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ORIGINAL ARTICLE

Radiotherapy as a bridge to liver transplantation for hepatocellular carcinoma

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Summary

About 20% of the patients with advanced hepatocellular carcinoma (HCC) who are listed for liver transplantation (LT) are eventually delisted as a result of local tumor progression. Herein, we report our experience with conformal radiotherapy (CRT) as a novel bridge to LT. From July 2006 to August 2008, CRT was delivered in five or six fractions to patients with HCC listed for LT in whom either prior local therapies had failed or those not suitable for standard local therapies because of poor liver function or anatomic issues. Radiotherapy (RT) volumes and doses were individualized to spare the uninvolved liver with the goal of stabilizing the most aggressive HCC(s) in an attempt to reduce the chance of delisting as a result of tumor progression. Ten patients with tumor diameters ranging from 25 to 108 mm were treated. Eight out of 10 tumors were beyond Milan criteria. The median age was 55 (range 36–64). Seventy percent of the patients were male subjects. The median medical MELD score was 11 (range 9–17). The median irradiated HCC volume was 79 cc (range 15–798 cc). The median RT delivered dose was 33 Gy (range 8.5–54 Gy), in one to six fractions. The median dose to the uninvolved liver was 13.3 Gy (range 1.8–16.5). Nine patients completed their CRT as planned and one patient was transplanted after the first fraction. The treatment was well tolerated: Grade 1 nausea was reported in three patients, the platelet count decreased from 154 to 98 in one patient, and there were no other complications. No treated tumors progressed during or after the treatment. Two tumors remained stable; the rest had 10–50% regression, which was sustained on follow-up imaging. The median follow up was 14 months (range 3–20). Local tumor control was achieved in all treated tumors.Two patients were delisted as a result of cancer progression outside the treated field (one in the context of systemic metastases; yet another with progression of other untreated HCC in the liver). Three patients are still waiting for transplantation. Five patients underwent LT with no complications attributable to the CRT. Explant pathology, available for five patients, showed tumor necrosis and fibrosis with sparing of the untreated parenchyma. All transplanted patients treated with CRT are cancer-free. CRT is a safe and efficacious local bridging therapy for patients with advanced HCC who are on the waiting list for LT. Further studies are warranted to compare the effectiveness of CRT to other local treatment regimens for HCC.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor. Liver transplantation (LT) and resection remain the only options for cure.Out of the total patients with HCC on the waiting list, 20–30% of the patients have substantial disease progression while still awaiting LT, leading to removal from the waiting list [1–3]; in order to reduce progression, all patients are considered for local treatment whilst awaiting LT. Radiofrequency ablation (RFA) [4], percutaneous ethanol injection (PEI) and transcatheter arterial chemoembolization (TACE) [5] have become a standard of care for HCC as a bridge to LT despite the lack of a controlled trial confirming a survival advantage or of superiority of one treatment over another. Herein, we report our center's experience with the safety and efficacy of conformal radiotherapy (CRT) as another treatment option for bridging therapy. CRT has been used to achieve regression and stabilization as a primary treatment for liver tumors [6,7], resulting in median survivals ranging from 11 to 25 months [7,8]. In our institution, CRT has been used as a second-line bridging therapy in selected high-risk patients outside the realms of standard treatments. Herein, we report for the first time the safety and effectiveness of CRT in the treatment of HCC as a bridge to LT.

Methods

All patients undergoing LT for HCC at our institution were considered for local treatment while being on the waiting list for LT. We have no size or number restrictions when listing for HCC, there should not be any macrovascular invasion, and for patients outside the Milan criteria [9] a biopsy should not be showing poor differentiation – 'Toronto Criteria'. Anatomical location, tumor size and relationships, degree of liver dysfunction and response to previous treatment were used to determine the most appropriate treatment. RFA and TACE were the primary treatments in suitable patients. Since July 2006, CRT was offered to patients who were either unsuitable, or, had failed other forms of local therapy. These patients were judged by the transplant team to have HCC with a high risk of progression, which would lead to delisting. Suitability for conventional treatments was based upon tumor size, proximity to major vasculature, number of lesions, degree of liver dysfunction and previous response to treatment. Treatment decisions were made in a multidisciplinary setting. Patients were selected carefully for CRT, with tumors chosen in a location and of a size that would allow some of the uninvolved liver to be spared completely from CRT, to reduce the risk of toxicity, especially in Child-Pugh B or C patients, where the risk of liver toxicity following radiation therapy is higher and not well established.

Conformal RT fields and dosages were adjusted to maximize the radiation doses to the tumor whilst avoiding the normal parenchyma. A CRT treatment goal was to limit the dose delivered to liver not involved with tumor. In this initial cohort of cirrhotic patients, CRT dosages were limited to 54 Gy or less, given in five or six fractions over 2 weeks. The liver volume spared from CRT (<10 Gy) was maximized, and the mean normal liver dose was limited to <20 Gy, to reduce the risk of liver toxicity and decompensation (Fig. 1). The estimated risk of liver toxicity was kept to <5% using the Lyman–Kutcher–Burman normal tissue complication model [10]. Radiation doses to surrounding visceral structures were kept below our routine tolerance doses to avoid toxicity in nonhepatic tissues. The treatment goal in this initial cohort was to

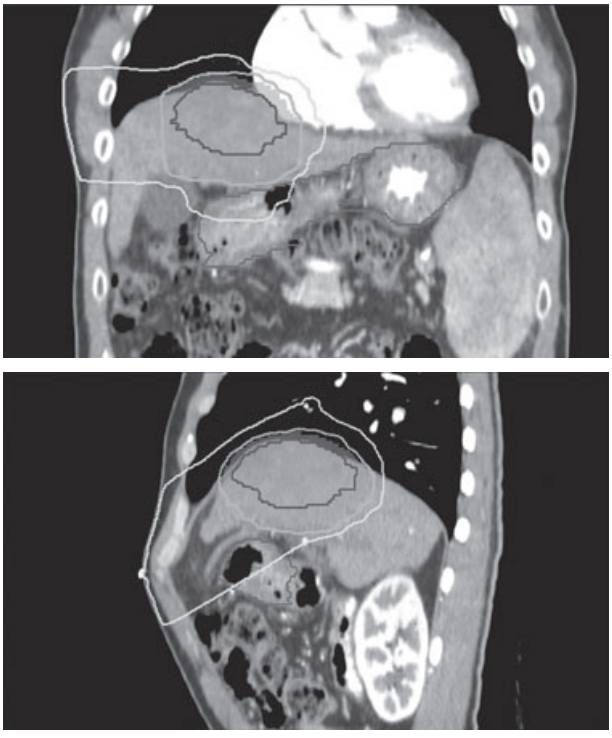

Figure 1 Conformal radiotherapy (CRT) treatment planning diagram with a prescribing a dose of 36 Gy (light blue isodose line) given in six radiation fractions with rapid dose drop off shown by the 20 Gy dose (yellow isodose line). The tumor (red line) is treated with a planning margin (orange colorwash) to incorporate tumor motion from breathing and other geometric uncertainties. The stomach (dark blue line) is excluded from high doses as is the uninvolved normal liver.

stabilize the dominant HCC, reduce the risk of local tumor progression and hence delisting.

A comprehensive database was maintained on all patients listed for LT and undergoing treatment with CRT. Demographic and treatment data were recorded with toxicities and treatment responses collected prospectively. This data was supplemented with review of the charts, on an institutional ethics review board-approved study. All patients were followed with serial measurements of the alpha fetoprotein (α-fp), liver function tests and triple phase CT scans (or MRI) [11] of the chest and abdomen at 3-month intervals after CRT. The response to therapy was determined by the change in size and enhancement of follow-up imaging, the degree of necrosis and was classified according to the Response evaluation criteria in solid tumors (RECIST) [12]. Serum determinations of α-fp were also examined pre- and post-CRT to assess response to therapy.

Serial biochemical determinations of liver function and model for end-stage liver disease (MELD) scores were obtained to assess the impact of CRT on liver disease progression. Transplantation data were collected and once transplanted perioperative morbidity and mortality data were recorded to assess the impact of CRT on the course of transplant.

The explants were sectioned at 1-cm intervals to detect all tumors present. The HCC targeted by CRT was examined in detail by sampling a full-face section of the tumor including surrounding nontumorous liver. Paraffin-embedded, formalin-fixed sections were stained with hematoxylin and eosin for microscopic evaluation of tumor morphology, and with Elastic Trichrome for evaluation of vascular invasion, peritumoral parenchymal changes. Necrosis of the target lesion was evaluated at microscopy and estimated as a percentage of the full-face section of the tumor. The criteria for estimation of pathologic response, i.e. tumor necrosis, were established for the purpose of this study as follows: complete pathologic response: 100% tumor necrosis and absence of any viable-appearing tumor tissue, significant pathologic response: 50–99% tumor necrosis in cross section, mild pathologic response: 1–49% tumor necrosis in cross section, no pathologic response: no tumor necrosis present. Veltri *et al.* [13] defined complete necrosis as 90% necrosis. However, we chose to have a category of complete necrosis as 100% necrosis to be stringent with our evaluation. Pathologic examination was performed by two hepatopathologists.

The data were analysed using STATA v8.0 (Stata Corp., College Station, TX, USA), to perform nonparametric measures of association using the Mann–Whitney *U*- and Wilcoxon signed-rank tests to determine differences between independent and paired samples with continuous data. A *P*-value of <0.05 was considered significant.

Results

Conformal radiotherapy was used as a bridge to transplantation in 10 patients between July 2006 and August 2008. Of these seven out of 10 (70%) were male subjects. The median age of patients was 55 years old (range 36–64). In seven out of 10 (70%) patients, the underlying liver disease was hepatitis C virus; in the other three, it was caused by hepatitis B virus, alcohol, and Alagille's syndrome. The median pretreatment medical MELD score was 8.5 (range 2–16). The Child-Pugh scores are included in Table 1.

Five out of 10 (50%) patients had received failed treatment with either RFA or TACE prior to consideration of CRT (Table 1). Five out of 10 (50%) were deemed unsuitable for either RFA or TACE, and hence CRT was the primary treatment modality prior to LT in these patients. Eight out of 10 tumors were outside the Milan criteria [9]. There were no patients with macrovascular invasion on preoperative imaging; however, there was one patient who had tumor invasion into a necrotic left hepatic duct following a failed RFA treatment.

All patients tolerated the CRT well. There was no dose-limiting toxicity and nine out of 10 (90%) completed the full treatment of CRT with one patient being transplanted after a single 8.5 Gy fraction (of a planned course of 6 fractions). The median diameter of the largest tumor was 62 mm (range 25–108), with the median number treated being two (range 1–3). The median dose of CRT was 33 Gy (range 8.5–54) in five or six fractions, with a median treatment volume of 79 cc (range 15–798 cc). The median volume of residual normal liver was 1348 cc (range 614–2009 cc), with the median dose of RT to the liver volume (minus the combined HCC volume) being 15.5 Gy (range 1.8–17 Gy). Table 2 summarizes the CRT dosimetric data.

Grade 1 toxicity was reported in three patients who complained of nausea. One patient experienced a reduction in the platelet count from 154 to 98. There were no other reported toxicities and there were no significant changes in the pre-and post-treatment biochemistry. The liver enzymes and synthetic function of the liver did not deteriorate with treatment. There was no significant change in bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, platelets or INR. The median post-CRT medical MELD was 8 (range 1–20) which was not significantly different from that before treatment ($P = 0.92$).

The median α-fp prior to CRT was 89 (8–1111). There was a significant ($P = 0.039$) reduction in α-fp following CRT with a median of 23 (5–336). Seven patients had a partial radiological response following CRT (Fig. 2), two patients had stable disease in the treated field and one

Table 1. Patient characterstics.

Patient	Age	Child-Pugh score	MELD	Max. tumor diameter (mm)	Number	Initial α-fp IU/ml	Previous treatment	Reasons not suitable for conventional treatment	Histological grade (WHO)	Microvascular invasion	Tumor necrosis (%)
1	62	B-7	5	60	2	1111	No	Unsuitable for TACE because of thrombocytopenia and shunting	–	–	–
2	54	B-7	15	62	1	1	No	Unsuitable for TACE because of thrombocytopenia and CRF	–	–	–
3	63	A-5	3	38	1	125	TACE	Failed multiple TACE treatments	Moderate	No	90
4	64	C-10	7	48	3	132	TACE	Failed multiple TACE treatments	–	–	–
5	36	A-5	10	108	>10	11	No	Complete occlusion of SMA/Celiac artery	Moderate	Yes	40
6	63	B-7	3	25	1	46	RFA	Previous embolization of RHA for bleed following RFA	Moderate	No	60
7	51	B-8	16	65	>10	48	No	Liver dysfunction and multifocal tumor not anatomically suitable for TACE	Moderate	Yes	90
8	56	B-9	13	22	2	491	RFA(2)	Necrosis of biliary tree following RFA	Moderate to poor	Yes	0
9	55	A-5	10	73	1	992	No	Unsuitable for TACE because of thrombocytopenia.	–	–	–
10	55	A-5	2	88	>10	53	TACE (2)	Failed multiple TACE treatments	–	–	–

CRF, chronic renal failure (not requiring dialysis).

patient received a transplant after one fraction of RT and hence radiological response was not assessable. The median reduction in tumor diameter following CRT was 11 mm (range 0–27 mm), which was significant ($P = 0.02$).

There was infield tumor control in all patients treated with CRT. Two patients were removed from the waiting list and died prior to transplantation. In the first patient there was development of new HCC within the untreated segments of liver with progressive deterioration of liver function with death ensuing because of decompensation of liver disease. The second patient developed lung metastasis.

Five patients have undergone LT and three patients are still awaiting transplantation. There have been no adverse events during LT attributable to CRT. The median waiting time between completion of CRT and transplant was 157 days (range 0–372). One patient had arterial reconstruction with an aortic conduit, the others all had standard arterial anastomosis between the donor common hepatic and gastroduodenal artery bifurcation. The venous reconstructions were all performed in a standard fashion with four out of five patients having the inferior vena cava replaced and one out of five patients having a piggy back reconstruction. The portal veins were all anastomosed end-to-end. There were no vascular complica-

Table 2. Treatment characteristics.

Patient	Tumor volume (cc)	Treatment dose	Minimum dose to 0.5 cc tumor	Treatment fractions	Normal liver volume	Liver receiving >10 Gy	Liver receiving >20 Gy	Mean liver dose	Maximum dose to 0.5 cc visceral structures
1	68	45	24.8	6	1467	680	372	14	9.5
2	105	54	52.6	6	1919	707	520	13.9	25.5
3	30	38.4	24.6	6	1638	371	233	7	25.4
4	87	36	34.6	6	2011	1113	767	16.5	25.1
5	798	23	19.6	5	1088	721	592	16.1	23.2
6	15	41.4	42.1	6	895	456	334	15.7	15.7
7	71	45	43	6	2134	1005	749	15.5	17.8
8	15	8.5	8.65	1	1368	521	279	1.8	27.1
9	121	36	33.9	6	928	445	369	15.5	9
10	472	30	31.5	6	1106	707	437	17	23.7

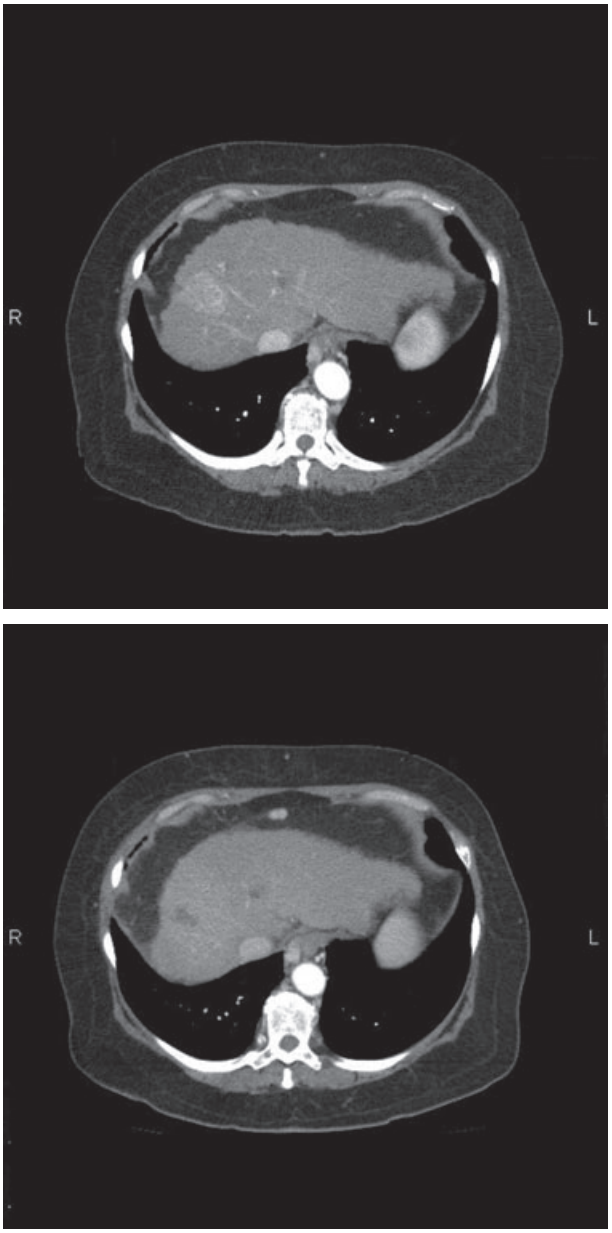

Figure 2 CT showing radiological response, with a zone of necrosis and no uptake of contrast on arterial phase.

tions in the transplanted group. There were no patients who had perioperative graft dysfunction or prolonged hospitalization. There was no correlation between dose of RT and the peak liver enzymes post-transplant.

The median follow-up in all patients is 8 months (range 2–26), and in patients who underwent liver transplant the median follow-up is 6 months (range 3–21). There were no recurrences of tumor following transplantation. The recurrence-free survival of all patients treated with CRT was 70%. To date, there has been no reported CRT-related toxicity to surrounding organs in any of the treated patients.

Explant pathology was available for all patients who underwent transplantation. The results are summarized in Table 1. All patients who received the full course of CRT had a demonstrable pathological response with the degree of necrosis (Figs 4 and 5) ranging from 40% to 90%. The patients who had TACE prior to RT had the greatest degree of fibrosis within the tumor, with almost complete necrosis of the residual HCC. One patient received only 8.5 Gy in a single fraction and the explant pathology, obtained 1 day after CRT did not show any evidence of necrosis. All the tumors were surrounded by a dense fibrous wall, with occasional arteries showing features consistent with endarteritis obliterans related to the CRT. The untreated liver was relatively spared, not showing any features consistent with RT exposure.

Discussion

The treatment for patients with HCC who are awaiting LT is still in evolution. Our initial experience suggests that CRT is a safe and effective alternative to PEI, RFA and TACE. Historically, there have been technical challenges with the planning and delivery of CRT in a controlled fashion to tumors of the liver, with difficulties localizing tumors whilst accounting for movement and breathing. Coupled with this, there have been challenges delivering a tumoricidal dose of radiation whilst avoiding toxicity to the surrounding structures and minimizing the whole liver radiation dose. Over the past 15 years many of the technical challenges with RT delivery have been overcome with improvements and introduction of new technologies [14–16]. Worldwide, there had been a resurgence in the use of CRT in the treatment of both primary and secondary liver tumors in patients who have failed or are unsuitable for conventional therapy. CRT offers an attractive alternative because it is efficacious for tumors of all sizes and unusual distributions, including tumors unsuitable for RFA and TACE where the therapy is limited by the size of the tumor, its location, the underlying liver disease severity and associated vascular abnormalities. CRT is also convenient for the patient, being noninvasive and of short duration, with treatments typically lasting 15–20 min over 5 or 6 days depending on the dosing regimen.

There have been several reports on the safety and efficacy of CRT used alone or in combination in the palliative treatment of patients with HCC [6,7,17–20] with complete radiological response seen in 3–80% of patients, and a partial response seen in 12–44%. In these series the radiation therapy was well tolerated with grade 3 or 4 toxicities reported in up to 30%, with the majority of

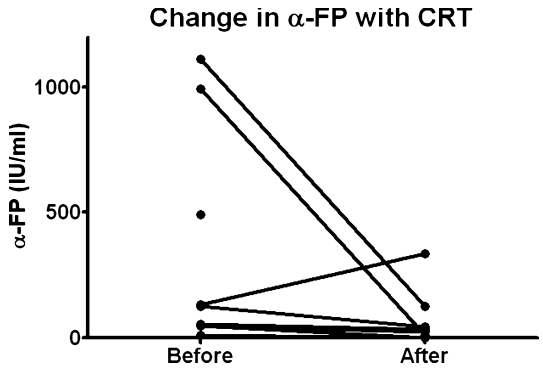

Figure 3 α-fp response to CRT in individual patients.

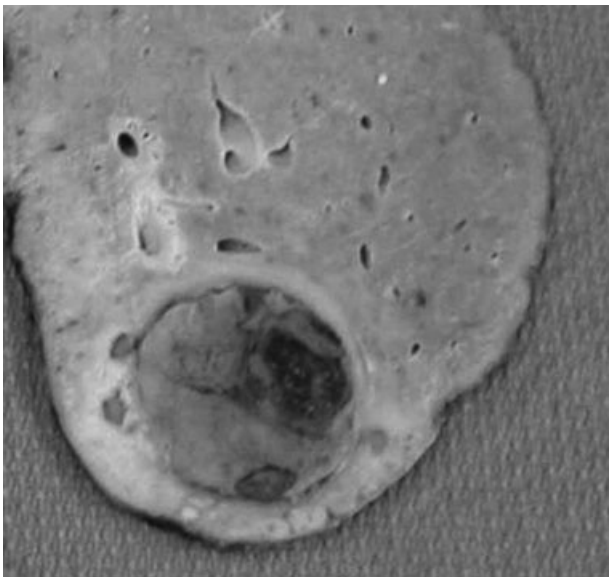

Figure 4 Explanted liver showing a radiation site with almost complete tumor necrosis in a patient with no other therapy prior to radiation.

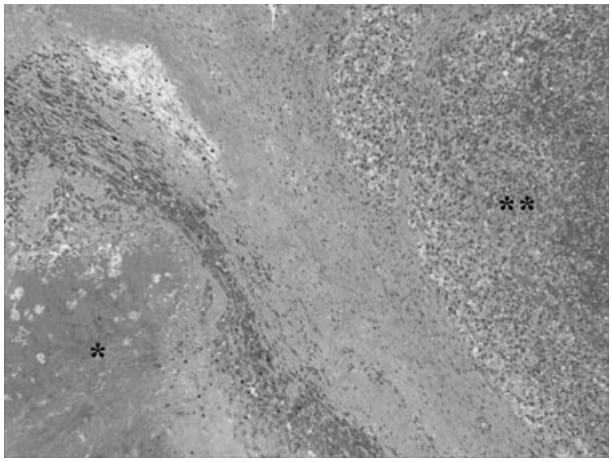

Figure 5 Microscopy of treated tumor in Fig. 4. *Necrotic tumor. **Marks residual viable-appearing HCC.

patients being asymptomatic. To date, there have not been any published series focusing on the use of CRT as a bridge to LT and as a result, there is no directly comparable group of patients. Proton radiotherapy has been used successfully as a bridge to transplant in selected centers [17].

The complication and toxicity profile in our group of patients compares favorably with that reported in relation to TACE and RFA, which are frequently complicated by moderate-to-severe abdominal pain and significant liver dysfunction. Only three patients complained of Grade 1 nausea. Complications have reported with greater frequency with similar treatment regimens used in a palliative setting. When CRT is used in a palliative setting, grade 1 and 2 toxicities have been reported to occur in up to 30% with grade 3 and 4 toxicities occurring in up to 41% of patients [6,7,18]. There have also been treatment-related deaths in these series, which we have not experienced in this cohort. The risk of radiation-related toxicity is increased, and less well understood, in patients with impaired liver function (worse Child-Pugh or MELD scores). The reasons for the lower rates of toxicity in this series probably relates to the individualized lower doses delivered, a highly preserved liver volume and appropriate patient selection. Also, because of the small numbers the true complication and toxicity rates may be underestimated.

In our cohort there were no patients who achieved a complete radiological response, which is lower than that reported in the literature. In comparison to patients treated with CRT in a palliative setting with the highest complete radiological responses (80%) where the doses were taken to 66 Gy [6] in 2 Gy fractions, our patients received lower median(33 Gy) radiation dose in 4.6–9 Gy fractions. Also larger tumors were treated in this study, as a result of the expanded criteria LT program in Toronto, with 80% of tumors in our cohort being beyond the Milan criteria (>3 tumors or maximal diameter of single tumor >50 mm) compared with one tumor <50 mm or two tumors <30 mm in diameter. RT dosages were lower than those used in non-LT patients with Childs A cirrhosis in order to minimize the risk of liver toxicity. The liver volume spared from RT (< 10 Gy) was kept as large as possible, by using CRT beam arrangements that avoided CRT beams that travelled though the spared portions of the liver and by reducing the prescription dose if necessary. This was our first experience treating patients with Child's B or C cirrhosis which has been an exclusion criteria in our phase I or II trials of definitive or palliative

CRT. Furthermore, the treatment intent was to stabilize the HCC and reduce the risk of delisting with the goal that LT would be definitive treatment for the HCC.

Half of out cohort had received at least one previous treatment with RFA or TACE, in some patients these treatment were multiple with CRT considered when there was no demonstrable tumor response on follow-up imaging. The other half were unsuitable for conventional treatment because of tumor position, liver dysfunction or tumor size and number. All patients in our cohort had in field control of the treated lesions and in seven out of 10, there was a reduction in size on serial imaging. CRT-achieved response and control in this group of patients with large, multifocal tumors who were unsuitable or had failed to respond to conventional therapy.

It has been reported that and increase in α-fp prior to transplantation is associated with a higher rate of tumor recurrence following transplantation [21], in our series a significant reduction in α-fp was seen following CRT. Figure 3 shows the change in α-fp following CRT. Of the two patients with tumor progression who subsequently were delisted and died, one had an increase in their α-fp following treatment (this was the patient with liver progression outside the treated field) from 132 to 326 IU/ml. All other patients experienced a decrease in their α-fp following CRT ranging from 8 to 986 IU/ml, this reduction approached but did not reach (statistical) significance. To date, there has been control of all tumors and no recurrence in all those transplanted, and of the three who are still listed awaiting transplantation none have had tumor progression in the treated field.

Conformal radiotherapy was well tolerated in this group and there have been no adverse consequences attributable to the treatment during or after LT. This is similar to what has been seen in patients treated with proton beam RT for HCC who have subsequently gone on to liver transplantation [17].

The explants in all patients have shown that when RT was completed the degree of tumor necrosis ranged between 40% and 90%. At the same time, there was relative sparing of the surrounding parenchyma. Figures 4 and 5 demonstrate the macroscopic and microscopic response to CRT with almost complete necrosis and fibrosis of the treated tumor. We have found that the degree of necrosis and fibrosis was greatest when the patients had undergone TACE prior to CRT suggesting a synergistic effect. The pathological findings in the explant correlated with the reductions in size of tumor and arterial enhancement seen on preoperative imaging.

In patients with HCC awaiting transplantation the dropout rate varies depending on the size of tumors and the method of organ allocation. It has been reported that drop off the liver transplant waiting list varies between 25–38.7% at 12 months [22–24] for tumors within the Milan criteria. Our cohort has been followed for a median of 8 months and two out of 10 patients have progressed outside the treated field and been taken off the transplant waiting list, the others have been transplanted or are waiting with well controlled disease. This cohort represents a group of patients with larger and potentially more aggressive tumors and despite this, we have only seen a 20% drop off rate during our follow-up period.

Conclusion

In this pilot study, CRT was seen to be a well tolerated, and safe method for local control of HCC prior to liver transplant in the face of previous treatment failure or in the absence of other suitable treatment. CRT did not make transplantation more difficult, nor did it have an adverse effect on the outcome following transplantation. This initial positive experience suggests that further studies of CRT prior to LT are warranted to determine its role relative to PEI, RFA and TACE as bridging therapy.

Authorship

CS, LD, ML, PG and DG: Involved in study design, writing of manuscript, collection of data and revision of manuscript. MG and SF: reviewed all pathological specimens and wrote parts of the manuscipt and were involved in revision. AG, MC, IM, GL and ER: reviewed the study design and reviewed the manuscript providing substantive revisions.

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