg/m² weekly was given for six doses from the first day of radiotherapy. All patients were treated in an identical method by definitive-intent radiation therapy in both arms.

Results: All patients were eligible for toxicity and response analysis. After a median follow-up of 24 months, there is a significant difference in overall survival (OS), relapse-free survival (RFS) and metastasis-free survival (MFS) in favor of the CCRT arm. The 2-year overall survival rates were 100% for the CCRT arm and 77% for the RT arm ($P = 0.01$). The 2-year metastasis-free survival rate was 92% for the CCRT arm versus 80% for the RT arm ($P = 0.02$). The 2-year relapse-free survival rate was 96% for the CCRT arm versus 83% for the RT arm ($P = 0.02$).

Conclusion: Concurrent chemo-radiotherapy with weekly oxaliplatin is feasible and improves the survival rate as well as the metastasis-free survival rate and relapse-free survival rate in the patients with locoregionally advanced nasopharyngeal carcinoma. Therefore, further randomized study including oxaliplatin is warranted.

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POSTER

Results of nasopharynx cancer treated with high dose 3-dimensional conformal radiation therapy technique

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Background: Authors have used a unique 3-dimensional conformal radiation therapy technique in treating nasopharynx cancer (NPC), and named it 'Samsung Medical Center (SMC) technique'. Herein, we would report the clinical outcomes of NPC patients treated with this method.

Material and methods: SMC technique is based on "serial shrinking field" concept by 1.8 Gy daily fractions. The initial radiation volume includes all gross lesions plus clinically negative lymphatics (36 Gy), the second volume typically eliminates the electively included lymphatics (54 Gy), and the final boost volume is confined to the gross lesions (72 Gy). The

typical initial beam arrangements are 4 non-coplanar beams (anterior; right superior-anterior oblique; left superior-anterior oblique; and anterior-inferior oblique). From Oct. 2000 till Nov. 2004, 74 NPC patients were treated by this technique. 50 patients (67.6%) received cisplatin-based chemotherapy concomitantly and 24 patients (32.4%) were treated by radiotherapy alone. The male and female ratio was 59 (79.7%) and 15 (20.3%), and the median age was 49 (20–75) years. The median follow-up period was 23 (5–54) months. On 10 patients, rival plans using IMRT technique under RTOG guideline were generated and comparisons of the dosimetric parameters (TCP, NTCP) were performed.

Results: There were 2 patients with local failures, who were successfully salvaged with re-irradiation. Regional failures developed in 7 patients, and distant metastases in 11 patients. The 4-year loco-regional relapse-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) rates were 80.7%, 82.2%, 70.4%, and 76.8%, respectively. Multivariate analyses on prognostic factors revealed that younger age ($p = 0.03$) and good performance status (ECOG 0,1, $p = 0.04$) were significantly favorable with respect to OS, and concurrent chemotherapy was marginally significant with respect to DFS ($p = 0.05$) and LRFS ($p = 0.05$). The dose coverage in all target volumes and the normal organs were not significantly different between SMC technique and IMRT, however, the mean time of treatment delivery was much shorter with SMC technique than with IMRT (20 vs 50 min).

Conclusions: We could achieve improved clinical outcomes compared with historic data by high dose radiation using SMC technique. SMC technique seems to be very effective, time-saving, and enables adjustment based on tumor shrinkage.

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Preliminary results of phase I and II study of "simultaneous modulated accelerated radiation therapy" (SMART) for non-disseminated nasopharyngeal carcinoma

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Purpose: To introduce our preliminary results with intensity-modulated radiotherapy (IMRT) using SMART (Simultaneous Modulated Accelerated Radiation Therapy) boost technique in the treatment of nasopharyngeal carcinoma. The end points of this study were compliance, acute toxicity, initial tumor response, clinical feasibility, and dose statistics of this protocol.

Methods and Materials: Twenty patients who underwent IMRT for non-disseminated nasopharyngeal carcinoma at the Asan Medical Center between September 2001 and December 2003 were evaluated by prospective analysis. According to the 1997 American Joint Committee on Cancer staging classification, 1 had Stage II, 11 had Stage III, and 8 had Stage IV disease. The IMRT plans were designed to be delivered as a SMART using the "step and shoot" technique with a MLC (multileaf collimator). Daily fractions of 2.4 Gy and 2 Gy were prescribed and delivered to the GTV and CTV including clinically negative neck node, respectively. The prescribed dose was 72 Gy to the gross tumor volume (GTV), 60 Gy to the clinical target volume (CTV) and metastatic nodal station, and 46 Gy to the clinically negative neck. This fractionation schedule was completed in 6 weeks with 5 daily fractions weekly. All patients also received weekly cisplatin during radiotherapy. Acute and late normal tissue effects were graded according to the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria, subjective salivary function, weight loss, feeding gastrostomy, admission and the need for treatment split. Initial tumor response was assessed by physical examinations including nasopharyngoscopy and FDG-PET scan.

Results: Median follow-up period was 27 months (ranging from 15 to 44 months). All but one patient completed the treatment without any interruption. This patient interrupted 2 weeks due to severe pharyngitis and malnutrition. Five patients (25%) had RTOG Grade 3 mucositis while 9 patients (45%) had Grade 3 pharyngitis. Seven of 20 patients (35%) had weight loss greater than 10% of their pretreatment weight. Eleven patients (55%) required intravenous fluids, tube feeding or both. There were no Grade 3 or 4 xerostomia and all patients had experienced improvement of salivary gland function. All patients showed complete response and loco-regional control rate was 100%. Two patients were found to have multiple bone metastases at 3 months follow-up and multiple liver metastases at 10 months follow-up, respectively. To date, there have been one nodal and one local recurrence in the complete responders.

Conclusion: "Simultaneous Modulated Accelerated Radiation Therapy" (SMART) boost intensity-modulated radiotherapy technique allows parotid sparing as evidenced both clinically and by dosimetry. It may also be biologically more effective. Initial tumor response and loco-regional control was promising. It is clinically feasible. A larger population of patients and a long-term follow-up are needed to evaluate ultimate tumor control and late toxicity.

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POSTER

Hypothyroidism after radiotherapy for nasopharyngeal cancer patients

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Purpose: To determine the incidence of post-treatment hypothyroidism in nasopharyngeal carcinoma (NPC) patients after radical treatment, and to investigate the possible factors that could predict the onset of hypothyroidism.

Material and methods: From December 1983 to April 2003, 408 NPC patients received regular annual thyroid hormone prospectively after radical treatment. There were 286 males and 122 females. The median age was 47.3 years. Thyroid function was prospectively evaluated by measuring thyroid stimulating hormone (TSH) and serum free thyroxine (FT4). Low level of FT4 is classified as clinical hypothyroidism. The studied risk factors included age, gender, tumor extent, treatment modality, radiation dose, neck boost, re-irradiation, and chemotherapy.

Result: With a median follow-up of 4.3 years (range, 0.54–19.7 years), the incidence of low FT4 at 3 year is 4.9%, 5 year 9.0% and 10 year 18.8%. Hypothyroidism was more common in younger age (<30 years) ($P = 0.007$), female gender ($P = 0.041$), and those treated with conformal therapy (3D) technique ($P = 0.041$). T and N stage, chemotherapy, re-irradiation and neck electron boost did not affect the hypothyroidism. Younger age and conformal therapy are significant factor that determined the clinical hypothyroidism. Patients with elevated TSH will develop low FT4 at median 1 year later.

Conclusion: There are 20% of NPC patients will experience clinical hypothyroidism at 10 years after treatment. Younger age and conformal therapy will increase the risk of hypothyroidism. Regular thyroid hormone follow-up was suggested for these patients.

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POSTER

Brain necrosis in nasopharyngeal cancer patients – prospective study with MRI

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Introduction: To evaluate the incidence of brain necrosis (BN) after radical treatment in nasopharyngeal cancer (NPC) patients with prospective magnetic resonance image study.

Material & methods: There were 452 NPC patients completed radical treatment and received annual MRI following after radical treatment in Chang Gung Memorial Hospital from 1995/1/1 to 2000/12/1. One hundred and forty five patients received conventional bil-opposing treatment (COT) for 68–72 Gy with 1.8–2 Gy per fraction and 5 fractions per week. Seventy six patients received concomitant boost radiotherapy (CBT) for 72.3 Gy with twice daily radiotherapy at the last of two weeks. Twenty nine patients received twice daily radiotherapy (BID) for 81.6 Gy with 1.2 Gy per fraction and two fractions per day. Two hundred and two patients received 3D conformal radiotherapy boost (3DCRT) after 46–46.8 Gy of bil-opposing treatment to total 72–76 Gy with 1.8–2.0 Gy per fraction and five fractions per day. Seventy seven patients received brachytherapy boost. One hundred and twenty four patients received induction chemotherapy as part of treatment. All the patients received MRI as initial staging and radiotherapy treatment targeting reference. MRI was done 3 months after radical radiotherapy then annually at least 5 years after radical radiotherapy. The brain necrosis was defined as T2 image change or necrosis change in brain tissue in the following up MRI.

Result: The overall incidence of BN in NPC patients was 11.2% in 3 year and 25.1% in 5 year. The elder patients have more chance to have BN than younger patients (34.3% vs. 17.3% in 5 year). Advanced overall stage, advanced T stage, more external radiotherapy dose and re-irradiation have more BN risk. The BN incidence in COT, CBT, BID and 3DCRT was 20.8%, 50.4%, 39.4% and 5.3% respectively in 5 year. T stage, external radiotherapy dose, age, re-irradiation and treatment technique do impact to BN after multi-variant analysis.

Conclusion: The incidence of BN is not low in conventional opposing radiotherapy technique in radical NPC treatment. The use of 3DCRT technique will decrease significantly decreased but CBT or BID will increase the brain necrosis incidence.