Original Article

Death Related to Pleural and Pericardial Effusions Following Chemoradiotherapy in a Patient with Advanced Cancers of the Esophagus and Stomach

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Abstract. Chemoradiotherapy improves therapeutic outcome in many different types of cancer. However, there is concern about the occurrence of delayed complications, as patients are surviving longer. Because patients with esophageal cancer receive a wide range of irradiation field to the mediastinum and the heart, they may have delayed complications of heart and lung functions as previously reported in Hodgkin's disease. We presented a case of death related to uncontrollable pleural and pericardial effusions in a patient with advanced cancers of the esophagus and stomach who achieved a complete remission following chemoradiotherapy and salvage gastric resection, focusing on detailed pathophysiological conditions related to concurrent chemoradiotherapy. (Keio J Med 56 (4) : 124–129, December 2007)

Key words: esophageal cancer, chemoradiation, pleural effusion, pericardial effusion.

Introduction

Chemoradiotherapy improves therapeutic outcome in many different types of cancer, including cancer of the head and neck, esophagus, lung and uterine cervix, and biological basis for chemoradiotherapy has been reported.[1] More recently, patients with gastric cancer have been reported to achieve a complete remission following chemoradiotherapy,[2,3] although irradiation has scarcely been used in gastric cancer so far. Chemoradiotherapy, which has been conventionally performed mainly for inoperable esophageal cancer, is currently used in the treatment even for early esophageal cancer and there is a report stating that it is comparable to surgery in terms of therapeutic outcome.[4] Nevertheless, patients treated with chemoradiotherapy are considered to be at an increased risk for potentially concurrent adverse effects of irradiation and chemotherapy. There is concern about the occurrence of delayed complications, as patients are surviving longer owing to the improvement of therapeutic outcome of chemoradiotherapy. Because patients with esophageal cancer receive a wide range of irradiation to the mediastinum and the heart, they may have complications, including pleural effusions due to mediastinal fibrosis, as previously reported in post-irradiation complications in Hodgkin's disease.[5–10] We encountered a patient with advanced synchronous cancers of the esophagus and stomach who achieved a complete remission with chemoradiotherapy, followed by salvage resection of gastric cancer, but died of uncontrollable massive pleural and pericardial effusions. Pathological findings from postmortem examination were available. We report herein a case of death related to pleural and pericardial effusions following chemoradiotherapy, focusing on detailed pathophysiological conditions related to concurrent chemoradiotherapy.

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Case Presentation

A 71-year-old male developed difficulty swallowing in January 2003. Detailed examinations conducted in February led to the diagnosis of advanced cancers of the esophagus (Squamous cell carcinoma, LtMt- , Type2, T3N3M0, stage III) and the stomach (Well differentiated adenocarcinoma (tub1), Group V, U Less-Ant cType2T3(SE)N2M0, T3N2M0, stage IIIB). Fig. 1 shows endoscopic photos and pathological findings of specimens. External irradiation was given at a total dose of 60 Gy in 30 fractions of 2 Gy each during a period from March through April, while reducing the irradiation field to the primary esophageal and gastric cancer lesions (Fig. 2). Simultaneously, CDDP was administered by drip infusion at a dose of 6 mg/m^2 and 120 mg of TS-1 was orally administered on the day of radiotherapy. Endoscopic and pathological assessment of response to chemoradiotherapy, conducted in May, revealed a complete response for esophageal cancer and a partial response for gastric cancer (Fig. 3). Subsequently, the control of the esophageal lesion was persistent, but the gastric lesion gradually increased in size. Thus, chemotherapy, consisting of drip infusion of CDDP at a dose 10 mg/week and oral TS-1 at a dose of 120 mg/day, was started in December 2003 and continued for one month. However, because no favorable outcome was attained, the patient underwent total gastrectomy with D1+ β dissection and Roux-en-Y gastric bypass in February 2004. Although histopathological diagnosis of the stomach was a moderately differentiated tubular adnocarcinoma with Inf β, int, ss, ly1, v1, pPM (-), pDM (-), and n2 (+), postoperative pathological examination judged lymph node involvement as (-) (Fig. 4). The patient was followed on an outpatient basis. A follow-up CT scan obtained in October revealed a small amount of pericardial effusions, as well as pleural effusions on the left side (Fig. 5). In November, the patient was readmitted to our hospital because of he had developed dyspnea and edema of the lower extremities. On admission, his body temperature was 36.7℃, blood pressure 114/83mmHg. Blood gas analysis values on room were pH7.501, $PaCO_2$ 31.3mmHg, PaO_2 66.4mmHg, HCO_3 24.2mmol/l, BE 1.3mmol/l, and SaO_2 93.5%. Blood chemistry revieled mild liver dysfunction, with WBC7000/μl, Hb 14.7g/dl, Plt 11.1x104/μl, TP 7.0g/dl, Alb 3.2g/dl, TB 2.4mg/dl (DB 1.0mg/dl), BUN 34.4mg/dl, Cr 1.0mg/dl, AST 57IU/L, ALT 34IU/L, LDH 389IU/L, ALP 494IU/L, AMY30IU/l, and CRP 0.16mg/dl. These elevated parameters had declined on the second day and normalized within a few days. Tumor markers were within normal limits; CEA 2.0ng/ml, CA19-9 18.0ng/ml, and SCC 0.2ng/ml. Chest CT scan showed a large bilateral pleural and pericardial effusions without thickening of either the visceral or the parietal pleura and no pulmonary masses were detected (Fig. 6). There was no remarkable mediastinal lymphadenopathy. CT scan and ultrasonography of the abdomen revealed edema of the mesenterium and mild ascites, but no remarkable hepatic findings, such as dilated bile ducts, liver-enlargement, or splenomegaly. There was no detectable lymph node swelling, nor was there any evidence of deep venous thrombosis.

A consulting cardiologist assessed the patient's cardiac function using echocardiography and recommended diuretics and steroids. A 20 mg dose of furosemide and 16 mg of dexamethasone were infused continuously, and for 3 days 20 g/day of albumin were given followed by a 100 mg bolus shot of potassium canrenoate. A repeat of chest X-ray showed no significant changes in the pleural effusion. The cardiologist re-assessed the cardiac function, and judged pericardiocentesis to be unnecessary. Bilateral-thoracentesis and drainage were then performed. The drained fluid was clear and yellowish. Repeated pleural effusion cultures were all negative. In addition to surgical drainage, the aforementioned medications were continued. Dexamethasone was tapered to 8mg on the 6th day and continued for additional 6 days. The furosemide was raised to 40mg/day. And administration of 20g of albumin per day was continued until death. Difficulty breathing was transiently alleviated, but jaundice and generalized edema progressed rapidly, ultimately leading to the patient death in December. The cardiologist evaluated our patient's cardiac function several times and consistently confirmed that pericardiocentesis was not necessary, even as late as the day before death. Five cytological examinations of pleural effusion fluids were conducted during the clinical course. Two consecutive results were class II. The third result was class III, showing atypical large cells, but the pathologist suggested that these findings might be attributable to inflammatory reaction. The last two cytological examinations were both consistent with class I. An autopsy was performed after obtaining the family's consent. Pathological postmortem examination revealed no evidence of recurrent cancer of the esophagus or stomach, including the lymph node area. There was a finding of fibrinous pericarditis in the heart (Fig. 7), causing cardiac tamponade associated with pericardial effusions of 1000 ml (thin bloody). This may in turn have resulted in marked findings, such as congestive edema of the bilateral lungs (left: 520 g, right: 780g) (Fig. 8 A, B), pleural effusions (left: 2000 ml, right: 1000 ml), and severe hepatic congestion (970 g) (Fig. 8 C, D). Furthermore, abdominal ascites (680 ml) and generalized edema were noted, as well as fibrinous pleuritis in the lungs (Fig. 9). Secondary finding associated with irradiation in the lower part of the thoracic spine area was markedly hypocellular marrow, composed largely of fat cells.

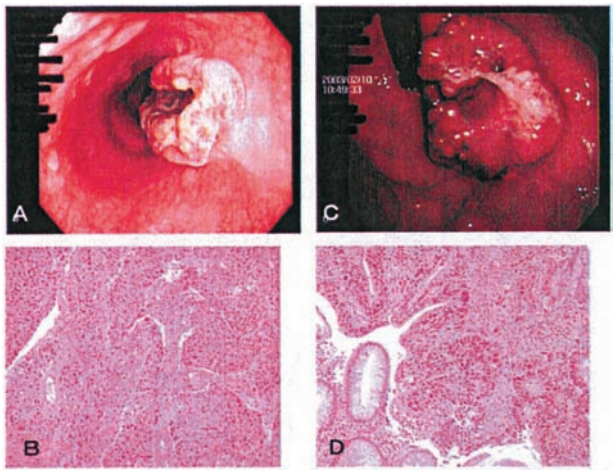

Fig. 1 Esophageal lesion is endoscopically shown as LtMt 1/3Circ. Type 2 (A) and pathologically as moderately differentiated squamous cell carcinoma (B); gastric lesion is endoscopically shown as U Less-Ant eType2 (C) and pathologically as moderately differentiated tubular adenocarcinoma (D).

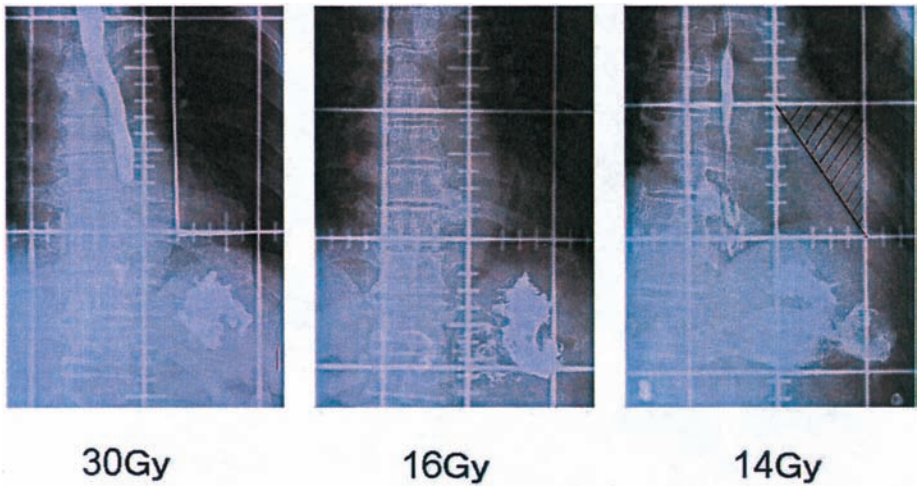

Fig. 2 A wide-range of irradiation of 30 Gy was delivered through two antero-posterior opposed fields to the lower part of the esophagus and the stomach, including the surrounding lymph node area, followed by irradiation of 30 Gy limited to the esophageal and gastric lesions. Last 14 Gy of a total dose of 60 Gy was given through two oblique fields, excluding the spinal cord from the irradiation field.

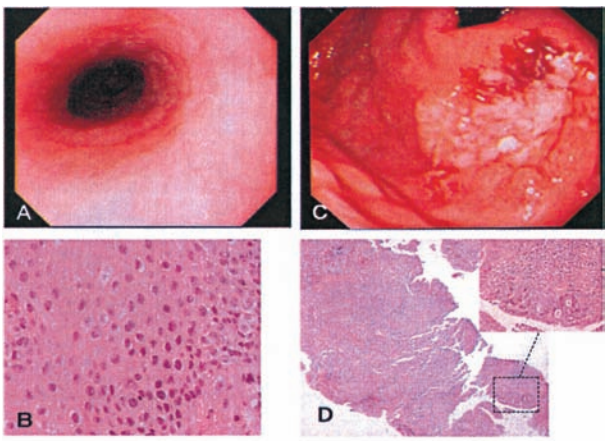

Fig. 3 Both endoscopic and pathologic findings of the esophageal lesion show CR (A, B); for the gastric lesion an endoscopic finding show PR, although a markedly reduced tumor can be seen (C), but pathologically residual cancer cells can be seen, although they were few (D).

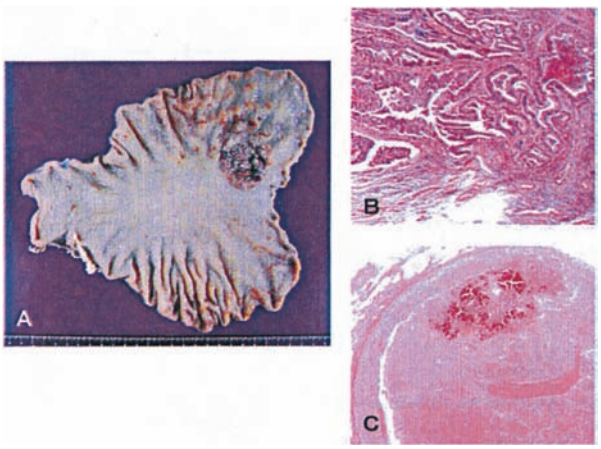

Fig. 4 Specimen collected after total gastrectomy reveals macroscopically residual cancer (A) and microscopically regrowth of cancer cells (B). Residual cancer cells can be histopathologically seen as moderately differentiated tubular adenocarcinoma with Inf β, int, ss, ly1, v1, pPM (-) and pDM (-), but lymph node metastasis is negative (C).

Discussion

Pulmonary complications of irradiation for chest lesions, especially radiation pneumonitis, have been so far frequently reported.[11–15] However, data concerning post-irradiation pleural effusions are limited to case reports of Hodgkin's disease.[5,6,10] There are also only a few reports on pericarditis and myocardial infarction associated with irradiation.[7–9] Conventional radiotherapy for esophageal cancer is usually indicated for advanced cancer. In view of the fact that the rate of curable advanced cancer is low, no report is available concerning delayed complications of radiotherapy. Recently, the number of curable advanced esophageal cancer has also increased as a result of chemoradiotherapy.[4] Ishikura *et al*. reported complications following definitive chemoradiotherapy for esophageal cancer. In their report, complete remission was attained in 78 of 139 patients treated with chemoradiotherapy, and ten of these 78 patients had pleural and pericardial effusions and five died of intercurrent disease.[16] In the case of this study, the patient had synchronous advanced cancers of the esophagus and stomach. In addition, because the patient was elderly, radical surgery or treatment with curative intent was unlikely. However, the patient remarkably responded to chemoradiotherapy. Complete response of esophageal cancer to chemoradiotherapy was achieved, and subsequently the patient underwent salvage surgery for gastric cancer, leading to complete remission of double cancer. However, massive pleural and pericardial effusions thereafter occurred and were uncontrollable. Ultimately, the patient died of these effusions. An autopsy was performed and detailed findings were available concerning pathophysiologic conditions of pleural and pericardial effusions related to chemoradiation.

There was no pathological evidence of recurrence of esophageal or gastric cancer. Cancerous lesions had completely resolved. In this patient, fibrinous pericarditis was the most outstanding feature that may have been caused by irradiation. Such pericarditis was associated with pericardial effusions, thereby resulting in cardiac tamponade. Possible causes of death in this patient were cardiac tamponade-associated congestive edema and pleural effusions of the bilateral lungs and hepatic congestion. Pleuritis was also noted outside the irradiation field, as well as within it, which appeared to be a secondary finding due to thoracocentesis and an indwelling drainage catheter.

Life prolongation might have been expected by pericardiocentesis. However, pericardiocentesis was not performed in this patient. According to echocardiography, the ejection fraction was sufficiently high (80%), and the cardiologist concluded that there was no evidence of cardiac tamponade. Moreover, with laboratory results yielding no evidence of recurrence, the pericardial effusions were highly likely to have been associated with cancer recurrence.

When pleural and pericardial effusions have occurred after chemoradiotherapy for esophageal cancer, it may be difficult to determine whether such effusions occur associated with treatment or cancer recurrence, leading to difficulty in the selection of appropriate treatment. Pericardiocentesis may be helpful in prolonging patient's life if pleural and pericardial effusions are related to treatment, like in this patient. With this in mind, accurate diagnosis and careful assessment of such pleural and pericardial effusion are required. The patient received 46 Gy of conventional two antero-posterior opposed fields irradiation to the slightly left side of the mediastinum and 14 Gy of two opposed fields irradiation upward to the right and downward to the left. Thus, high-dose irradiation was given to the mediastinum, heart, and inner side of the left lung field. Therefore, it is highly likely that the patient may have first had pericardial effusions and pleural effusions on the left side, followed by cardiac tamponade occurring in association with an increased amount of pericardial effusions. This may in turn have led to hepatic congestion and generalized edema. It seems essential to avoid unnecessary irradiation to the mediastinum and heart in planning radiotherapy for esophageal cancer, by employing three-dimensional radiotherapy planning, including multi-portal irradiation and intensity modulated radiation therapy,[17–19] that has already been used in radiotherapy for other types of cancer.

Conclusions

We presented a case of death related to uncontrollable pleural and pericardial effusions in a patient with advanced cancers of the esophagus and stomach who achieved a complete remission following chemoradiotherapy and salvage gastric resection. When pleural and pericardial effusions have occurred following chemoradiotherapy for esophageal cancer, physicians must consider the possibility of treatment-related complications. Three-dimensional treatment planning will also be needed in irradiation for esophageal cancer.

References

1. Wilson GD, Bentzen SM, Harari PM: Biologic basis for combining drugs with radiation. Semin Radiat Oncol. 2006 Jan; 16(1): 2–9
2. Yamashita H, Nakagawa K, Tago M, Igaki H, Nakamura N, Shiraishi K, Sasano N, Ohtomo K: The experience of concurrent chemoradiation for Japanese patients with superficial esophageal squamous cell carcinoma: a retrospective study. Am J Clin Oncol. 2005 Dec; 28(6): 555–9
3. Murakami M, Kuroda Y, Nakajima T, Okamoto Y, Mizowaki T, Kusumi F, Hajiro K, Nishimura S, Matsusue S, Takeda H: Comparison between chemoradiation protocol intended for organ pres-

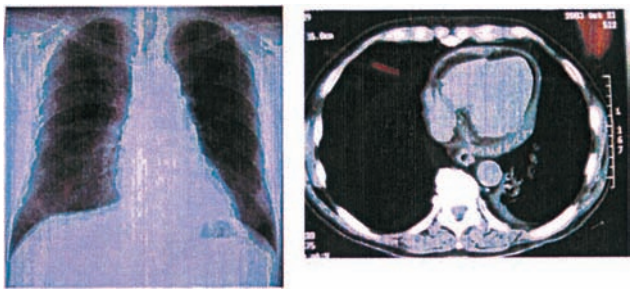

Fig. 5 Slight radiation pneumonitis can be seen in the lung field surrounding the lower part of the mediastinum, and CT scan reveals a small amount of pericardial effusions and pleural effusions on the left side.

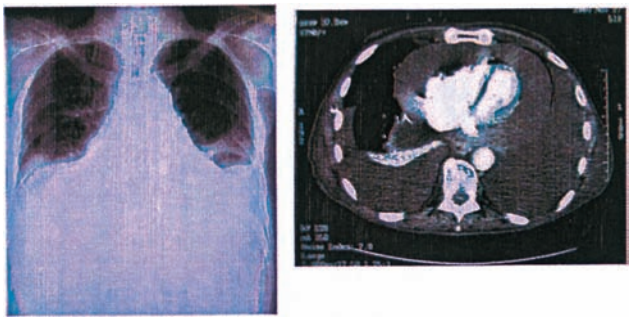

Fig. 6 A large amount of pleural effusions on the bilateral sides and pericardial effusions can be seen. Subcutaneous edema is marked.

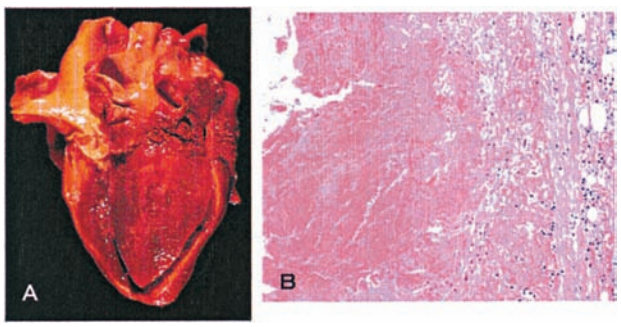

Fig. 7 The serosal surface of heart is macroscopically coated with the exudate (A), and microscopically the exudate comprises fibrin with mild inflammatory cells (B), showing fibrinous pericarditis.

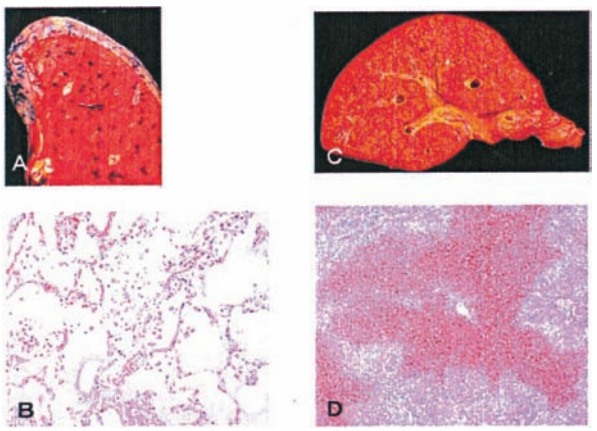

Fig. 8 The cut section of liver shows a variegated, mottled, red appearance (A), and the histological section reveals the congestion of centrilobular sinusoids (B). The lung (left) is notable for wet and red macroscopic appearance (C), showing microscopically the congestion and the intraalveolar pink fluid collection (D).

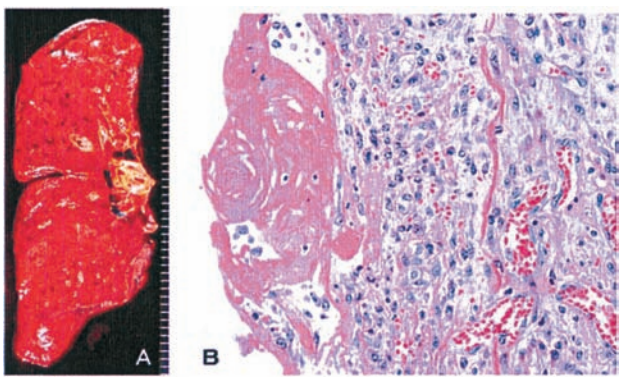

Fig. 9 Right lung shows the appearance of venous congestion and edema as well as the pleural exudates (A). The surface of pleura was covered with fibrin, accompanied with the mild infiltration of inflammatory cells (B).

ervation and conventional surgery for clinical T1-T2 esophageal carcinoma. Int J Radiat Oncol Biol Phys. 1999 Sep 1; 45(2): 277–84
4. Saikawa Y, Kubota T, Takahashi T, Akatsu Y, Nakamura R, Yoshida M, Shigematsu N, Otani Y, Kumai K, Hibi T, Kitajima M: Is chemoradiation effective or harmful for stage VI gastric cancer patients? Oncol Rep. 2005 May; 13(5): 865–70
5. Rodriguez-Garcia JL, Fraile G, Moreno MA, Sanchez-Corral JA, Penalver R: Recurrent massive pleural effusion as a late complication of radiotherapy in Hodgkin's disease. Chest. 1991 Oct; 100(4): 1165–6
6. Morrone N, Gama e Silva Volpe VL, Dourado AM, Mitre F, Coletta EN: Bilateral pleural effusion due to mediastinal fibrosis induced by radiotherapy. Chest. 1993 Oct; 104(4): 1276–8
7. Benoff LJ, Schweitzer P: Radiation therapy-induced cardiac injury. Am Heart J. 1995 Jun; 129(6): 1193–6
8. Veinot JP, Edwards WD: Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. Hum Pathol. 1996 Aug; 27(8): 766–73
9. Yamamoto N, Noda Y, Miyashita Y: A case of refractory bilateral pleural effusion due to post-irradiation constrictive pericarditis. Respirology. 2002 Dec; 7(4): 365–8
10. Fragoulis KN, Handrinou E, Papadopoulos V, Dardoufas K, Falagas ME: Delayed effusive pericarditis and recurrent pleural effusion after radiation treatment for Hodgkin's disease responsive to per os doxycycline. Eur J Haematol. 2006 Feb; 76(2): 176–9
11. Park KJ, Chung JY, Chun MS, Suh JH: Radiation-induced lung disease and the impact of radiation methods on imaging features. Radiographics. 2000 Jan-Feb; 20(1): 83–98
12. Ooi GC, Kwong DL, Chan KN, Ngan H, Lock DT, Lam WK, Chan FL, Au G, Tsang KW: Serial HRCT lung changes after 3-field radiation treatment of breast cancer. Clin Radiol. 2000 Nov; 55(11): 817–24
13. Loyer E, Fuller L, Libshitz HI, Palmer JL: Radiographic appearance of the chest following therapy for Hodgkin disease. Eur J Radiol. 2000 Aug; 35(2): 136–48
14. Abratt RP, Morgan GW. Lung toxicity following chest irradiation in patients with lung cancer. Lung Cancer. 2002 Feb; 35(2): 103–9
15. Choi YW, Munden RF, Erasmus JJ, Park KJ, Chung WK, Jeon SC, Park CK: Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. Radiographics. 2004 Jul-Aug; 24(4): 985–97
16. Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, Muto M, Ogino T, Yoshida S: Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol. 2003 Jul 15; 21(14): 2697–702
17. Hong TS, Crowley EM, Killoran J, Mamon HJ: Considerations in treatment planning for esophageal cancer. Semin Radiat Oncol. 2007 Jan; 17(1): 53–61
18. Chandra A, Guerrero TM, Liu HH, Tucker SL, Liao Z, Wang X, Murshed H, Bonnen MD, Garg AK, Stevens CW, Chang JY, Jeter MD, Mohan R, Cox JD, Komaki R: Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiother Oncol. 2005 Dec; 77(3): 247–53. Epub 2005 Nov 17
19. Wang SL, Liao Z, Liu H, Ajani J, Swisher S, Cox JD, Komaki R: Intensity-modulated radiation therapy with concurrent chemotherapy for locally advanced cervical and upper thoracic esophageal cancer. World J Gastroenterol. 2006 Sep 14; 12(34): 5501–8