# Early effect of radiation on the liver function tests of patients with thoracic and abdominal tumors during radiotherapy

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**ABSTRACT**

The liver is an organ at risk (OAR) in radiotherapy of thoracic and abdominal tumors such as gastric, distal esophagus, lower lung and breast, bile duct, pancreas and whole abdomen. In this study the alteration in liver functional tests (LFT) of these patients during radiotherapy was investigated. To that end, the level of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), direct and total bilirubin were checked out at different times (before radiotherapy and every 2 weeks after the start of radiotherapy and followed up to 2 months after the end of treatment). The results showed that LFT level increased during radiotherapy while they gradually decreased after treatment. Our results showed that the LFT serum is a very sensitive and useful biomarker for evaluation of the radiotherapy effects.

**Key words**: liver functional test; thoracic and abdominal tumors; radiotherapy

## INTRODUCTION

Radiation therapy is an integral part of the treatment of patients inflicted with cancer. It is estimated that over 60% of patients with cancer will have radiotherapy as part of their total course of treatment. Radiation therapy affects both tumor cells and uninvolved normal cells [1]; the former benefits through killing tumor cells but the later leads to detriment of patient as it causes some significant complications in patients. Although the liver was once believed to be relatively Radioresistant, hepatic morphologic and functional alterations have been observed after radiation therapy [2,3].Hepatic radiation is most often unintentional and occurs when the liver is unavoidably included in the treatment portal for lower breast and lung, distal esophageal, gastric, bile duct, pancreatic carcinoma or lymphoma and whole body. Patients who receive a single 12Gy dose of external beam radiation or 40 to 55Gy fractionated dose over 6 weeks can develop radiation Hepatitis. Nearly 75% of patients receiving whole liver irradiation have abnormal liver function tests [3,4].After radiotherapy for cancers of the abdominal and lower thoracic, the interpretation of changes in the liver functional tests (LFT) during follow up can be problematic [5]. Some observer have associated alteration in LFT with visible vascular or density temporary modification in irradiated liver regions [6], suggesting a possible alternative origin for LFT abnormalities in patients with no sign of metastasis [5].If the area of irradiated hepatic tissue is small, the classic signs and symptoms of hepatic radiation injury such as hepatomegaly and ascites are not present. If the liver receives high doses of radiation during childhood, atrophy may result. If other structures such as the kidney or vertebral bodies are included in the part, they are underdeveloped as well [3].Radiation–induced liver disease (RILD) has been reported to be one of the most important complications in patients who undergo abdominal and lower thoracic radiotherapy and limiting dose escalation is a major factor for liver irradiation [7].The purpose of this study was to analyze LFT and hepatic

dysfunction after radiotherapy in patients with abdominal and lower thoracic cancers and to determine the relationship between hepatic dysfunction and liver dose.

## PATIENTS AND METHOD

The present study was carried out on 123 patients who received radiotherapy for abdominal and lower thoracic cancers (e.g. gastric, distal esophagus, pancreas, bile duct, right breast and lung,…) from December 2014 to October 2015 in Tohid hospital, Sanandaj. There were 64 women and 59 men with the age range between 27 to 90 years (mean 57 years). The patients had not history of liver metastasis or other liver disease. Of the 123 patients, 40 cases (%32.5) had esophagus tumor, 30 cases (%24.4) had breast cancer, 27 cases (%22) had gastric tumor and 26 cases (%21.1) had other tumors. 83 patients received chemotherapy before radiotherapy and others received chemo radiotherapy. Concomitant chemotherapy was administered to all patients either as continuous 5FU infusion (250-300 mg/m²/d for adjuvant gastric adenocarcinomas, extra hepatic cholangiocarcinoma and adjuvant pancreatic carcinoma) or as a combination of weekly administrations of Cisplatin or Carboplatin with a continuous 5FU infusion (250 mg/m²/d) for locally advanced pancreatic adenocarcinomas. Irradiation was done by 3D conformal radiotherapy based on a simulation CT and calculated with the same TPS (Isogray version 4.1 from Dosisoft Company). Treatment carried out with an Elekta machine producing x-ray beams of 6 to 15 MV. Most of these patients delivered 45 to 50.4 Gy. The fraction size ranged from 1.8 to 2 Gy (median 2 Gy) for 5 days per week. The planning target volume was defined as the CTV (Clinical Target Volume) plus an approximate 1-2cm margin in all directions. To evaluate the effect of radiotherapy on Liver Functional Tests (LFT) including ALT, AST, and ALP, direct and total bilirubin levels before and after radiotherapy were analyzed. These tests were included on most routine laboratory tests. The combined elevation of these enzymes indicates the presence of liver disease Blood tests were examined 0-14 days before the start of radiotherapy (median 1 day). Patients had blood tests every 2 weeks (weeks 2, 4, and 6) after start of radiotherapy. In addition these patients followed up for 2 months after radiotherapy. Statistical tests were performed using the SPSS software (version 23). A P-value of $<0.05$ was considered to indicate statistical significance. Cases where transaminase or ALP levels exceeded the normal upper limits slightly after radiation were not of clinical significance. Cases where transaminase or ALP levels elevate more than double pretreatment values and exceed normal limits after radiation were also not of clinical significance if the pretreatment values were low. All the steps of this study, including sampling, data collection, and broadcasting the study results in the form of article are done with the full consent of the patients.

## RESULT

In this study, 123 patients have been treated by three-dimensional conformal radiotherapy for abdominal and lower thoracic cancers. Patients age ranged from 27 to 90 years (mean 57 years). 15 patients received 1.8 Gy per fraction and others received 2 Gy. Maximal doses received to PTVs ranged from 45 to 50.4 Gy. None of the patients had hepatic disorders such as chronic hepatitis or hepatic tumors. The average level of serum ALT , AST , ALP , direct and total bilirubin with the statistical significance of standard deviation are given in table 1.Mean pre-radiotherapy LFTs were in the normal range. LFT activity was raised after start of radiotherapy [Figs 1-5]. There was a statistically significant increase ($P<0.05$) in serum level of LFTs. Maximal level of LFTs was observed at the end of treatment (mean 32th day after start of treatment). These liver tests values between pretreatment and post treatment were significantly different. LFT levels decreased afterwards and most tests of patients got nearly normalized. The figures show LFT levels altered after radiotherapy.

**Table 1.** Alteration in liver functional tests of patients with abdominal and thoracic tumors during radiotherapy. All values are the mean. ±SD

| LFT | normal range | pre radiotherapy | 14 days | 28 days | 42 days | 72 days | 102 days |
|---|---|---|---|---|---|---|---|
| ALT | 5-40 (u/l) | 26.29±3.93 | 27.25±3.94 | 33.23±4.44 | 41.02±5.7 | 37.55±5.38 | 33.64±4.9 |
| AST | 7-65 (u/l) | 25.88±3.21 | 26.22±2.96 | 31.33±3.89 | 36.85±4.97 | 35.07±4.57 | 31.93±4.14 |
| ALP | 50-150 (u/l) | 228.63±20.06 | 240.5±18.79 | 247.72±18.42 | 265.57±19.87 | 252.87±18.09 | 236.45±17.53 |
| Bilirubin(D) | 0.1 – 0.3 (mg/dl) | 0.18±0.03 | 0.19±0.02 | 0.22±0.02 | 0.24±0.03 | 0.21±0.03 | 0.20±0.03 |
| Bilirubin(T) | 0.3 - 1 (mg/dl) | 0.6±0.04 | 0.62±0.05 | 0.65±0.05 | 0.68±0.05 | 0.65±0.05 | 0.62±0.04 |

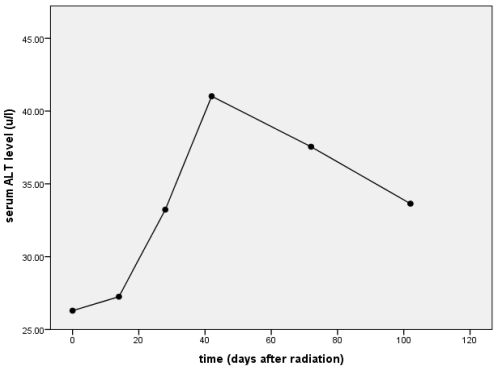


**Figure 1.** Alteration serum ALT level after radiotherapy

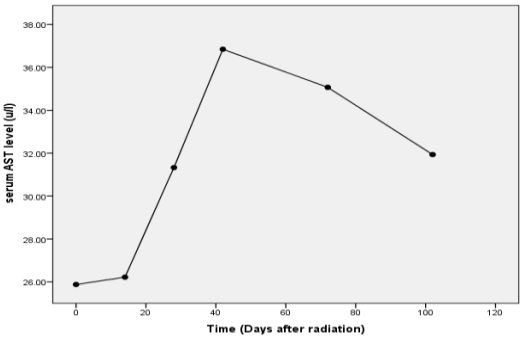


**Figure 2.**Alteration serum AST level after radiotherapy

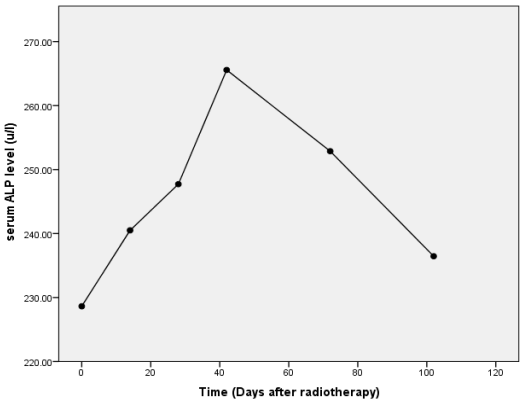


**Figure 3**. Alteration serum ALP level after radiotherapy

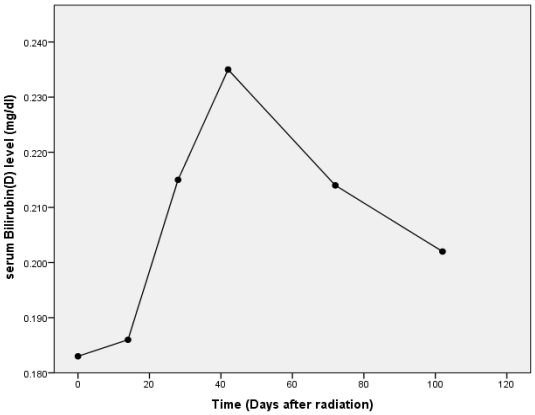


**Figure 4.** Alteration serum bilirubin (D) level after radiotherapy

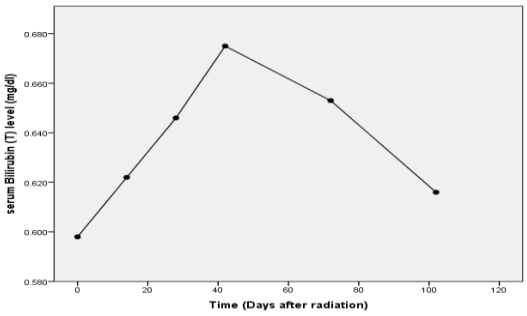


**Figure 5**.Ateration serum bilirubin (T) level after radiotherap

Pretreatment ALT values for 11 patients and AST values for 6 patients were more than normal levels. Transaminase levels increased gradually during radiation therapy. A more than 1.5 five-fold increase for ALT and 1.42 five-fold increase for AST levels were observed at the end of radiotherapy. Then transaminase levels decreased at post radiotherapy. 101 patients (%82) had abnormal ALP levels prior to treatment. After start of radiation therapy, ALP level increased and it received to 1.16 five-fold normal level at the end days of treatment. Pretreatment total bilirubin values in 9 patients were above normal range. Direct and total bilirubin raised post treatment and these received to 1.2 times normal level proximally.

## DISCUSSION

Liver is one of the main organs at risk for many abdominal and lower thoracic tumors undergoing radiotherapy [7,8]. When these tumors received radiation, a part of the liver is placed in the field treatment. Liver receives high dose radiation if it is placed in the vicinity of the tumor. Therefore reduction in treatment volume of these serial organs is critically important [9].

The present study evaluated changes in the LFT level in these patients. First LFT level was checked before radiotherapy then these patients were followed up every 2 weeks towards the end of treatment. In addition these patients were followed up for 1 month and 2 months after the end of radiotherapy.Reference values for human were displayed as 5 – 40 (u/l) for ALT, 7 – 65 (u/l) for AST, 50 – 150 (u/l) for ALP, 0.1 – 0.3 (mg/dl) for direct bilirubin and 0.3 – 1 (mg/dl) for total bilirubin.The results of this study confirmed that liver radiation induced LFT changes. Rate of changes was different in patients [10]. In the previous studies, some recorded an elevated activity while others showed a decrease activity. Jin hong jung et al , Matthew H.stenmark et al , Hidekaju nakata et al and Jaggandha Rao Peela et al reported that liver radiation increased LFT level [7, 11-13] but Tadej Dovsak et al , Saung – Gu Yeo et al , Kultigin Cavusoglu showed that liver radiotherapy caused a decrease in LFT level [14,16].The present study showed that radiation elevated serum LFT levels. LFT levels increased gradually during radiotherapy and it reached its peak at the end of treatment. Regression coefficient showed relationship between dependent variables (liver tests) and all studied independent variable. It discovered that factors such as patient's age, liver dose, chemotherapy and treatment duration had the most effect on the LFT levels. The liver function tests are very important for diagnosis, evaluation of severity and correct management of radiation – induced injury even with the fluctuations observed. It is difficult to explain the changing mechanism of serum LFT parameters. It is likely that these increases could be related to cell destruction [16]. As is known LFT are synthesized by hepatocyte cells and are sensitive and specific enzymes for liver disease [19]. Any elevation in these levels may be commented as an indicator of liver disease [16-18]. Therefore the simultaneous increase in LFT levels during radiotherapy may probably be related to radiation – induced liver injury.

## CONCLUSION

This study indicated that radiotherapy for abdominal and thoracic tumors increased LFT levels; it can also be concluded that radiation damages healthy cells, leading to liver dysfunction. Radiotherapy treatment should be planned in order to reduce liver dose. Dose restriction for healthy liver should be further evaluated.

*"The authors declare no conflict of interest"*

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