RARELY REPORTED LIVER TOXICITY IN PATIENTS WHO WERE HEPATITIS B CARRIER AND UNDERWENT CHEMOIRRADIATION FOR GASTRIC CANCER

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Purpose *:* This study is to report the clinical and dosimetric parameters of six patients who were carriers of type B chronic hepatitis and developed grade 3 or 4 hepatic toxicity after adjuvant or definitive concurrent chemoirradiation for gastric cancer.

Materials and Methods *:* From December 1993 through July 2001, 82 patients with gastric adenocarcinoma underwent radiotherapy as adjuvant or definitive treatment. Ten patients were carriers of type B chronic hepatitis on serology test. Six of 10 patients who developed grade 3 or 4 hepatic toxicity within 4 months after radiotherapy, formed the basis of this study. Five patients underwent external-beam radiotherapy with 45 Gy/1.8 Gy/25 fractions and 18 MV photons delivered to the tumor bed and regional lymphatics over 5 weeks. One patient had the radiotherapy with 50.4 Gy/28 fractions. Concurrent chemotherapy consisted of 3-6 (median: 5) weekly cycles of intravenous infusion with 5-fluorouracil 2 gm/m^2 and leucovorin 300mg/m^2 for 24 hours. Dose-volume histograms of the critical organs were used for the dosimetric factors in these patients.

Results *:* Six patients developed grade 3 or 4 hepatic toxicity, with a median interval of 38 days from completion of radiotherapy. One patient died of this complication and five patients recovered. All but one patient had either serologic or histological evidence of reactivation of chronic viral hepatitis. Mean dose of liver of the 6 patients ranged from 10.4 Gy to 22.9 Gy (mean: 17.2 Gy), while the percent volume receiving more than 30 Gy of radiation ($V_{30\ Gy}$) ranged from 7% to 37% (mean: 24%). Mean normal tissue complication probability (NTCP) was 3.3%, ranging from 0.03% to 6.8%. Mean hepatic dose, $V_{30\ Gy}$, and NTCP were all significantly lower than those of the 12 patients with hepatocellular carcinoma and radiation-induced liver disease after three-dimensional conformal radiotherapy.

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Conclusion **:** Hepatic toxicity after concurrent chemoirradiation, in patients who were carriers of type B chronic hepatitis and underwent treatment for gastric cancer, deserves special attention and was rarely reported in the literature. The tolerance of liver to radiation was even lower than expected in the presence of concurrent chemotherapy.
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Key words: Hepatic toxicity, Concurrent chemoirradiation, Gastric cancer

INTRODUCTION

Gastric cancer continues to be one of the most important gastrointestinal cancers [19]. Surgical resection remains the main curative treatment and plays the most important role in approximately 50% of patients [5]. Radiotherapy has been gradually integrated into the multi-modality treatment for patients with gastric cancer in the past dacades [14]. Recent randomized trial has proved the survival benefit with the addition of post-gastrectomy adjuvant concurrent chemoirradiation (CCRT) for patients with adenocarcinoma of the stomach or gastroesophageal junction [13]. Radiation-induced liver disease (RILD) has been reported to be one of the most important treatment-related complications in patients with hepatic irradiation [10]. Dosimetric factors were found to be associated with the occurrence of RILD [11]. In addition, hepatic toxicity with the presentation of reactivation of type B viral hepatitis was seldom reported for patients undergoing chemotherapy for the hematologic malignancies [22]. Among the few series of patients with hepatitis reactivation after chemotherapy for solid tumors, Yeo et al. described 15 of 78 cases with reactivation of hepatitis B during chemotherapy and emphasized the important risk factors such as male sex, younger age, seropositive status, and the underlying lymphoma [23]. Although there has not been any report indicating the significant risk of RILD for patients undergoing combined chemotherapy and radiotherapy, a certain portion of liver is undoubtedly included in the radiation portals for patients with gastric cancer undergoing radiotherapy [14]. In this study we described the rarely reported hepatic toxicity and the dosimetric analysis for 6 patients with definitive or adjuvant chemoradiotherapy for gastric cancer.

MATERIALS AND METHODS

From December 1993 through July 2001, eighty-two patients with biopsy-proven primary gastric adenocarcinoma underwent radiotherapy at Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan. The inclusion criteria of this study were the completion of the planned radiotherapy and the adequate follow-up interval of at least 4 months from the last day of radiation treatment. Three patients had definitive radiotherapy for their unresectable gastric cancer, while 79 patients had post-gastrectomy adjuvant radiotherapy. Among them, ten patients were found to be carrier of type B chronic viral hepatitis by the serology test. Six of these 10 patients were diagnosed with grade 3 or 4 hepatic toxicity according to Common Toxicity Criteria Version 2.0 by National Cancer Institute [20]. In brief, it is defined as either anicteric elevation of alkaline phosphatase level of at least twofold and non-malignant ascites, or elevated transaminases of at least fivefold the upper limit of normal or of pre-treatment level, within 4 months after completion of radiotherapy. At the time of diagnosing grade 3 or 4 hepatic toxicity, abdominal sonography or computed tomography, and abdominal paracentesis if ascites is

present, need to be done for confirmation of no disease recurrence.

Radiation portals were designed to cover the tumor bed, the regional lymph nodes, and 1.5-2 cm beyond the proximal and distal margins of resection. The tumor bed was defined by pre-operative imaging studies. Perigastric, celiac, paraaortic, hepatoduodenal, hepatoportal, and pancreaticoduodenal lymph nodes were included in the radiation fields. The dose to the isocenter was 50.4 Gy in the treatment for one patient and 45 Gy for the other 5 patients, with 1.8 Gy per fraction and 5 fractions a week. Anterior-posterior and posterior-anterior (AP/PA) portals were used in one patient, while 4-field box technique was used in the other 5 patients. Radiation was delivered with 18-MV photons. The dose constraints for the critical structures were less than half of the hepatic volume exposed to more than 30 Gy, the equivalent of at least one kidney spared from more than 20 Gy, and no portion of the spinal cord with more than 50 Gy of radiation.

Dose-volume histogram (DVH) was generated from the computerized treatment plan of three-dimensional conformal radiotherapy for each patient. Several dosimetric parameters of the critical organs were calculated from the DVHs. V_{30Gy} was the percent volume of liver with radiation dose more than 30 Gy. RK_{20Gy} was the percent volume of right kidney with radiation dose more than 20 Gy. LK_{20Gy} was the percent volume of left kidney with radiation dose more than 20 Gy. SP_{40Gy} and SP_{45Gy} were the percent volumes of spinal cord with radiation dose more than 40 Gy and 45 Gy, respectively. The normal tissue complication probability (NTCP) model of Lyman was also used [12]. In NTCP model:

$$NTCP = (1 / \sqrt{2}\,\pi) \int_{-\infty}^{t} \exp(-t^2/2)\, dt$$

$$t = (D - TD_{50}(v))/(m \times TD_{50}(v))$$

$$v = V/V_{ref}$$

$TD_{50}(v)$ was the 50% tolerance dose for uniform irradiation of the partial volume v. The partial and whole liver radiation tolerance doses were related by a power law relationship:

$$TD(1) = TD(v) \times v^n$$

Vref was the volume of normal liver. The parameter "n" was the volume effect parameter and the value of 0.32 from the literature was applied [2]. The parameter "m" was the steepness of the dose-complication curve for a fixed partial volume, and the estimate of 0.15 was used [2]. $TD_{50}(1)$ of 40 Gy was applied in the calculation [2]. The effective volume method of Kutcher and Burman was used to provide estimates of equivalent dose and volume pairs for uniform partial organ irradiation from the DVH's summarizing the non-uniform irradiation [9].

Patients were followed regularly after completion of radiotherapy. Follow-up office visits were arranged on a monthly basis for 4 months. Physical examination, complete blood counts, and blood chemistries were obtained on every visit. Imaging studies were obtained as needed if any evidence of RILD is suspected.

RESULTS

Six of the ten patients, who had type B chronic viral hepatitis before the treatment of gastric cancer, were diagnosed with equal to or more than grade 3 hepatic toxicity after CCRT. Five patients were male and 1 female. Among these 6 patients, one patient underwent definitive radiotherapy and 5 patients had post-operative adjuvant radiotherapy. All 6 patients received concurrent chemotherapy during radiotherapy. The regimens of chemotherapy included intravenous infusion with high-dose 5-fluorouracil 2000-2600 mg/m^2 and leucovorin 300 mg/m^2 for 24 hours, given once a week. The cycles of concurrent chemotherapy ranged from 3 to 6, with a median of 5 cycles. Three patients received one cycle of chemotherapy with etoposide, leucovorin, and 5-fluorouracil, 3 weeks before the initiation of radiotherapy. Patient

characteristics were shown in Table 1. As compared to the other 72 patients who were not type B hepatitis carriers, only one patient developed equal to or more than grade 3 hepatic toxicity after CCRT.

All 6 patients presented with malaise, hyperbilirubinemia, and elevated levels of serum transaminases. One of the 6 patients also had anicteric elevation of alkaline phosphatase level of at least twofold and massive non-malignant ascites. The interval between completion of radiotherapy and the diagnosis of grade 3 or 4 liver toxicity ranged from 26 to 74 days, with a median of 38 days. All but one patient had either serum type B viral hepatitis DNA titer of more than 5pg/ml, or histological finding of chronic hepatitis reactivation on liver biopsy. The maximal hematological toxicity during radiotherapy was grade 1 in 1 patient, grade 2 in 4 patients, and grade 3 in 1 patient. All 6 patients were treated with supportive care, and four of them were also given anti-viral agent (Lamivudine). Five patients recovered completely after the treatment, but the remaining one patient who had no anti-viral medication died of hepatic failure. The 4 patients treated with Lamivudine had their transaminases returned to normal range within a median interval of 51 days (range: 43-100 days), as compared to 194 days in the fifth patient with no Lamivudine.

In dosimetric analysis, the average mean dose of liver was 17.2 ± 4.7 Gy, ranging from 10.4 Gy to 22.9 Gy. $V_{30\ Gy}$ ranged from 7% to

Table 1. Patient characteristics for 6 patients with severe hepatic toxicity after chemoirradiation for gastric cancer

Patient No.	1	2	3	4	5	6
Sex	male	male	female	male	male	male
Age	57	50	40	71	40	51
Stage	T3N3M0	T4N2M0	T3N0M0	T1N1M0	T3N1M0	T3N3M0
Type of RT*	adjuvant	adjuvant	adjuvant	adjuvant	adjuvant	definitive
RT dose	45Gy	50.4Gy	45Gy	45Gy	45Gy	45Gy
Pre-RT chemo**	ELF^ x 1	none	ELF x 1	None	ELF x 1	HDFLx2
Interval from RT	29 days	26 days	63 days	74 days	26 days	47 days
Max hematological toxicity during RT	Grade 2	Grade 1	Grade 2	Grade 3	Grade 2	Grade 2
HBV DNA	3326mEq/ml	3.3pg/ml	64pg/ml	33pg/ml	1485pg/ml	>200pg/ml
Outcome of toxicity	mortality	recovery	recovery	recovery	recovery	recovery

*RT: radiotherapy

** chemo: chemotherapy

^ELF: etoposide, leucovorin, 5-fluoroiracil

Table 2. Dosimetric parameters for 6 patients with severe hepatic toxicity after chemoirradiation for gastric cancer

Patient No.	1	2	3	4	5	6
Dose (Gy)	45	50.4	45	45	45	45
Mean dose of liver (Gy)	13.1	10.4	22.9	18.5	20.7	17.6
V30 Gy (%)	7	8	37	24	35	33
NTCP* (%)	0.16	0.03	6.78	2.23	3.98	6.66
RK20 Gy (%)	53	35	28	28	58	20
LK20 Gy (%)	35	19	13	4	8	55
SP40 Gy (%)	0	0	0	0	0	76
SP45 Gy (%)	0	0	0	0	0	73

*NTCP: normal tissue complication probability

37%, with a mean of 24%. The average NTCP was as low as 3.3%, ranging from 0.03% to 6.8%. The details of the dosimetric parameter of the 6 patients were shown in Table 2. As compared to the 12 patients with RILD after three-dimensional conformal radiotherapy for hepatocellular carcinoma [3], the 6 patients in this study had significantly lower mean dose of liver (17.2 Gy vs. 24.9 Gy, $p = 0.02$), $V_{30\,Gy}$ (24% vs. 42%, $p = 0.02$), and NTCP (3.3% vs. 36.0%, $p = 0.004$).

DISCUSSION

Radiation therapy has been used in a variety of setting for the treatment of gastric cancer. MacDonald et al. recently reported the results of the Intergroup Trial which randomized stage IB-IV patients with or without post-gastrectomy adjuvant chemoradiotherapy [13]. They found the addition of adjuvant chemoirradiation to be associated with benefits in local/regional control and survival. Walsh et al. demonstrated the preliminary analysis which randomized patients with or without pre-operative CCRT [21]. The arm with chemotherapy and radiotherapy had less regional/distant metastasis and longer survival. The study from China similarly randomized patients with adenocarcinoma of gastric cardia into two arms, pre-operative radiotherapy plus surgery or surgery alone [24]. Benefits in survival and local/regional nodal disease control were shown with pre-operative radiotherapy.

In this study we reported 6 patients with grade 3 or 4 hepatic toxicity after adjuvant or definitive CCRT for gastric adenocarcinoma. Hepatic toxicity was rarely reported in previous series, probably due to the relatively low dose (45-50 Gy) of radiation in the treatment. MacDonald et al. used 45 Gy and reported 17% of patients with grade 3 or higher CCRT-related toxic effects but no patient with hepatic toxicity [13]. Walsh et al. used 40 Gy and neither had any patient with hepatic toxicity in their trial [21]. Regine WF and Mohiuddin M retrospectively reviewed their patients with adjuvant radiotherapy or CCRT in addition to surgery [15]. Three patients had grade 3 or higher gastrointestinal toxicity and interrupted treatment. There was no hepatic toxicity. The study in China did mention the serology test of chronic viral hepatitis before preoperative CCRT [24]. However, they did not the detailed treatment-related toxicity after moderate dose (40 Gy) of radiation. Schnirer II et al. designed the pilot study using concurrent 5-fluorouracil/paclitaxol plus local radiotherapy with 45-50.4 Gy for patients with locally advanced carcinoma of the esophagus and gastroesophageal junction [18]. They did not find any treatment-related liver toxicity. The other reason for the rare hepatic toxicity, except the moderate prescribed dose, may be attributed to the location of liver being outside the target area of adjuvant or definitive treatment. Similar situation was encountered for patients with pancreatic cancer. Abrams RA et al. reported a possible case of late radiation hepatitis in the trial of adjuvant CCRT for pancreatic and periampullary adenocarcinoma [1]. It deserves attention that they used prophylactic whole liver irradiation with 23.4-27 Gy in this study.

The regimens of chemotherapy in our concurrent treatment were high-dose intravenous 5-fluorouracil and leucovorin. High-dose 5-fluorouracil of equal to or more than 2000 mg/m^2 have been used in the definitive treatment of locally advanced gastric cancer [7,8]. However, most of the trials with high-dose 5-fluorouracil did not include patients with concomitant radiotherapy. In contrast, the most extensive experience in hepatic irradiation at Michigan University Medical Center [16,17] used regional chemotherapy, intra-hepatic arterial infusion of FudR, did not show the similar hepatic toxicity to those in our patients with systemic chemotherapy. The impact of chemotherapy on the occurrence of RILD in patients with HCC

undergoing radiotherapy was considered less significant for its regional injection from transcatheter arterial chemoembolization (TACE) and the required interval of one month between TACE and radiotherapy.

RILD, defined as equal to or more than grade 3 liver toxicity within 4 months after completion of radiotherapy, has been described as one of the most important complications after hepatic irradiation [10]. Dosimetric parameters, such as mean dose of liver and NTCP, were found to be correlated with the occurrence of RILD [11]. Dawson et al. further optimized the parameters in Lyman model and damage-injury model with the DVH data of their patients [4]. They concluded the liver to be compatible with parallel organ by the similar trend between the significance of mean hepatic dose and the optimized large volume effect parameter. In contrast, our own series with exclusively hepatocellular carcinoma revealed the poorer tolerance of liver with the obtained parameters close to those from the literature [3]. The differences between the two series were from the unique features of a large proportion of chronic viral hepatitis and pre-existing cirrhosis of liver in our patients. In the current series our 6 patients with grade 3 or 4 liver toxicity were all type B hepatitis carriers. The high incidence (6/10) of severe liver toxicity deserves special attention when giving CCRT to patients with chronic viral hepatitis. All our patients except with liver toxicity had either serologic or histological evidence of reactivation of chronic hepatitis. Four of the six patients had full recovery from the liver toxicity after anti-viral medication, within a wide range of 43-100 days. The fifth patient with no Lamivudine required even longer period (194 days) for the full recovery. The only patient who died of this complication did not receive the anti-viral medication. All these evidence supported the liver toxicity from reactivation of chronic viral hepatitis, which was different from the toxicity from the damage of hepatobiliary system in the reports from the western countries. It is possible that Lamivudine successfully suppressed the reactivation of chronic viral hepatitis. Whether the routine use of Lamivudine for all carrier patients or for patients with any evidence of hepatic toxicity still deserves further observation and investigation for the limited number in this report.

The dosimetric comparison between the 6 patients in this study and the 12 patients with hepatocellular carcinoma and RILD, showed even lower tolerance of liver to radiation with CCRT. All the 12 patients except one with hepatocellular carcinoma and RILD were hepatitis B carrier. The characteristics of liver of these 12 patients were similar to that of the 6 patients in this study. The main difference was the use of concurrent systemic chemotherapy for patients with gastric cancer. In the presence of systemic chemotherapy with 5-fluorouracil, the threshold of liver damage may be further reduced. Five of the six patients presented with only grade 1 or 2 hematological toxicity, which indicated the less likely mechanism of liver toxicity from the suppressed immune system by chemotherapy. 5-Fluorouracil has been employed to enhance the therapeutic activity of other antineoplastic agents or modalities such as cisplatin and ionizing radiation with which it can synergize [6]. Whether high-dose 5-fluorouracil plays the role in increasing the hepatic damage by irradiation, needs to be confirmed in future studies. However, the insufficient data collection of comprehensive viral serology items, such as HbeAg and pre-CCRT HBV DNA, limits the interpretation of the etiology of this complication.

In conclusion, a significant proportion of patients who were carriers of type B chronic viral hepatitis had grade 3 or 4 hepatic toxicity after adjuvant or definitive CCRT for gastric cancer. The tolerance of liver to irradiation of this subgroup of patients may be even lower in the presence of systemic chemotherapy. Close

follow-up and early detection of this complication is demanded for the recovery. Further study of the underlying mechanism of liver damage in this situation is urgently needed.

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文獻中少見的 B 型肝炎帶原者接受胃癌之合併放射化學治療後的肝臟毒性報告

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目的：本研究在報告 6 位 B 型肝炎帶原者及同時罹患胃癌病人在接受術後輔助或全程合併放射化學治療後產生第三或四級肝臟毒性的臨床及劑量學數據。

材料與方法：1993 年 12 月至 2001 年 7 月間，82 位經切片證實為胃腺癌病人接受手術後輔助或全程合併放射化學治療，其中 10 位病人經血清學檢查為 B 型肝炎帶原者，10 位中的 6 位病人在接受手術後輔助或全程合併放射化學治療後產生第三或四級肝臟毒性，為本研究的主要對象。5 位病人接受 45 Gy ／ 1.8 Gy ／ 25 次，1 位病人接受 50.4 Gy ／ 1.8 Gy ／ 28 次的 18 MV 光子射束體外放射治療於腫瘤切除區域及附近淋巴區域。同步合併化學治療使用每週 1 次靜脈連續注射 24 小時的 5-fluorouracil 2 gm/m^2 及 leucovorin 300 mg/m^2，共接受 3-6 療程（中位數：5 療程），3 位病人另接受 1 次放射治療療程開始前 3 週的 etoposide，5-fluorouracil，leucovorin 前導化學治療。第三或第四級肝臟毒性根據美國國家癌症中心之常見毒性標準定義為非惡性腹水形成及鹼性磷酸鎢上昇 2 倍以上，或肝指數（GOT/GPT）上升至正常值上限或治療前的 5 倍以上。病人完成治療接受每月 1 次的身體檢查及血液血球計數與生化檢查。劑量體積圖使用於正常器官劑量參數的分析工具。

結果：6 位病人放射治療後中位數 38 天發生第三或第四級肝臟毒性，5 位病人完全康復，1 位病人死於此併發症。5 位病人病發時有血清學或病理學的慢性肝炎急性發作證據。合併放射化學治療療程中的最大血液系統毒性為第 1 級 1 位，第 2 級 4 位，第 3 級 1 位病人。6 位病人的平均肝臟劑量範圍為 10.4 Gy 到 22.9 Gy（平均數 17.2 Gy），肝臟接受超過 30 Gy 劑量的體積比例範圍為 7% 到 37%（平均數 24%），平均的正常組織併發症機率為 3.3%，範圍為 0.03% 到 6.8%，這三項參數的平均數顯著低於另外 12 位肝癌病人接受三度空間順形放射治療後發生放射線引起之肝臟病變的劑量參數平均數。

結論：B 型肝炎帶原者罹患胃癌接受合併放射化學治療後發生肝臟毒性的現象，是文獻上少見且值得特別注意的。在給予化學治療的同時，肝臟對放射線的忍受度更形下降。進一步對肝臟傷害形成機轉的研究是急切需要的。

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關鍵詞：肝臟毒性、合併放射化學治療、胃癌