

RESEARCH ARTICLE

Whole Liver Palliative Radiotherapy for Patients with Massive Liver Metastases

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Abstract

Background: The purpose of this retrospectively study was to examine the effectiveness and tolerability of a radiotherapy technique for the palliation of symptomatic liver metastases. **Materials and Methods:** Twenty-seven patients with liver metastases were enrolled and received targeted whole liver irradiation consisting of mean 1,8 Gy in five to twelve fractions to a total mean dose 17Gy. Symptoms at baseline were hepatic pain (26 patients), lost of weight (6), lack of appetite (2), and night sweats (1). Seventeen patients (63%) had failed previous treatment with chemotherapy and/or high-dose steroids. **Results:** Individual symptom response rates were 100% at 4 weeks. Partial or complete global symptomatic responses were noted in 11 patients (40%) after 2 months. After 3 months, 8 patients (28%) reported loss of pain. The treatment was well tolerated with one patient (3%) experiencing grade 3 toxicity (one vomiting and one diarrhoea). Overall the median survival time was 4.9 months (range 1 - 14 months). One year survival was 39%. **Conclusions:** This is simple and well-tolerated treatment but to achieve good palliation effects we should carefully selected patients whose conventional treatment does not bring good analgesic control.

Keywords: Hepatic metastases - palliative radiotherapy - palliative treatment

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Introduction

The liver is a common site of metastases. Lung, breast and gastrointestinal cancers are frequent cause of liver metastases and for some patients the liver may be the only site of disease. Curative resection of liver metastasis is possible in fewer than 25% of patients and two-thirds of patients receiving liver resections show liver disease recurrence with 2 years (Nordlinger et al., 2002; Krishan et al., 2006; Lochan et al., 2007; Malik et al., 2007). The standard of care in patients with unresectable liver metastases is chemotherapy.

In recent years, several new methods of non-surgical ablation of liver malignancies, such as cryotherapy, radiofrequency ablation, laser hyperthermia, chemoembolization, ethanol injection, intraoperative, brachytherapy and stereotactic body radiotherapy (SBRT) have been proposed with variable success (Cunningham et al., 1978; Chung et al., 2005; Lochan et al., 2007; Tree et al., 2013)

Radiotherapy can either be used as a palliative modality in patients with painful metastases, or it can be employed as a potentially curative therapy for patients with medically or technically unresectable primary or metastatic lesions who have no evidence of extrahepatic disease. In the palliative setting, whole liver irradiation has long been known to be beneficial in patients with

symptomatic disease. With doses in the 20-30 Gy range, up to 90% of patients obtain significant improvement in liver function and pain control (Turek-Maischeider et al., 1975; Prasad et al., 1977; Sherman et al., 1978; Borgelt et al., 1981; Hoyer et al., 2012). However, whole liver irradiation has not been shown to result in improved survival (Russell et al., 1993).

The aim of the work is to assess the tolerance and efficacy of irradiation of the entire liver in patients with liver metastases.

Materials and Methods

Between January 2009 and February 2011 at the Radiotherapy Department in Regional Hospital, Lubuski Center of Oncology in Zielona Gora 27 patients with liver metastases received whole-liver radiotherapy (RT) and were retrospectively analyzed. Inclusion criteria were liver metastases defined in imaging studies and principal symptoms prior to RT which were mild to moderate abdominal pain and voltage perihepatitis resulting from the growing liver metastases. Patient characteristics are shown in Table 1. 11 patients were females and 16 patients were men and the median age was 64 years (range, 39 - 80). Median status performance in Zubrod was 1. Primary tumor sites were the colon in 16 patients, the stomach in 7 patients and the pancreatic in 4 patients,

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respectively. In all cases the tumor had characteristics of adenocarcinoma cases tumor. In most cases the tumor grade was not assessed.

All patients exhibited liver metastases in imaging studies- CT- scan and ultrasonography. The number of metastases more then 5 were in 24 patients and the median diameter were 40mm (range, 10-120mm). 26 patients had hepatic pain (abdominal distension), 6 weight loss, 2 lack of appetite, 1 night sweats.

Surgery was not performed on the liver metastases because multiple organ metastases and chemotherapy alone was given to 17 patients and all received multiple cycles of chemotherapy before RT (median 6 cycles) based on 5FU+LV.

There is no information regarding the number of patients who received the 2nd and 3rd line chemotherapy. Ten patients had not systemic treatment because of medical comorbidities. All the patients had satisfactory results of blood morphology and liver tests. According to our protocol the palliative radiotherapy would apply only in cases when palliative chemotherapy could not carried out or in patients who did not agree to chemotherapy because of medical comorbidities - 10 patients.

Radiotherapy

All patients were placed in supine position with arms above their heads. The points of position from laser system are subcutaneously marked by tattoo. Computered tomography data were transferred to a three-dimensional conformal RT planning system (PROWESS). For each

Table 1. Patient and Clinical Tumour characteristics in 27 patients with liver metastase

| | |
|--------------------------------|---------------|
| Gender | 27 (100%) |
| Male | 16 (59) |
| Female | 11 (41) |
| Age | |
| Median (range) | 64 (39–80) |
| ECOG performance status | |
| 0 | 5 (19) |
| 1 | 19 (70) |
| 2 | 2 (7) |
| 3 | 1 (4) |
| Primary cancer location | |
| Colon | 16 (59) |
| Stomach | 7 (26) |
| Pancreas | 4 (15) |
| Maximum tumour diameter, (mm) | |
| Median (range) | 40 (10 – 120) |
| Number of Metastases | |
| 1-3 | 2 (7) |
| 4-5 | 1 (4) |
| >5 | 24 (89) |
| Histologic diagnosis | |
| Adenocarcinoma | 27 (100) |
| *Presenting symptoms before RT | |
| Hepatic pain (distention) | 26 (96) |
| Losing weigh | 6 (22) |
| Losing appetite | 2 (7) |
| Night sweats | 1 (4) |

*Patients with multiple presenting symptoms; the major symptoms are listed

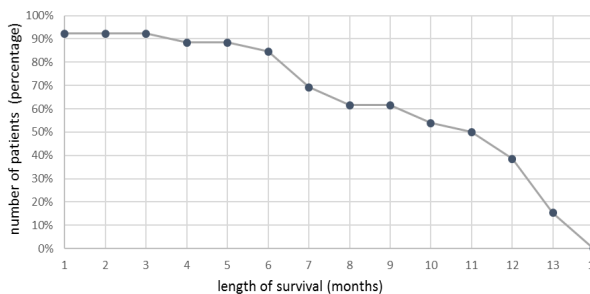


Figure 1. Analysing the survival rate using the Kaplan-Meier survival curve in 27 patients who had undergone palliative radiotherapy of liver metastases

patient clinical target volume including whole liver without of margin to minimize radiation damage to neighboring normal organs. RT was administrated via a linear accelerator that emits X-rays of 15MV. For 21 patients a daily dose 1,8 of Gy per fractions was administrated 5 times per week to total dose of 18 Gy. 6 patients received daily dose from 1,5 to 1,8 Gy per fraction (median 1,6 Gy) to total dose from 9 Gy to 18 Gy (mediana 14 Gy) in five to twelve fractions. Afret irradiation the patients were monitored for 4 weeks. During this time the patients general status was checked as well as biochemical parameters of the liver and pain intensity. For all patients mean daily dose per fraction was 1,8 Gy and mean total dose was 17 Gy in 10 fractions.

Statistical analyses

The overall survival (OS) was calculated from the first day of radiation treatment: The survival curves were constructed using the Kaplan-Meier method. Statistical analyses of categorical variables were performed using the arithmetic mean coefficient of dominance. The relationship between survival and one or more covariates was examined using the Cox proportional-hazards regression model. The risk for early death was estimated using the Hazard Ratio (HR).

Two-sided P values of less than 0.05 were considered significant. All analyses were performed using the programme R 2.11.1 for Windows XP.

Results

After a month from treatment subjectively palliation (pain relief) was achieved in 27 patients (100%). During the subsequent control after 2 months post-irradiation, loss of pain was reported by 11 patients (40%). After 3 months post-irradiation, loss of pain was reported by 8 patents (28%). The only adwers effect of this treatment was nausea in mild-intensity in 9 patients (33%) and diahrrea in 1 patients (3%). Overall, the median survival was short 4,9 months (range 1-14 months) and death was usually due to progression of disease. One year survival was 39%. Non statistically signitificant dependence between the total survival time and the number and diameter of metastases was noted. Morphology parameters before radiotherapy: mean hemoglobin (HGB) - 12,3 g/dl(p=0,73), mean erythrocytes (RBC) - 4,1 106/µl(p=0,47), mean platelet (PLT) - 199 K/µl (p=0,96) and leukocytes (WBC) - 6,7103/

μ l ($p=0.70$) have non statistically significant for survival in multivariate Cox analysis.

Discussion

The survival rates depend on the these factors as: poor tumor differentiation, increasing size and number of metastases, tumor staging, presence of extra-hepatic metastasis, elevated carcino embryonic antigen (CEA) levels and positive nodal status (Chua et al., 2011; Gallinger et al., 2013).

For patients in better clinical condition (without massive metastases) after liver metastasectomy the parameters of survival are quite good (1-, 3- and 5-year rates were 93%, 59% and 39.9%, respectively, and the median survival was 37 months (range 1-163) (Cokmert et al., 2014).

This study is experience with patients which had different primary local disease and different doses fraction. None of our patients exhibited extrahepatic metastases. Previous chemotherapy alone was given to 17 patients Ten patients patients had not systemic treatment because of medical comorbidities and none of our patients did not underwent metastasectomy for liver metastases. You can admit that the group due to age and comorbidities have only possibility hospice care. Patients with supportive care only live 4-10 months from the time of diagnosis of metastases diseases (Bengtsson et al., 1981). However in short time subjectively palliation (pain relief) was achieved in 100% of the patients.

Several studies have investigated the effectiveness of whole liver external-beam irradiation in the management of patients with liver metastases (Turek-Maischeider et al. 1975; Prasad et al., 1977; Sherman et al., 1978; Borgelt et al., 1981).

In an interesting study (Yin et al., 2014) treated 19 colorectal liver metastases patients using whole liver radiotherapy with boost on massive lesion and chemotherapy and 100% patients showed decreased pain, as measured by a reduced need for analgesics (median survival time was 19 months, 1- and 2- year overall survival rates were 78.3% and 14.3%). The mean number of liver lesions treated per patient was 3 (range, 2 to 6) and the maximal diameter of all the lesions was 7 cm (range, 6 to 12 cm).

Most of the patients included in our study had liver metastases from colorectal primaries following chemotherapy and were treated with total doses of 18 Gy at 1.8 Gy fractions. In this group 89% patients had more than 5 tumor metastasis and median of tumor diameter was 40mm. We report short the median survival time - 4.9 months and death was usually due to progression of disease.

The authors, Eble et al. (1993) and Krishnan et al. (2006) presented longer median survival time respectively - 12.6 months and 11 months. Sherman et al. (1978) reported a one-year actuarial survival of 21% and pain relief usually lasting for the duration of the patient's survival.

Although this is small sample size, our patients received on short survival time good analgesic effect.

The adverse side effect of liver irradiation was in 9 patients (33%) - nausea in mild-intensity and diarrhea in 1 patients (3%). Similar reported Krishnan et al. (2006) and Suwinski et al. (2006), who point to a small percentage of side effects during liver radiotherapy. Low-dose WLRT is a useful treatment for symptom palliation in patients with end-stage cancer (Mendez and Hoyer, 2012) and we achieved a painless and effective treatment the patients who have massive liver metastases and the who are burdened with comorbidities.

The conclusion must be drawn carefully from a single-institution experience with a small sample size. Our data suggest that 10 fractions course whole-liver RT can improve symptoms in end-stage cancer patients with massive liver metastases.

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