Radiation-Related Vocal Fold Palsy in Patients with Head and Neck Carcinoma

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Objective: *Recurrent laryngeal nerve damage is a rare complication after receiving conventional radiotherapy for treatment of head and neck cancers and will always be underestimated. The purpose of the present study was to focus on the prevalence of vocal cord paralysis after irradiation and the natural history in those patients.*
Material and Method: *All patients who received more than 60 Gy radiation dose of convention radiotherapy for treatment of head and neck carcinoma from Phramongkutklao Hospital and Nation Cancer Institute of Thailand were recruited in the present study during follow-up period between May 2006-December 2007. The subjects had to have good mobility of bilateral vocal cords with no recurrence or persistent tumor before the enrollment. Baseline characteristic and the associated symptoms of the recurrent laryngeal nerve paralysis were recorded. Laryngeal examinations were done by fiberoptic laryngoscope and in suspicious cases; stroboscope and/or laryngeal electromyography were also performed. The vocal fold paralysis was diagnosed by reviewing recorded VDO by 2 laryngologist who were not involved in the present study.*
Results: *70 patients; 51 male and 19 female were recruited. 5 patients (7.14%) were diagnosed to have vocal cord paralysis and 2 patients (2.86%) were found to have vocal cord paresis confirmed by electromyography. Most of them were the patients with nasopharyngeal cancers (6/7) with the only one had oropharyngeal cancer (1/7). All of the paralysis/paresis was unilateral lesion; 4 on the left and 3 on the right side. The duration from the patients completed radiotherapy to the time of the diagnosis of vocal cord palsy was 14-35 months. The measure of agreement or Kappa value with 95% CI was 0.818 $\pm$ 0.245. Associated symptoms of vocal cord palsy are hoarseness (100%), dysphagia (28.6%) and aspiration (28.6%).*
Conclusion: *A significant number of vocal fold palsy may occur in patients with head and neck carcinoma after receiving conventional radiotherapy. Subcutaneous fibrosis or compromised blood vessels at the skull base or the neck area may be important risk factors for development of the complications and further studies are need to solve the pathogenesis.*

Keywords: *Vocal fold palsy, Radiation, Head and neck carcinoma*

J Med Assoc Thai 2012; 95 (Suppl. 5): S23-S28
Full text. e-Journal: *http://jmat.mat.or.th*

It has been believed that cranial nerves have a remarkable degree of resistance to injury by radiotherapy. In the past 40 years, with the use of kilo voltage radiotherapy, the damage to peripheral nerves was the rare events because the skin tolerance to radiotherapy was the limiting factor in dosage. Nowadays, with the development of the modern x-ray machines, mega voltage technique, peak dosage is beneath the skin and it is supposed to increase risk of deeper tissues or nerve damage[1]. Recently, intensity modulated radiation therapy (IMRT) has been developed. Although it has more precision in target tissue and has less complication, however, this technique is available in only some academic centers because it has very high cost.

In patients with head and neck carcinoma, radiotherapy-induced peripheral nerve palsies have been reported although quite rare. The present study from Taiwan based on 1,032 patients reported 1% of cranial nerve palsies from complication of conventional radiotherapy[2]. The others sporadically reports included the hypoglossal nerve which was the most common finding[3-7,11] the optic nerve[8], the trigeminal nerve[9], the abducens nerve[10], the accessory nerve[2,3] the vagus nerve[2,3] and the recurrent laryngeal nerve[3,5,12-15].

The CN II, V, VI, X, XI palsies as mentioned above should not be difficult to recognize by general physicians. But the latter one, recurrent laryngeal nerve

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palsy, is always neglected by most of the physicians and most of the studies. The presenting symptoms of recurrent laryngeal nerve defect might be vague, but suffering, ranging from mild to serious manifestations which need to be diagnosed by laryngoscope. These could be presented with hoarseness, voice fatigue, hypersecretion of throat, difficulty swallowing, chronic cough which lead to misunderstanding as the common complications from radiation or from primary diseases. The more serious presenting were choking and some time, airway obstruction[3,14,15]. The latency time of first recognized varied from 1-34 years after radiotherapy[3,15,16]. These nerve defects are always under diagnosed and under awareness, even though by otolaryngologists.

Because most of the previous literatures studied the radiotherapy related- peripheral nerves palsies in general aspects or were sporadic case reports[4,5,17], the aim of the present study was to emphasize on recurrent laryngeal nerve defect which cause many distressing-unaware symptoms and may be helpful in the treatment planning in these post-irradiation patients with head and neck cancers.

Material and Method

Patients

The present study was conducted by joining two academic centers, Phramongkutklao College of Medicine and Nation Cancer Institute of Thailand. The data were collected during the follow-up period of the head and neck cancer patients. The time period of the study was 1 year and a half between May 2005 to December 2006 and recruited all the patients with head and neck cancers who received radio-portal dose more than 60 Gy included skull base and neck area.

The inclusion criteria were: 1) the patients with head and neck cancers of nasopharynx, oral cavity, larynx or hypopharynx with good mobility of bilateral vocal cords who received radiotherapy that included skull base or neck area 2) doses of at least 60 Gy to the skull base or neck area 3) the radiotherapy completed at least 6 months to decrease tissue edema 4)age more than 18 years-old.

The exclusion criteria were 1) patients with recurrent tumors or a suspicion of residual or persistent diseases 2) incomplete radiotherapy 3) patients who initially had intracranial involvement 4) patients who had initially recurrent laryngeal nerve defect either from their diseases or from neck dissections 5) patients who had mediastinum involvement or metastasis 6) patients who had re-irradiation 7) recurrent laryngeal nerve palsy persisted less than 3 months after it was recognized.

Methods

Eligible patients were recruited during the follow-up period and their demographic data were collected on the radiotherapy time, dose, fractionation and radiation-portal route. Complete ENT examination and general physical examination were performed. Videoendoscopy assessments including fiberoptic laryngoscope or laryngostroboscope were done in all subjects and the vocal folds status were recorded in blinded serial numbers. Sign and symptoms of recurrent laryngeal nerve palsy were also recorded if persisted.

The numbers of recorded videoendoscopy were reviewed by two blinded senior otolaryngologists who were not involve in the present study. The assessments of recurrent laryngeal nerve palsy were done. The inter-observer variation between these two otolaryngologists was analyzed by measure of agreement (Kappa) to assess the validity. Disagreements of the diagnosis were discussed by re-display the videotape by the two evaluators to make the final consensus.

Radiation therapy techniques (Fig. 1)

6 MV Linear accelerators were used with 2D Planning technique. Superior field margin was 2 cm beyond tumor from CT including base of skull in case of nasopharynx cancer. Posterior field margin covered spinous process and was 2 cm beyond mastoid process in nasopharyngeal lesions or 1.5 cm margin of enlarged lymph node. Anterior margin was posterior third of maxillary sinus and nasal cavity in cancer of nasopharynx or 2 cm from anterior extension of the tumor. Inferiorly margin was the thyroid notch or 2 cm for lower border of tumor from CT.

The treatment of lower neck used single anterior field with midline block or central larynx block

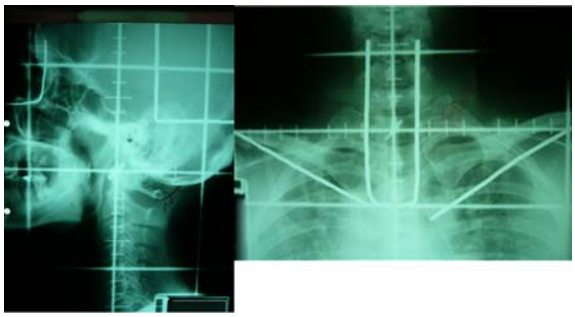

Fig. 1 Radiation therapy field

extended inferiorly to the lower border of the sternoclavicular joint. The midline line laryngeal block was not used in larynx and hypopharyngeal cancer. The radiotherapy for all patients included initial, large, bilateral opposed fields for the primary tumor to 40-44 Gy for spinal block, followed by bilateral cone down fields after 50 Gy to total dose of 66-70 Gy. A dose of 1.8-2 Gy was given daily for 5 days a week. The total dose of 44-50 Gy was performed for N0 necks and 70 Gy to gross lymph nodes.

The diagnosis of recurrent laryngeal nerve palsy was done when the laryngoscopy revealed one or both vocal cords paralysis or paresis without others identified causes. The definition of vocal cord paralysis was total immobility of the one or both vocal cords. The definition of vocal cord paresis was the decreased movement or asymmetrical movement of the one or two vocal folds but not complete immobility. In cases of questionable recurrent laryngeal nerve palsy, laryngeal electromyography (LEMG) were performed to confirm diagnosis.

If the recurrent laryngeal nerve palsy was found, the extensive physical examination and investigation including CT or MRI of the skull base and /or neck area were performed to rule out recurrent or residual diseases.

Results

There were 70 eligible patients, 51 males and 19 females, age range from 20-65 years. They had generally received greater than 70 Gy of external beam radiotherapy for head and neck cancer. A peak dose of 200 rad was given daily to the skull base or neck area for five days a week (Table 1).

From 70 subjects, there were 7 patients who be found to have recurrent laryngeal nerve immobility. Among these 7 patients, 5 had complete paralysis (Fig. 2) and 2 had paresis confirmed by laryngeal EMG (Fig. 3). Most of them were the patients with nasopharyngeal cancers (6/7) with the only one was oropharyngeal cancer (1/7). Only one patient (#2) received chemotherapy. In the subgroup of patients with complete paralysis, all of them exhibited unilateral lesion with 3 on the left and 2 on the right side. In the paresis subgroup, 2 patients were founded the have 1 unilateral right, 1 unilateral left. All of the palsies were on the same side of the radiation portal routes. The estimated incidence of this recurrent laryngeal nerve palsy after complete radiotherapy was 10% (7/70). If attention is paid in only vocal cord paralysis, not paresis, the incidence was 7.14% (5/70). For the vocal fold paresis, the prevalence was 2.86% (2/70). The latency period of the palsy detection range from 14-35 months (average 22 months) (Table 2). CT and MRI were all negative for recurrent tumor or mediastinum mass.

The associated symptoms of the recurrent laryngeal nerve palsy were hoarseness (100% or 7/7), dysphagia (28.5% or 2/7) and aspiration (28.5% or 2/7). No airway obstruction or airway compromise was found.

Measure of agreement

The inter-observer variation between 2 clinicians was shown and analyzed by the measure of

Table 1. Characteristics of patients with irradiation-related recurrent laryngeal nerve palsy versus normal patient group (n = 70)

Characteristics	TVC paralysis group (n = 7)	Non-TVC paralysis group (n = 63)
Gender		
Male:Female	7:0	44:19
Age (year)	35-56 (44)	20-65 (41)
Fraction dose (cGy)	180-200	180-200
Tumor/neck dose (cGy)	7,000/4,000-6,000	5,000-8,000/4,000-6,000
Tumor site		
Oropharynx	1	5
Hypopharynx	0	2
Oral cavity (tongue)	0	3
Larynx	0	0
Nose	0	0
Salivary glands	0	0
Nasopharynx	6	52
Unknown primary	0	1

agreement. The Kappa value with 95% CI was 0.818 ± 0.245. This result showed the good agreement between 2 observers.

Discussion

From the present study results, the radiation-related recurrent laryngeal nerve palsy had a higher incidence than previous literature. This 7.14% incidence rate was also obviously higher than idiopathic vocal fold paralysis in general population which was very rare. According to a retrospective study from Taiwan[3], which collected data from 1,200 irradiated patient's pool, they found 6 bilateral recurrent laryngeal nerve palsy from19 subjects with cranial nerve X-XII palsies. This crude incidence was 0.5%. The data had a low positive rate because the authors define the vocal palsy to be only bilateral paralysis to avoid idiopathic vocal fold paralysis. Another study found only 1 recurrent laryngeal nerve paralysis from 218 post-megavoltage radiotherapy supraglottic cancer patients but they did not describe the definition or method of the diagnosis[4]. The other study from Dr. Huang on 1,032 post-irradiation patients reported 1% of cranial nerves X-XI palsy without explanation of the details of the finding results[2].

There were other sporadic case reports which revealed the recurrent laryngeal nerve paralysis. Most of them were found to be bilaterally defects[3,5,12-14].

Fig. 2 Left true vocal cord paralysis in patient #3

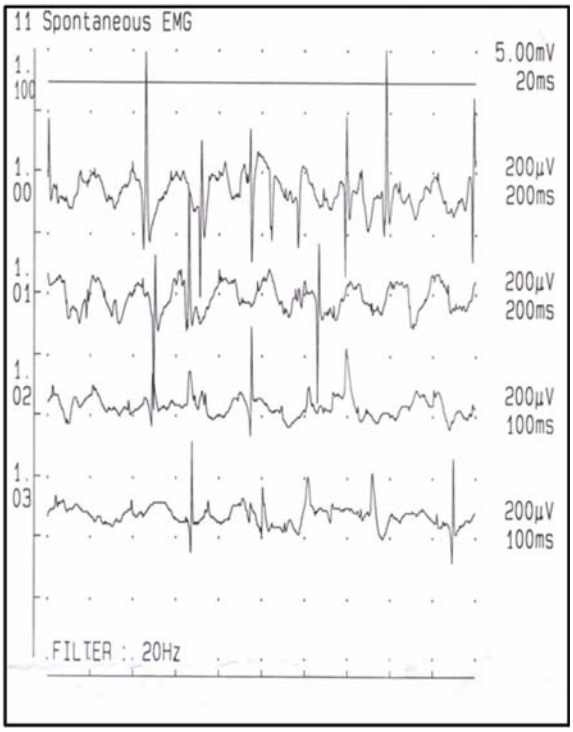

Fig. 3 LEMG in patient with true vocal cord paresis. Spontanoues activities were identified

Table 2. Characteristics of 7 patients with irradiation-related recurrent laryngeal nerve palsy

Patient	Gender	Age (yrs)	Primary tumor, stage	Fraction dose (cGy)	Tumor/neck dose (cGy)	Latency (months)	Palsy site	Associated symptoms
1	male	69	Nasopharynx (T2N1M0)	200	7,000/5,000	27	Left	hoarseness dysphagia aspiration
2	male	45	Nasopharynx (T3N1M0)	200	7,000/6,000	16	right	hoarseness
3	male	61	nasopharynx (T2N1M0)	200	7,000/5,000	18	right	hoarseness aspiration
4	male	46	nasopharynx (T2N2M0)	200	7,000/6,000	14	left	hoarseness dysphagia
5	male	39	Nasopharynx (T2N1M0)	200	7,000/5,000	27	left	hoarseness
6	male	40	Oropharynx (T1N1M0)	200	7,000/4,500	35	paresis	hoarseness
7	male	35	Nasopharynx (T1N1M0)	200	7,000/4,000	25	paresis	hoarseness

These might be from the obvious airway symptoms which were the late unrecognized complications of the radiation.

The 7.14 % positive rate of recurrent laryngeal nerve palsy from the present study was quite higher than expected. This might be because the authors had intension to find the pathology in every recruited patient by laryngoscope. In routine clinical practice or in some studies, the physicians did not focus to undertake laryngoscope to every post-irradiation patient, especially in nasopharyngeal cancer who never had laryngeal lesions before. So, the diagnosis of vocal fold palsies was made when airway symptoms occurred. Accurate clinical assessment, therefore, is necessary to detect this intra laryngeal complication promptly. The subclinical vocal fold paresis can be evaluated by laryngeal electromyography in some setting[15]. However, from the present study, no bilateral vocal cord paralysis was found which may need more sample size to identify this situation in further study.

The pathogenesis of the peripheral nerve neuropathy was believed to be secondary to subcutaneous fibrosis[4]. Necropsies were performed on the patients who had received high dose irradiation and had developed neuropathy. Macroscopically there was marked fibrosis surrounding the affected nerves. Microscopically, the section showed extensive myelin loss, atrophy and fibrous replacement of fibrils. For comparison, a necropsy was done on a post-irradiation patient without neuropathy. In this case no fibrosis was visible either macro or microscopically[1]. The experimental irradiation of myelinated nerves in animals has shown the extensive vascular changes, Schwann cells were affected and lead to permanent depletion to functional impairment[16]. The nerve lesions were therefore probably caused by fibrous tissue pressure, by blood supply interference by this pressure or by direct changes in the nerve blood vessels[17].

Interestingly, almost all of the recurrent laryngeal palsy found in the present study was from nasopharyngeal cancer patients. Five of seven patients in this study had severe neck fibrosis similar to the study from by Lin[3]. The nerves palsy might be from the compromised blood vessels at both skull base and neck area or compression of the nerves during passage through the neck but the reason is unclear. Further study with more sample size is warranted.

All of the recurrent laryngeal nerve palsy in this study had symptom of hoarseness. More than one-fifth had dysphagia and aspiration. So, these should be the warning signs to suspect and be aware of this complication after the radiotherapy.

Conclusion

The differentiated between nerve palsy from irradiation complication and that due to tumor recurrence is critical, so, a long observational period is needed to ensure these issues. Furthermore, radiation-related peripheral neuropathy can occur 1-34 years after the therapy[13], which means we should follow the patients and observe the late complication over a period of time because this laryngeal cranial nerve palsy can be a disastrous events if it is left unawareness.

Potential conflicts of interest

None.

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ภาวะสายเสียงเป็นอัมพาตภายหลังการฉายแสงรังสีรักษาในผู้ป่วยมะเร็งศีรษะและลำคอ

ปริยนันทน์ จารุจินดา, สมจินต์ จินดาวิจักษณ์, ณัชชาวดี สิงหวราช

วัตถุประสงค์*: ภาวะเส้นประสาทสายเสียงไม่ทำงานเป็นภาวะแทรกซ้อนที่พบได้ไม่บ่อย หลังการรักษาด้วยการฉายแสงรักษามะเร็งในบริเวณศีรษะและลำคอ จุดประสงค์ของการศึกษานี้เพื่อหาความชุกของภาวะนี้ และรวมถึงข้อมูลพื้นฐานที่เกี่ยวข้อง*

วัสดุและวิธีการ*: ประชากรที่ศึกษาคือ ผู้ป่วยที่รับการฉายแสงแบบพื้นฐานมากกว่า 60 Gy เพื่อรักษามะเร็งศีรษะและลำคอที่ โรงพยาบาลพระมงกุฎเกล้า ตั้งแต่ พฤษภาคม พ.ศ. 2549 ถึง ธันวาคม พ.ศ. 2550 โดยผู้ป่วยต้องมีการทำงานของสายเสียงเป็นปกติทั้ง 2 ข้างมาก่อนการรักษา ข้อมูลพื้นฐานและอาการร่วมอื่น ๆ จะได้รับการบันทึก การส่องตรวจกล่องเสียงทำโดยกล้องใยแก้วนำแสง ในกรณีมีข้อสงสัยจะทำการตรวจเพิ่มเติมโดยกล้องสโตรโบสโคปและการตรวจกล้ามเนื้อกล่องเสียงด้วยไฟฟ้า (EMG) การวินิจฉัยภาวะสายเสียงเป็นอัมพาต ทำโดยการทบทวนภาพอัดวีดีทัศน์ ซึ่งกระทำโดยการตัดสินของแพทย์หู คอ จมูก ผู้เชี่ยวชาญ 2 คน ที่ไม่มีส่วนเกี่ยวข้องในการวิจัย*

ผลการศึกษา*: พบผู้ป่วย 70 คน โดยเป็นชาย 51 คน เป็นหญิง 12 คน ผู้ป่วย 5 คน (7.14%) พบภาวะสายเสียงเป็นอัมพาตจากวีดีทัศน์ และอีก 2 คน (2.86%) พบสายเสียงอัมพาตยืนยันโดยการตรวจ กล้ามเนื้อกล่องเสียงด้วยไฟฟ้า ผู้ป่วย 6/7 คน เป็นมะเร็งหลังโพรงจมูก และผู้ป่วย 1/7 คน เป็นมะเร็งในช่องปาก ผู้ป่วยทั้งหมดมีสายเสียงอัมพาตข้างเดียวโดย 4 คน พบข้างซ้าย 3 คน พบข้างขวาระยะเวลาจากการฉายแสงครบจนถูกค้นพบว่า มีภาวะสายเสียงเป็นอัมพาตอยู่ในช่วง 14-35 เดือน ความสอดคล้องของการวินิจฉัยของแพทย์ หู คอ จมูก 2 คน ในการวินิจฉัยภาวะนี้ (kappa value) = 0.818 $\pm$ 0.245 อาการของภาวะนี้คือเสียงแหบ 100% กลืนลำบาก 28.6% และสำลัก 28.6%*

สรุป*: พบจำนวนผู้ป่วยภาวะสายเสียงเป็นอัมพาตหลังได้รับการฉายแสงแบบชนิดพื้นฐานอย่างชัดเจนมากขึ้นในการศึกษานี้ซึ่งภาวะนี้อาจเกิดจากภาวะพังผืดในเนื้อเยื่อหลังการฉายแสง สาเหตุที่แท้จริงควรได้รับการศึกษาต่อไป*