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RESEARCH ARTICLE

Outcomes of Palliative RT to Liver in Liver Metastases

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Abstract

Introduction: Various techniques are available to treat and alleviate pain and other symptoms in liver metastasis (LM) or advanced hepatocellular carcinoma (HCC) patients. One of such technique is the external beam radiotherapy to whole liver. This study aimed to evaluate the feasibility, efficacy, tolerability and patient's reaction to external beam radiotherapy (EBRT) in palliation of symptoms and quality of life (QoL) LM patients or HCC patients. **Material and Method:** A total of 50 patient of either liver metastasis or HCC were included and planned on single 8Gy/fraction to whole liver radiotherapy. Ultrasonographic guided marking of liver was done prior to treatment and pretreatment dexamethasone and antiemetic was given. Evaluation was done at 1 week and 1 month after the end of treatment. **Results:** After the whole liver radiotherapy, significant improvement was reported in the bilirubin level (68%), pain level (75.5%), and nausea (32%). Talking about the quality of life, the radiotherapy was reported to found potentially effective in enhancing the quality of life among the patients. Greatest percentage improvementwas reported for pain (75.6%), Global health status (39.6%), physical functioning (32.4%), rolefunctioning (36%), social functioning (36%) and appetite loss (30.6%).

Keywords: Liver metastasis- Hepatocellular carcinoma- Radiotherapy- Palliation

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Introduction

Cancer refers to the disease with abnormal and uncontrolled growth of cells. There can be several reasons for the cancer which includes multiple changes in the gene expression that lead to dysregulated balance of proliferation of the body cells. This ultimately led to the increase in the cell's population invading the tissues and metastasizing to the distant sites. This is leading to the causing significant morbidityand might lead to significant mortality rate in case of absence of treatment [1].

According to Globocan 2018, the lung cancer was reported to be the most common diagnosed cancer which was approximately found in 11.6% of the total cases and is the reason for significant deaths due to cancer which is around 18.4% of the overall cancer deaths. This data is closely persuaded by the breast cancer in females (11.6%), cancer in prostate (7.1%), and colon- rectal cancer (6.1%) for incidences and, the mortality case because of cancer includes colon- rectal cancer (9.2%), cancer in stomach (8.2%), and liver cancer (8.2%), in both sexes. It has been reported that the incidences rate and the mortality rate because of liver cancer is two to three times higher in men in most of the regions in the world. This is why the liver cancer is positioned at fifth rank in terms of global incidences cases while it is ranked second in terms of mortality rates in males [2].

The liver is reported to be the most probable sites of metastases. Frequent causes of liver metastases (LM) are lung cancer, breast cancer, and gastrointestinal cancers and for some patients the liver may be the only site of secondaries [3]. Hepatocellular carcinoma (HCC), which comprises around 75%-85% while intrahepatic cholangiocarcinoma is around 10%-15% of total primary liver malignancies cases [2]. HCC is generally diagnosed at an advanced stage. Common symptoms of pain, anorexia, fatigue and vomiting are seen in HCC as well as in liver secondaries [4].

The severe symptoms have been reported in most of the cases in the liver cancer patients as they become refractory to medical therapy which is available in the system for some period prior to their death. Management of the hepatic pain and other associated symptoms is quite challenging. The most common prescribed drug for

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relieving the pain in the cancer patient includes the opioid. However, in the liver cancer patient with impaired function of liver, the opioid drug and its metabolite get accumulated and precipitated which lead to encephalopathy and excessive sedation in the patient. Thus, there is utmost need for the better strategy in order for palliating the pain as well as discomfort in the patients suffering from liver metastasis and the HCC [5].

Generally systemic therapy is employed in patients suffering from LM and HCC along with the curative resection, transarterial chemo-embolization (TACE), or best supportive care (BSC). For the unresectable liver metastasis cases, the standard of care includes the chemotherapy. Several new techniques and methods for non surgical ablation has been innovated and emerged for the liver malignancies that includes radio frequency ablation (RFA), cryotherapy, chemoembolization, laser hyperthermia, ethanol injection, intra operative brachy therapy(IOBT) as well as stereotactic body radiotherapy (SBRT). These therapies have been used in the LM and HCC patients with varied level of success [4].

The whole liver irradiation in the LM and HCC patient has been found to be beneficial for the palliative care with symptomatic disease. There is limited research regarding whole liver palliative radiotherapy in LM and HCC.

For analyzing the feasibility, efficacy, tolerability and patient's reaction to external beam radiotherapy (EBRT) in palliation of symptoms and QoL in patients with liver metastases (LM) or hepatocellular carcinoma (HCC).

Materials and Methods

The study area

Acharya Tulsi Regional Cancer Treatment And Research Institute, Sardar Patel Medical College and associated group of hospitals, Bikaner.

The study population

A total of fifty patients of histological proven liver metastases and HCC are undertaken for the study.LM from various primary sitesare taken in our study. Cancer gall bladder, lung and breast are reported to be the most common primary (14% each) for LM patients while 12% are of HCC. Table 1 is showing demographic distribution of patients taken in our study according to the site of primary, age,sex, and KPS scoring. Majority of patients are of 60-65 age.

Inclusion criteria:

• Symptomatic cases of LM or HCC, where the tumor is found to be unsuitable for resection, radiofrequency ablation, transplantation, systemic therapy (patients already taken multiple cycles of chemotherapy), conformal RT, or SBRT.

• Patients refusing for chemotherapy due to co-morbid medical conditions.

• 60 or more than 60 KPS performance. Expected survival for > 3 months.

• Platelet count > 25000/mm^3

• Hemoglobin > 8 gm%

• International normalized ratio < 3

• Bilirubin < 100 µmol/L

• AST and ALT < 10xnormal

Exclusion criteria:

• Patients who have previously received the radiotherapy (RT) or the selective internal radiation therapy (SIRT) to the abdomen.

• In the case when the patient has received targeted therapy or the systemic therapy within 2 weeks prior to the radiotherapy.

• In the case when the patient received TACE within 4 weeks prior RT.

• In the case when child pugh score of the patient is ≥ C.

• Patients with severe active co-morbidities for example congestive heart failure, or unstable angina within 6 months.

• CNS metastases.

Pre-treatment Evaluations:

• General physical examination and complete history of the patient with clinical performance status assessment of the patient. Complete history of presenting complaints, habits, past history and family history will be recorded.

• General physical condition, nutritional status, and anemia will be evaluated. Clinical examination to analyze the ascites. Systemic examination for excluding any evidence associated with distant metastasis will be done.

• Systemic examination of respiratory, cardiovascular, gastro intestinal and nervous system.

• Detailed local examination of primary or secondary site is performed. Examination of the abdomen for liver size, any tumor masses, any tenderness, and abdominal bruits will be done. All patientsare staged according to the American Joint Committee on Cancer (AJCC) staging, 2018 staging.

Laboratory Studies:

• Complete blood count (CBC)

• PT-INR

• Liver function test (LFT) and Renal function test (RFT)

• Viral markers- HBsAg, HCV, HIV

• Alfa-fetoprotein (AFP)

Imaging Studies:

• Ultrasonography abdomen or

• CT/MRI of whole abdomen and pelvis

Pre-treatment medication-

All patients are provided with 1 mg of oral granisetron and 2 mg of oral dexamethasone for around 1 hour before the RT.

Treatment planning and contouring:

2-D radiotherapy planning and marking performed with the help of ultrasonography. The prescription dose is 8Gy inonefraction. The dose of 8Gy in a single fraction with anterior-posterior opposed or oblique pair beams is given.

Results

50 patients are undertaken out of which 44 had liver metastatic and 6 had hepatocellular carcinoma. Among metastatic cases 7 were of carcinoma breast, 6 of Ca colon, 7 of Ca gall bladder, 7 of Ca lung, 6 of Ca oesophagus, 6

Table 1. Demographic Characteristics of Patients

Type of primary	No. of patients (n=50)	Percentage (%)
Ca Breast	7	14
Ca Colon	6	12
Ca Gall bladder	7	14
Ca Lung	7	14
Ca Esophagus	6	12
Ca Ovary	6	12
Ca Urinary bladder	5	10
Hepatocellular Carcinoma	6	12
Age group (in Years)		
<45	7	14
46-50	9	18
51-55	7	14
56-60	8	16
61-65	10	20
>65	9	18
Gender		
Male	24	48
Female	26	52
Karnofsky score		
60	15	30
70	16	32
80	10	20
90	9	18

Table 2. Improvement Status in Bilirubin Levels after 1 Week and 1 Month

Bilirubin	At 1 week		1 month	
	No. of patients	Percentage	No. of patients	Percentage
Improved	34	68	25	55.50
Stable	11	22	16	35.50
Progressed	5	10	4	8.80
Total	50	100	45	100

of Ca ovary and 5 of Ca urinary bladder (Table 1). Median age in the study was 56 years. Age group 61-65 had the highest number of patients (20%) followed by age group >65 year (18%) and 46-50 years (18%).

Majority of patients were with karnofsky score of 70; n= 16 (32%) and 60; n= 15 (30%) (Table 1). Patients enrolled in the proposed study are first evaluated about their liver function test especially total bilirubin level prior to treatment. The next evaluation performed on 1 week after and 1 month after treatment. Similar evaluation is performed for measuring the pain and nausea before treatment, one week after treatment, and 1 month after treatment.

The main observation in this study is regarding the improvement in the quality of life in terms of improvement in pain, nausea, and many more factors including the Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning, Fatigueness, Dyspnoea, Insomnia, Appetite loss, Constipation, and Diarrhoea.

At the end of 1 week, 38% cases had bilirubin level less than 30 micromol/litre compared to 10% prior to treatment. Cases with bilirubin level more than 70 micromol/litre were 30% prior to treatment compared to 16% after 1 week of radiotherapy. On analysis nearly 68% cases had improved bilirubin level (difference was >10 micro mol/litre on decreasing side), 22% had stable levels (difference less than 10 micro mol/ litre) and 10% progressed (difference more than 10 micro mol/ litre on increasing side) compared to baseline levels (Table 2).

At the end of 1 month, 45 patients were alive. Among them 31.1% cases had bilirubin level less than 30 micromol/litre compared to 10% prior to treatment. Cases with bilirubin level more than 70 micromol/litre were 30% prior to treatment compared to 11% after 1 month of radiotherapy (Table 2). On analysis nearly 55% cases had improved levels, 35.5%% were stable and 8.8% progressed (Table 2).

Table 3. Improvement Status of Pain after 1 Week and 1 Month

Pain	After 1 week		After 1 month	
	No. of patients	Percentage	No. of patients	Percentage
Improved	22	44	34	75.50
Stable	20	40	6	13.30
Progressed	8	16	4	8.80
Total	50	100	45	100

Table 4. Nausea Prior, after 1 Week, after 1 Month of Treatment

	Prior to treatment		1 week		1 month	
Nausea	No. Of patients	Percentage	No. Of patients	Percentage	No. Of patients	Percentage
Yes	31	62	15	30	17	37.70
No	19	38	35	70	28	62.20
Total	50	100	50	100	45	100

None of the patients had pain less than 5 pain grades on baseline, however 12% and 8.8% cases on 1 week and 1 month respectively had pain grade less than 5. Around 24% cases had 5-6 pain scale before treatment compared to 34% and 44.4% on 1 week and 1 month. Pain scale grade 7-8 was seen in 46% cases before, 36% after 1 week and 26.5% in cases 1 month after treatment. Severity 9-10 was seen in 30% cases before, 18% after 1 week and 19.9% in 1 month after treatment.

Pain improvement was seen in 44% cases at week while 40% had stable and pain progressed in 16% cases at 1 week. At the end of 1 month 45 cases were alive, among them improvement was seen in 75.5% of cases, stable in 13.3% cases and pain progressed in 8.8% of cases (Table 3).

Nausea was present in 62% cases before start of management and majority of the patients were on antiemetic. Improvement in nausea was seen in 32% cases just after 1 week of radiotherapy. Improvement was 24.2% at the end of 1 month. Though improvement was significant compared to baseline but reduced when compared to 1 week assessment. 3 Patients had experienced nausea and vomiting severe enough to hospitalise admission6.6% cases after 1 week and 1 month respectively (Table 4).

Study shows significant improvement of quality of life. Greatest percentage improvement was for pain (75.6%), Global health status (39.6%), physical functioning (32.4%), role functioning (36%), social functioning (36%) and appetite loss (30.6%). This difference was statistically significant (p value <0.05). No significant difference was observed for diarrhoea, constipation and emotional functioning. Overall, more than one third of patients had improvement in quality of life (Table 5).

Discussion

My study found the prevalence of cancer as 16% among the peoples above 65 years of age. The survey in 2018 also diagnosed the cancers in people up to 75 years of age. The percentage of cancer among peoples above age of 65 years was found to be 1.6% in males and 0.6%

Table 5.Quality of Life Assessment

EORTC QLQ C30	Mean baseline score	At one month	% of patients with improvement
Physical functioning	54	66	32.40
Role functioning	47	56	36
Emotional functioning	74	79	10.80
Cognitive functioning	70	76	14.40
Social functioning	56	68	36
Fatigue	75	54	23.40
Nausea and vomiting	42	22	25.20
Pain	82	40	75.60
Dyspnoea	68	32	17.60
Insomnia	74	34	24.40
Appetite loss	69	42	30.60
Constipation	40	24	14.40
Diarrhoea	13	6	1.80
Financial problems	52	38	18
Global health status	36	57	39.60

in females.

My present study also reported hepatomegaly and palpable liver in patients with either liver metastasis or HCC. I found that majority of patient had liver span of 12.1-14cm. There was only one patient with liver span larger than 18 cm. I also found that the incidence of liver metastasis was also associated with underlying liver disease. Around 44% of patients in the study had underlying liver disease either it was alcoholic hepatitis, hepatitis B or hepatitis C. Majority (56%) had no underlying disease. There were 11 patients who had alcoholic hepatitis, 6 had hepatitis B and 5 had hepatitis C.

In this present study, I found that radiotherapy is beneficial in LM and HCC patients as a potential palliative therapy in the case of unresectable lesion and offering the relief from the pain of metastasis. Several studies suggests that the palliative RT with doses in the 20-30 Gy range helps in improving the symptoms in around 90% of the patients with impaired liver function and pain. Similar result was revealed byCase et al in 1924 (6)where they reportedthe usefulness of hepatic irradiation in patients with metastatic disease [6]. The result by Phillips et al. 1954 (7) is also in correspondence with my result where they reported 36 patients who were treated to the entire liver with dose levels of 2000 to 3750 rad [7]. My result that represented the effectiveness of irradiation therapy in LM and HCC patients were corresponded by Ingold etal. 1965, MiladaTurek-Maischeideret al 1975, andPrasad B et al 1977 [8-10].

After providing palliative radiotherapy, I found that 63 percent of patients were alive at 3 months (HCC, 59%; LM, 70%), and 26% of patients were alive at 6 months (HCC, 24%; LM, 35%). Patients who had completed the modified Brief Pain Inventory (BPI) and QoL, EORTC QLQ-C30, and FACT-Hep questionnaires at 1 week, 1 month, 3 months, and 6 months after treatment were assessed for response. At 1 month, 48% of patients (HCC, 47%; LM, 50%) had clinically significant improvements in symptoms at its average in the past 24 hours. Improvements in the FACT-G and hepatobiliary subscale were seen in 23% and 29% of patients, respectively, at 1 month. The effectiveness of the palliative radiotherapy was also reported byBydderet al. (2003), Seung-Gu Yeo et al (2010), and Hany Soliman et al (2013) [4, 11, 12].

In this study, I found the RT to be tolerable and minimal toxicity was consistent with the Trans-Tasman Radiation Oncology Group study (also using premedication with an antiemetic and dexamethasone), in which 7% of patients had grade 3 toxicity (one patient with nausea and one patient with diarrhoea). This study of a single fraction of liver RT demonstrated useful palliation to a substantial proportion of patients with pain or abdominal discomfort from liver cancer, with minor toxicity. Similar effective and tolerable result of RT was demonstrated by Wolny-Rokicka Edyta et al (2015) [3].

There is limited research regarding whole- liver palliative radiotherapy in LM and HCC. Hence, the present study was designed to evaluate the feasibility, efficacy, and tolerability of low-dose palliative RT in patients with symptomatic LM or HCC.

In conclusion, in the symptomatic primary or secondary liver cancer's role of palliative radiotherapy is still a question. In this study, we tried to address the same issue and how the whole liver radiotherapy will help in alleviation of the symptoms and make the quality of life better. We included a total of 50 patients with primary and secondary liver cancers and treated with a single fraction of 8 Gy.

Whole liver radiotherapy resulted in improvement in pain in 44% at one week. Delayed improvement is reported with a total of 75% of patients at the end of one month. Improvement is also felt in terms of decreasing analgesic dose and frequency. Bilirubin levels are improved after one week (68%) which faded with time. No major toxicity (Radiation hepatitis) is observed except in 3 patients who experienced grade 3 nausea and vomiting resulted in hospitalisation. Along with pain other symptoms like nausea (51.6%), dyspnoea (62%), loss of appetite (52%), sleep pattern and habit (34%). Based on EORTC QLQ C30, improvement is reported in one third of patients. A total of 90% (45) patients were alive at the end of 4 weeks.

No patient showed severe rise in bilirubin levels, progression of pain, or progression to child Pugh score, rise in SGOT/SGPT or any severe toxicity leading to death. However single arm-based study, short follow up, small sample size is the limitations of this study. A comparative study with larger sample size and longer follow up will help to confirm the results of this study.

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Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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