The Effectiveness of Clinical Practice Guideline for Nasopharyngeal and Oropharyngeal Cancer to Reduce Acute Treatment Toxicity from Concurrent Chemoradiation

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Objective: *To evaluate the effectiveness of clinical practice guidline(CPG) for nasopharyngeal carcinoma (NPC) and oropharyngeal carcinoma (OPC) on reducing acute toxicity during concurrent chemoradiation (CRT).*
Material and Method: *The prospective study enrolled 74 patients diagnosed of NPC and OPC that underwent concurrent CRT.The feasibility of CPG was evaluated.*
Results: *Each checkpoint in CPG is feasible with 76% compliance of three in four points and 24% complete all points. Overall grade 3 or 4 skin reaction and mucositis are 9 and 8% respectively.*
Conclusion: *CPG that consisted of preventive methods to reduce acute skin and oral mucosa toxicities in NP and OP patients is easy to follow with 24 to 100% compliance. This can be feasible with consideration about immobilization device and energy treatment machine.*

Keywords: *Nasopharyngeal cancer, Oropharyngeal cancer, Concurrent chemoradiation*

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Nasopharyngeal carcinoma (NPC) and orophyngeal carcinoma (OPC) are common cancers in Thailand with an incidence rate of 3.3% of all cancer diagnosed in Siriraj Hospital[1].

Patients with locally advanced stage NPC despite good initial local control tend to develop locoregional recurrence and/or distant metastases after radiation therapy (RT) alone. A multicenter randomized trial conducted in North America (Intergroup Study 0099) that used concurrent chemo radiation (CRT) by adding cisplatin followed by adjuvant cisplatin and fluorouracil did showed significant survival benefit favoring combined modality arm with significant fewer loco regional failure and distant metastases[2].

For OPC, most patients present with locally advanced tumors and require a multimodality approach. CRT is preferred for T3-4 or N2-3 with improved locoregional control and survival as shown in several randomized trials and a metaanalysis[3-5]. Although OPC often predominated in these clinical trials, they were not site specific. However, this meta-analysis further justified the use of concurrent CRT as a standard non-operative treatment for this disease.

Improved treatment outcomes from concurrent CRT have come at the expense of increased toxicities that worsen patients' quality of life during and after RT.

Volumes of RT in NPC and OPC are a complex region composed of several structures with an inherent response to radiation such as mucosal linings, skin coverings, subcutaneous connective tissue, salivary gland, teeth, and bone.

Acute changes produced by RT consist of mucositis, desquamation of skin, decrease in serous output of saliva, and decreased acuity of taste buds. The prevention or reduction of acute side effects by prophylactic measures is simpler than treatment of already existing symptoms. The approaches with preventive intention include pre-RT dental care, improved technique of RT, and appropriate supportive care for patients during RT. Dental counseling is strongly recommended because only 11% of patients

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who reported regular visits with a dentist before diagnosis of oral cancer were judged to have no dental conditions that needed treatment[6]. The improved technique of RT are delivery of radiation from two opposing fields to reduce dose to healthy tissue and changing depth of dose description point base on patients' weight loss. The clinical practice guideline (CPG) for RT in NPC in Siriraj Hospital institution has been developed since 2001. Care team for the patients with NPC was also developed and involved the preventive methods mentioned above. The CPG was revised in 2005 to develop four checkpoints based on prevention as above for guideline compliance. These checkpoints were extended to be used in OPC. The objectives of the present study were to evaluate the feasibility and impact of this guideline on acute side effects during concurrent CRT in our patients.

Material and Method

Patient characteristics

The patients with locally advanced NPC and OPC who were evaluated by multispecialty approach (ENT, radiation oncologist, medical oncologist) in Siriraj tumor clinic to receive concurrent platinum-based RT in Siriraj hospital were prospectively enrolled in the present study. Other inclusion criteria's were squamous cell or undifferentiated cell type for NPC, squamous cell type for OPC, no previous RT in the same area, no previous chemotherapy within 21 days, ECOG performance status 0-1, age 15-75 years and no concurrent medication for radioprotection during RT. The exclusion criteria included pregnancy and history of previous malignancy (except adequately treated basal cell carcinoma of skin). The present study was approved by Siriraj Ethical Committee (SI136/2008).

Pre-treatment assessment

Pre-treatment evaluation included complete physical examination, computed tomography of nasopharynx and neck, chest x-ray, complete blood count, and renal and liver function tests. All patients were required to give written informed consent before registration.

Radiotherapy

All patients were irradiated with photon beam by cobalt-60 machine. Primary tumors and regional cervical lymph nodes were treated with conventional fractionation of two Gy per fraction, five daily fractions per week, for a total dose 66-70 Gy for gross tumors by shrinking-field technique (2 lateral opposing faciocervical fields with spinal cord-sparing field after 46 Gy). Anterior lower cervical field received only total 50 Gy if no clinically positive lymph nodes in this area. For clinically positive cervical lymph nodes, total dose was supplemented with electron beam.

Chemotherapy

Patients were planned to receive concurrent intravenous cisplatin during external RT either by 3-weekly on day 1, 22, and 43 (dose 100mg/m2) of RT or weekly (dose 40 mg/m^2) regimen. Patients received antiemetics based on the investigator's preference and patient's need. The complete blood count was checked before each chemotherapy cycle.

Patient assessment

For compliance to CPG, four points of patient compliance to CPG in Siriraj Hospital institution consists of 1: pre-RT dental care by dentists (yes = 1, no = 2), 2: RT by two lateral opposing fields per day (yes = 1, no = 2), 3: dose recalculation for change of tumor depth ($\geq$ 0.5 cm) after 30 Gy of RT (yes = 1, no = 2) and 4: individual patient counseling for best supportive care for four times during RT by well-trained nurses (yes = 1, no = 2).

For treatment toxicities, incidence of $\geq$ grade 3, acute treatment toxicities were recorded weekly according to CTC. AC version 3.0 during course of RT. For NPC, the results in the 3-weekly chemotherapy group would be compared to those in historical data. The historical data was collected from NPC patients treated with concurrent CRT in Siriraj Hospital between April and November 2003.

Statistical analysis

The sample size was calculated using a two-sided test with 5% estimated loss of follow-up. The primary end-points was compliance to CPG and treatment toxicities. The patient characteristics and toxicity rates of NPC patients in 3-weekly chemotherapy group were compared to those in historical data using the chi-square test or Fishers' exact test. P-value of less than 0.05 was considered significant.

Results

Patient characteristics

Between October 2005 and March 2008, 80 patients were enrolled. The present study was prematurely closed because of slow accrual. Six patients were excluded for eligibility reasons and included four that had not received concurrent CRT as

in the plan and two that received incomplete RT course. Therefore, 74 patients were eligible for evaluation. Patients characteristics are shown in Table 1.

Radiotherapy

Patients were treated with conventional RT at median dose 70 Gy (range 66 to 70 Gy). Eleven (85%) patients in the weekly regimen group were immobilized in thermoplastic masks to increase reproducibility and accuracy of treatment. Only one patient in the 3-weekly regimen group used a mask. All patients received complete intended RT with more than a 7-day interruption in four patients due to treatment-related toxicity including skin reaction in two and neutropenia and/or leucopenia in two patients.

Chemotherapy

Among all 74 patients, 61 (82%) received concurrent cisplatin on 3-weekly regimen and 13 (18%) received concurrent weekly cisplatin during RT (Table 2).

Compliance to guideline

Table 3 shows compliance of the patients during treatment according to CPG from Siriraj Hospital institution. Twenty-three patients (92%) completed three points of guidelines with two (8%) completing all four points.

Treatment toxicities

There were no toxic deaths in the present study. Acute toxicities to skin and oral mucosa according to CTC. AC version 3.0 are listed in Table 4. For the overall group, grade 3 and 4 skin reaction and mucositis were 9 and 8% respectively.

In the 3-weekly group, 2% grade 3 and 4 skin reaction occurred. There was significant skin reaction in the weekly regimen group with 46% of patients developing grade 3 and 4.

For mucositis, 10% of patients in the 3-weekly group and no patient in the weekly group experienced grade 3 and 4 toxicity.

Table 1. Patients characteristics

Characteristics	No. of patients (n = 74)
Median age (year)	45 (16-72)
Gender	
Male	59
Female	15
ECOG performance status	
0	4
1	70
Primary site	
Nasopharyngeal cancer	56
Histology squamous cell CA	33
Undifferentiated cell CA	23
Stage	
I	-
II	5
III	30
IV	21
Oropharyngeal cancer	18
Histology squamous cell CA	18
Stage	
I	-
II	-
III	8
IV	10
Median RT dose (Gy)	70 (66-70)
Chemotherapy schedule	
3-week	61
Weekly	13

Table 2. Compliance to scheduled chemotherapy

Total No. of cycles given	No. of patients (%)
3-week group	
≤ 2	58 (95)
3	3 (5)
Median No. of cycles	2
weekly group	
≤ 3	4 (31)
4	2 (15)
≥ 5	7 (54)
Median No. of cycles	5

Table 3. Compliance to guideline

Compliance	No. of patients (%) (n = 74)
No. of compliance points	
3 in 4	56 (76)
4 in 4	18 (24)
Compliance for each point	
PreRT dental care by dentists	74 (100)
RT by 2 lateral opposing fields per day	74 (100)
Dose recalculation for change of tumor depth	56 (76)
Individual patient counselling	74 (100)

In the weekly group, the correlation between mask or no mask and skin reaction is shown in Table 5. To compare NPC patients in the 3-weekly chemotherapy group in the present study to those in historical data, patient characteristics in the two groups were well balanced as shown in Table 6. The incidence of skin reaction and mucositis were higher in the historical group but not statistical significant (p = 0.14 and 0.52 respectively) as in Table 7.

Table 4. Acute toxicities

Grade of toxicity	No. of patients (%)	
	3-week group (n = 61)	Weekly group (n = 13)
Skin reaction		
3-4	1 (20)	6 (46)
Mucositis		
3-4	6 (10)	-
Leucopenia		
3-4	13 (21)	3 (25)
Neutropenia		
3-4	7 (11)	1 (8)
Thrombocytopenia		
3-4	-	1 (8)

Table 5. Grade of skin reaction in weekly CT regimen group

Grade of skin reaction	No. of patients (%)	
	Mask	No mask
1-2	5 (45)	2 (15)
3-4	6 (55)	-

Discussion

NPC is an extremely radiosensitive tumor. The mainstay of treatment is radical external RT. Siriraj Hospital institution has developed single-institution CPG for RT in NPC by a panel of radiation oncologists based on scientific literature and experience since 2001 to recommend clinicians on treatment decision. In 2005, this guideline was revised to develop four checkpoints for compliance. These checkpoints were also extended to be used in OPC. In the present study, only patients who received complete treatment as in CPG were eligible for analysis. Intent-to-treat analysis was not done. The results in the present study showed that each checkpoint in this guideline is feasible with 76% compliance of 3 in 4 points, and 24% complete all points.

The result of the randomized study by Intergroup 0099 demonstrated significant advantage after concurrent cisplatin and RT followed by adjuvant cisplatin-fluorouracil in patients with locally advanced NPC. Delivery of concurrent CRT causes increased toxicity during treatment compared to those of RT alone. Toxicities during treatment represent the main reason for RT and/or chemotherapy discontinuation[2].

Since the publication of this trial, the standard practice for NPC in Siriraj Hospital has been concurrent

Table 6. Patient characteristics compared to historical data

Characteristics	No. of patients		p-value
	Present study (n = 43)	Historical data (n = 25)	
Age Median age (range)	45 (16-72)	44 (18-65)	
Mean	46	45	0.64
Gender			
Male	34	19	
Female	9	6	0.99
Primary site			
Histology squamous cell CA	25	13	
Undifferentiated cell CA	18	11	0.95
Stage			
I	-	-	
II	4	4	
III	17	3	
IV	22	18	0.42
Median RT dose (Gy)	70 (66-70)	70 (66-70)	

Table 7. Acute toxicities compared to historical data

Grade of toxicity	No. of patients (%)		p-value
	Present study (n = 43)	Historical data (n = 25)	
Skin reaction			
3-4	1 (2)	3 (12)	0.146
Mucositis			
3-4	1 (14)	5 (20)	0.52

CRT using cisplatin in stage IIB and beyond. Cisplatin acts both as a cytotoxic agent and as radiosensitizer. The scheduling of weekly intermediate-dose or 3-weekly high-dose regimens of cisplatin have all been used in various reports[7-12]. However, whether the weekly regimen is as effective as 3-weekly regimen remains to be addressed. The present study sought to evaluate the feasibility of combined modality treatment only in aspects of treatment tolerance and toxicity.

For the present study, overall grade 3 or 4 mucositis and skin reaction were 8 and 9% respectively. These rates are lower than those in the literature. Lee et al randomized the patients with NPC to CRT or RT. Both arms were treated with the same RT technique and dose fractionation. The CRT patients were given cisplatin 100 mg/m2 on days 1, 22 and 43. The present study revealed 62% and 20% grade 3-5 acute mucositis and skin reaction respectively in CRT arm[8].

Chua et al also used the same concurrent CRT in NPC patients in a randomized study. The main nonhematologic toxicities in patients receiving CRT were mucositis and emesis, with 23% experiencing Grade 3 mucositis and 4% grade 3 dermatitis[9].

Chen et al reported results in the patients with NPC who were randomized to receive cisplatin 40 mg/m[2] weekly concurrently with RT or RT alone. Grade 3-4 mucositis and skin reaction were 45 and 4% respectively in CRT arm[10]. Chan et al reported 4.9% mucositis in CRT arm from the same chemotherapy regimen[11,12]. Isobe et al also reported grade 3 dermatitis in two out of six patients and grade 3-4 pharyngitis in four out of six patients with this regimen[7].

For oropharyngeal cancer, North American Intergroup trial of concurrent CRT in patients with unresectable head-and-neck tumors compared RT alone in Arm A with concurrent CRT and single-agent cisplatin in arm B and arm C. Although it was not a site-specific study, OPC predominated in the study population. Arm B consisted of identical RT with concurrent single-agent cisplatin as in the present study and arm C using a split course of RT and concurrent combination fluorouracil and cisplatin. Side effects in arm B consisted of 7% grade 3-5 skin toxicity and 43% grade 3-5 mucositits. This Intergroup study firmly established concurrent CRT with single-agent cisplatin as a treatment standard for unresectable head and neck cancer[3].

Within the same dose range of RT in the present study, 2% grade 3 or 4 skin reaction occurred in the 3-weekly regimen group whereas 46% of patients in the weekly regimen group developed grade 3 or 4 skin reaction. The difference between the two groups is due to immobilization devices used for RT. In weekly regimen group, 55% of patients who used masks for immobilization experienced grade 3 or 4 skin reaction. For patients irradiated without masks, no one developed grade 3 or 4. This correlation can be explained by the basic principle of RT that skin-sparing effects will be lost in irradiated head and neck cancer patients given by cobalt 60 machine via masks compared to that by linear accelerator.

For mucositis, grade 3 or 4 was experienced by 10% of patients in the 3-weekly group without any occurrence in the weekly group.

The results in the 3-weekly chemotherapy group for NPC in the present study were compared to those in the historical data. The incidence of skin reaction and mucositis were higher in historical group but not significantly statistical.

The CPG consisted of preventive methods to reduce acute skin and oral mucosa toxicities in NPC and OPC patients and is easy to follow. However, limitation of using this CPG is that clinical practice of conventional RT technique for NPC and other head and neck cancer is currently reduced due to alternative 3-dimensional conformal and intensity modulated RT.

Conclusion

This CPG is feasible with 24 to 100% compliance and acceptable acute treatment toxicities. Consideration should be about immobilization device and energy treatment machine. The limitation of this CPG is currently accepted alternative 3-dimensional conformal and intensity modulated RT.

Potential conflicts of interest

None.

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การวัดประสิทธิภาพของแนวทางการรักษาในมะเร็งโพรงหลังจมูกและมะเร็งออโรฟาริงซ์ในการลดอัตราการเกิดผลแทรกซ้อนระยะเฉียบพลันระหว่างการฉายรังสีพร้อมเคมีบำบัด

นันทน์ สุนทรพงศ์, มธุรส สุขเกษม, จิราพร อู่วัฒนสมบัติ, นาตยา ศมศานติ์, กุลธร เทพมงคล

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของแนวทางการรักษาในมะเร็งโพรงหลังจมูกและมะเร็งออโรฟาริงซ์ในการลดอัตราการเกิดผลแทรกซ้อนระยะเฉียบพลันระหว่างการฉายรังสีพร้อมเคมีบำบัด*

วัสดุและวิธีการ: *การศึกษาแบบไปข้างหน้ารวบรวมผู้ป่วย 74 ราย ที่ได้รับการวินิจฉัยเป็นมะเร็งโพรงหลังจมูก และมะเร็งออโรฟาริงซ์รักษาโดยการฉายรังสีพร้อมเคมีบำบัดและประเมินความเป็นไปได้ของแนวทางการรักษา*

ผลการศึกษา: *แต่ละจุดตรวจทำได้โดย 76% สำหรับ 3 ใน 4 จุดตรวจและ 2% สำหรับทั้ง 4 จุดตรวจ อัตราผลแทรกซ้อนระยะเฉียบพลัน เกรด 3 หรือ 4 ของผิวหนังและเยื่อบุช่องปากเท่ากับ 9% และ 8% ตามลำดับ*

สรุป: *แนวทางการรักษาซึ่งประกอบด้วยวิธีป้องกันการเกิดผลแทรกซ้อนระยะเฉียบพลันของผิวหนังและเยื่อบุช่องปากในมะเร็งโพรงหลังจมูกและมะเร็งออโรฟาริงซ์สามารถปฏิบัติได้ตั้งแต่ 24-100% โดยต้องคำนึงถึงชนิดเครื่องมือยึดตรึงผู้ป่วยระหว่างฉายรังสีและพลังงานของรังสี*