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Phase I Trial of Dose-Escalated Whole Liver Irradiation with Hepatic Arterial Fluorodeoxyuridine/Leucovorin and Streptozotocin Followed by Fluorodeoxyuridine/Leucovorin and Chemoembolization for Patients with Neuroendocrine Hepatic Metastases

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Abstract

Objectives—We have previously shown that refractory neuroendocrine tumors can respond to moderate doses of chemoradiotherapy. We completed a dose-escalation phase I/II trial combining hepatic arterial (HA) chemotherapy, chemoembolization, and dose-escalated whole liver radiotherapy (WLRT) to determine the maximum safe dose of radiation that could be delivered and to make a preliminary assessment of response.

Methods—From 2002–2009, 19 patients with symptomatic neuroendocrine liver metastases who failed somatostatin analog therapy were enrolled. HA fluorodeoxyuridine, leucovorin, and streptozotocin were delivered, as concurrent WLRT was dose escalated from 24 Gy to 32 Gy in 2 Gy fractions, with a target rate of dose-limiting grade ≥3 radiation-induced liver disease (RILD) of 10%. Eight weeks later, for patients without grade ≥3 liver or grade ≥4 any toxicity, a 72-hour infusion of HA fluorodeoxyuridine and leucovorin was given, followed by transarterial chemoembolization (TACE).

Results—Eleven patients completed the entire protocol and received 24–32 Gy. No patients developed RILD; seven had grade 3–4 transiently increased liver function tests, and four had other grade 4 toxicities. Three patients (14%) had partial response, 16 (84%) stable disease. Median freedom from local progression and overall survival were 35.3 and 54.6 months, respectively.

Conclusions—32 Gy in 2 Gy daily fractions can be delivered safely when combined with HA chemotherapy and subsequent TACE. However, although objective responses were observed, this combination was not significantly better than our prior approaches. Further treatment

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intensification strategies, including individualized dose-escalation for radiation-tolerant livers, and improved radiosensitization should be investigated, along with improved systemic therapy.

Keywords

liver radiotherapy; neuroendocrine tumors; liver metastases; chemoembolization; phase I trial

Introduction

Neuroendocrine tumors (NET) are relatively rare malignant neoplasms whose incidence and prevalence have increased significantly over the past four decades. [1] Hepatic spread occurs in 30–85% of NET, leading to significant abdominal pain and hormonal syndromes. [2] Treatment options for NET metastatic to the liver often include systemic therapy, but more directed therapies can span from treatment of isolated lesions including surgery, ablation, TACE, radioembolization or high-dose radiotherapy; to rarely, treatment of the whole liver with transplantation. [3,4] For all liver-directed therapies, recurrences and progression are frequent, highlighting the need for additional therapeutic options. The hypervascular nature of NET and their dependence upon the hepatic artery (HA), make them attractive for chemoembolization, a process in which blood flow to a tumor is blocked at the same time a chemotherapy agent is delivered. This treatment can produce both clinical and radiographic responses in patients with neuroendocrine unresectable liver metastases. [5,6] Although long considered "radioresistant" tumors, NET respond to moderate doses of RT, with a 39% overall response rate and 90% palliation rate. [7] Previously we have combined low dose (24.2 Gy in 2.2 Gy fractions) whole liver radiotherapy (WLRT) with concurrent hepatic arterial (HA) fluorodeoxyuridine (FUDR)/leucovorin (LV) and subsequent chemoembolization with mitomycin C (MMC), and reported a 75% response rate. [8][8]

We hypothesized that higher doses of radiation could safely be delivered to the whole liver and combined with HA streptozotocin (STZ), a glucosamine-containing antibiotic with activity specifically in NET, [9] followed by chemoembolization. Here we report the results of phase I clinical trial to determine the dose of WLRT that could be delivered to symptomatic patients with extensive hepatic neuroendocrine metastases concomitantly with HA FUDR/LV and STZ followed by additional HA FUDR/LV and subsequent chemoembolization with MMC, and to make a preliminary response estimate for this approach.

Materials and Methods

This study was approved and monitored by the Institutional Review Board of the University of Michigan, and all patients provided written informed consent before enrollment in the study. Eligible patients were adults (≥18 years) with histologic proof of NET and dominant liver metastases, who were symptomatic, and/or had a progressive disease in the liver despite treatment with maximal doses of a somatostatin analog. The liver metastases were deemed not treatable with local therapy such as resection or radiotherapy (either fractionated focal therapy or stereotactic body radiotherapy). Patients were required to have a Karnofsky performance status of ≥80%, expected life expectancy >4 months, and adequate bone

marrow (granulocyte count >2000/mm^3, platelet count >90,000/mm^3), hepatic (serum albumin >2.0 g/dL, total bilirubin <2 mg/dL, international normalized ratio (INR) <1.2), and renal (creatinine <2.0% mg/dL) function. Patients previously treated with chemotherapy or non-hepatic radiation were eligible as long as they had recovered from all toxicity of prior therapy and had terminated chemotherapy at least 4 weeks prior to treatment. Exclusion criteria included cirrhosis, ascites, previous abdominal radiation, bleeding diathesis, severe peripheral arterial disease, portal vein thrombosis, and portal hypertension with hepatofugal flow.

To avoid the confounding element caused by chemotherapy and chemoembolization-induced toxicities, the treatment was divided to two parts (Figure 1). The first part consisted of HA FUDR/LV and STZ along with WLRT with progressive radiation dose escalation. The second part of the treatment, which consisted of HA FUDR/LV and chemoembolization with MMC, was delivered after at least an 8-week break.

Prior to treatment, a Tc99m-MAA HA perfusion scintigram was performed to document adequate liver perfusion without extra-hepatic perfusion. FUDR (3mg/m^2/d) and LV (300mg/m^2/d) were delivered as a 12-day continuous HA infusion by a percutaneously placed catheter. HA STZ (500 mg/m^2) was administered over 3 hours on days 5, 8, and 10. If the lung shunt from the Tc99m-MAA hepatic arterial perfusion scan was ≥25%, the FUDR and LV dose were reduced to 0.75mg/m^2/d and 75 mg/m^2/d, respectively, to account for reduced hepatic extraction of FUDR. Patients received intravenous 1 L 0.9% NaCl solution over 2 hours prior to STZ administration along with antiemetic premedication. STZ was withheld if urine dipstick test for protein was positive, or blood urea nitrogen, creatinine and serum electrolytes were abnormal.

For WLRT that was initiated on the second day of chemotherapy, patients underwent CT-based simulation in an immobilization device, with images obtained at voluntary end-exhale. The target volume encompassed the entire liver including any disease that extended beyond the margin of normal liver. An additional caudal margin was used to account for respiratory motion, the magnitude of which was determined by the cranial-caudal diaphragm motion observed on fluoroscopy. RT was delivered in 2 Gy daily fractions using 15–16 MV photons. If it was necessary to treat >90% of one kidney in excess of 20 Gy in order to encompass the entire liver, then >90% of the contralateral kidney received <18Gy. The prescribed dose of WLRT was planned to be escalated from 24 Gy to 32 Gy in 2-Gy increments using TITE-CRM (detailed below), stopping earlier if the rate of dose-limiting toxicity (DLT), which included grade ≥3 RILD, following the first part of the treatment expected to be ≥10%. While dose-escalation scheme was based on RILD toxicity only, patients who experienced any other grade ≥4 toxicity, excluding transient liver enzymes elevations lasting <2 weeks, and a carcinoid crisis, in 2 months following RT had their treatment stopped. The second part of treatment included FUDR (3mg/m^2/d) and LV (300mg/m^2/d) administered as a 72-h continuous infusion through a newly placed HA catheter. Embolization was then performed using particulate transcatheter polyvinyl alcohol (PVA) (0.5 cc of dry 255–350 μm particles) and MMC (20 mg). All patients were given broad spectrum intravenous antibiotics starting 12 hours prior to chemoembolization and continuing for 36 hours, or until afebrile for 48 hours, whichever was longest.

Patients underwent daily history and physical examinations and laboratory evaluations every other day during the infusional portions of treatment. Additionally, patients underwent history and physical examinations and laboratory evaluations at weeks 2, 4, and 7–8 after the first part of the treatment, at weeks 2, 4 and 8 after the second part of the treatment, and every 6 months thereafter. Abdominal CT or MRI was performed before the treatment, 8 weeks after each part, and every 6 months thereafter. The primary end-points of the trial were the dose of WLRT which, when given with HA chemotherapy had a 10% risk of RILD, and the proportion of patients who having undergone the first part without experiencing RILD, developed grade ≥4 toxicities (other than transient liver enzyme elevation and carcinoid crisis) after chemoembolization. The secondary end-points of the study were objective response rates 2 months after each part of the treatment, freedom from local progression (FFLP) and overall survival (OS). Toxicities of the treatment were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v.3. Complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) were defined according to Response Evaluation Criteria in Solid Tumors (RECIST).

The trial was designed using the time-to-event continual reassessment method (TITE-CRM) that assumes a simple model for the time-to-occurrence of a toxic response as a function of radiation dose, and thereby allows continuous recruitment throughout the trial by accessing information from all subjects enrolled in the trial when allocating a new patient to a higher dose level. [10,11] Initial estimates of the incidence of RILD required for the TITE-CRM algorithm at any dose level were calculated from the Lyman-type model of normal tissue complication probability. [12] According to this, the initial estimates of probabilities of dose-limiting RILD for each dose level of WLRT were 0.01 for 24 Gy, 0.02 for 26 Gy, 0.05 for 28 Gy, 0.1 for 30 Gy, and 0.15 for 32 Gy. When a patient was enrolled, the probability of RILD was estimated for each dose based on the initial estimates and the incidence of toxicity in patients already treated, weighted by the amount of time those patients have been followed. The dose that has toxicity closest to the target rate was selected. Dose escalation was restricted to one level between adjacent patients and could not be escalated unless at least one patient has completed the observation period for DLT at each previously tested radiation dose. The probability that the true rate of DLT exceeds 15% at 32 Gy was calculated from the posterior distribution, thus based on both the prior estimates and the observed data.

The follow-up times for freedom from local progression (FFLP) and OS (overall survival) were calculated from the beginning of the treatment and continued until documented local progression or death, whichever came first. Survival probabilities were estimated using the Kaplan-Meier method.

Results

Nineteen patients with symptomatic hepatic neuroendocrine metastases resistant to somatostatin analog therapy were enrolled between 2002 and 2009 (Table 1). While the majority of tumors (13 patients) were secretory, only 7 patients had clinically apparent reversible endocrine syndromes: 4 -carcinoid syndrome, 2 - Cushing syndrome, and 1 - hypoglycemia. The majority (13 patients, 68%) had of abdominal pain at the beginning of the trial. Eight patients were allocated to 24 Gy, 2 – to 26 Gy, 1 – to 28 Gy, 2 – to 30 Gy, and

6 to 32 Gy of WLRT. 16 patients completed the first part of treatment as planned; 2 - completed the first part with interruptions due to episodes of carcinoid crisis that required breaks for supportive care. One of the first patients allocated to 24 Gy-dose level developed acute renal failure and thrombocytopenia (both grade 4) after 14 Gy of WLRT, both attributed to systemic effects of STZ; In 5 patients, streptozotocin was dose reduced secondary to treatment related adverse events including fatigue, renal dysfunction, and nausea and emesis. Thirteen patients received the full treatment dose of STZ, 5 – reduced, and 1- none. The majority of moderate to severe adverse events that occurred during and immediately after the first part of the treatment were lymphopenia and temporary rise in liver function tests (all cases except one). No patient developed dose-limiting RILD at any dose level. Two patients had carcinoid crisis, requiring intensive therapy, and cardiopulmonary resuscitation in one case. The last case, which was possibly precipitated by angiography, was accompanied by a grade 4 increase in liver transaminases and grade 3 hyperglycemia. One patient had grade 4 diarrhea and leucopenia accompanied by grade 3 hypoalbuminemia, potentially due to systemic effects of FUDR.

Eight patients did not complete the TACE part of the treatment. For three patients (16%), treatment was stopped intentionally before chemoembolization because of non-hepatic treatment related grade 4 toxicities (renal failure, diarrhea) and grade 4 liver transaminases elevation, which was observed during and attributed to angiography procedure. Three patients discontinued their treatment because of exacerbation of existing medical conditions (none more than grade III) and deterioration of the performance status. A hepatic artery catheter could not be appropriately placed in one patient, and one patient refused.

Ultimately, 11 patients proceeded to chemoembolization. The second part of the treatment was well tolerated, with 1 episode of grade 4 carcinoid crises and frequent hepatic pain and fever (all except 2 cases were grade 1–2) which were managed successfully with antibiotics and pain medications. The probabilities of DLT were below the target rate for all doses of WLRT (Table 2). The probability that the true rate of DLT exceeds 15% at 32 Gy is 11%.

Response and survival

Radiographic response rates were obtained 8 weeks after the completion of each part of treatment (Figure 2). There were no CRs; 3 patients had PR (16%) and 16 (84%) patients had SD after the first part of the treatment. All 11 patients who proceeded to chemoembolization had SD after the second part of the treatment. Symptomatic relief after the completion of the protocol was reported by 16 patients (84%). Median FFLP for all patients was 35.3 months (95% CI: 9.3–58.9 months) (Figure 3). Seven patients died of their disease during the study period, 3 patients died of causes unrelated to treatment (1 - intracerebral hemorrhage, 1 - preexisting medical problems, and 1 - possible case of suicide), and 9 were still alive when the study was closed in July 2009. Median OS for all patients was 54.6 months (95% CI: 17.0–∞ months).

Discussion

This study is a result of our long-standing interest in hepatic irradiation with radiosensitizers for hepatic primary and metastatic tumors. Our previous reports have demonstrated that HA FUDR can be safely combined with hepatic irradiation. [8,13] Realizing the limits of WLRT dose escalation, we added chemoembolization with MMC, which resulted in higher response rates (both complete and partial) among patients with hepatobiliary tumors and non-colorectal liver metastases compared to patients with colorectal cancer (41% vs 12%, p=0.062). [8] Then HA STZ, a chemotherapeutic agent active in NET, was added in patients with metastatic neuroendocrine cancer to augment the antitumor activity of the regimen. Encouraged by responses to low-dose WLRT in patients with NET in the previous study, we conducted this radiation dose escalation study. Our conclusions, based on treatment of 19 symptomatic patients with neuroendocrine hepatic metastases are that 32 Gy in 2 Gy daily fractions of WLRT can be given safely with HA FUDR/LV and STZ, and that HA FUDR and chemoembolization with MMC can be safely delivered afterward. Chemotherapy-related and chemoembolization-related side effects were as expected after a dose reduction of STZ.

In a previous study, we found that previous alkylator chemotherapy increased the risk of RILD, and thus, we cautiously escalated whole liver dose with this new combination of STZ and chemoembolization. There was no RILD in any dose level. Analysis of predictive factors for RILD in this population of patients has revealed that patients with liver metastases are more tolerant to liver radiation than those with primary hepatobiliary malignancies. [12] The more indolent nature of NET, better functional status, and absence of risk factors commonly found in primary hepatobiliary cancers could account for the greater tolerability of liver to radiation-induced damage of this highly selective group of patients.

The 16% PR and 84% SD response rates, 35.3 month median FFLP and 54.6 month median OS observed in the study are difficult to compare to published reports because of differences in design, patients, reported variables, and response evaluation criteria. Earlier reports on chemoembolization, and embolization and chemotherapy in NET cited radiographic regression rates of 60% and 80%, respectively, with progression-free survival that ranged from 35 months for patients with islet cell carcinomas to 49 months for patients with carcinoid tumors. [5,8] A recent report on radiotherapy for local and metastatic pancreatic NET found 13% CR, 26% PR, 56% SD, 4% PD, and 90% symptomatic relief in patients receiving palliative treatment. The overall survival of 55 months in our current study compares favorably with the 24 months in that study, especially since all of our patients had symptomatic and/or progressive disease, although and over half of our patients had carcinoid tumors which generally have a relatively indolent course. A more recent report on HA radioembolization with ^{90}Y-resin microspheres in 42 patients with symptomatic unresectable neuroendocrine liver metastases described response rates similar to ours: 22.5% PR, 75% SD and 2.5% PD. [14] In reality, higher response rates of different therapies for NET have not translated into better survival rates. In fact, recent reports on the beneficial effects of somatostatin long-acting analog [15], everolimus [16] and sunitinib malate [17] on PFS of patients with metastatic NET cited a dismal response rates of 2%, 5% and 9.3%, respectively, while doubling the PFS from 4.6–6 months to 11–14.3 months at the same time. Interestingly,

everolimus, a mammalian target of rapamycin (mTOR) inhibitor, was also demonstrated to increase sensitivity of solid tumors to ionizing radiation, probably by targeting neoplastic vasculature. [18] While never tested formally in the setting in NET, established survival benefits for patients with NET, oral formulation and infrequent serious side effects combined with radiosensitizing properties of everolimus could make this agent a potential candidate for upcoming combined treatment studies. The benefit and safety of either systemic therapy [16,17,19] or liver directed therapeutic approaches, including external beam radiotherapy, radioembolization and their sequencing strategies following the development of treatment resistance to systemic therapy is not clear, and should be a subject of future clinical studies.

Additionally, with no observed RILD, another strategy would be to escalate WLRT dose further or add a boost to dominant areas of disease. TACE has been combined with high dose focal radiotherapy for hepatocellular carcinoma with improved responses, [20,21] and this may also be a promising approach for neuroendocrine metastases. However, with any further dose-escalation, we cannot rely on population-based approaches in which the most sensitive 5–10% of patients determine the maximum dose given to all population for an overall acceptable safety profile. We are developing methods to use pre- and during- blood and imaging tests to identify patients with high individual sensitivity to radiotherapy, who could potentially be harmed by dose-escalation, so that treatment can safely be intensified for other patients. [22,23]

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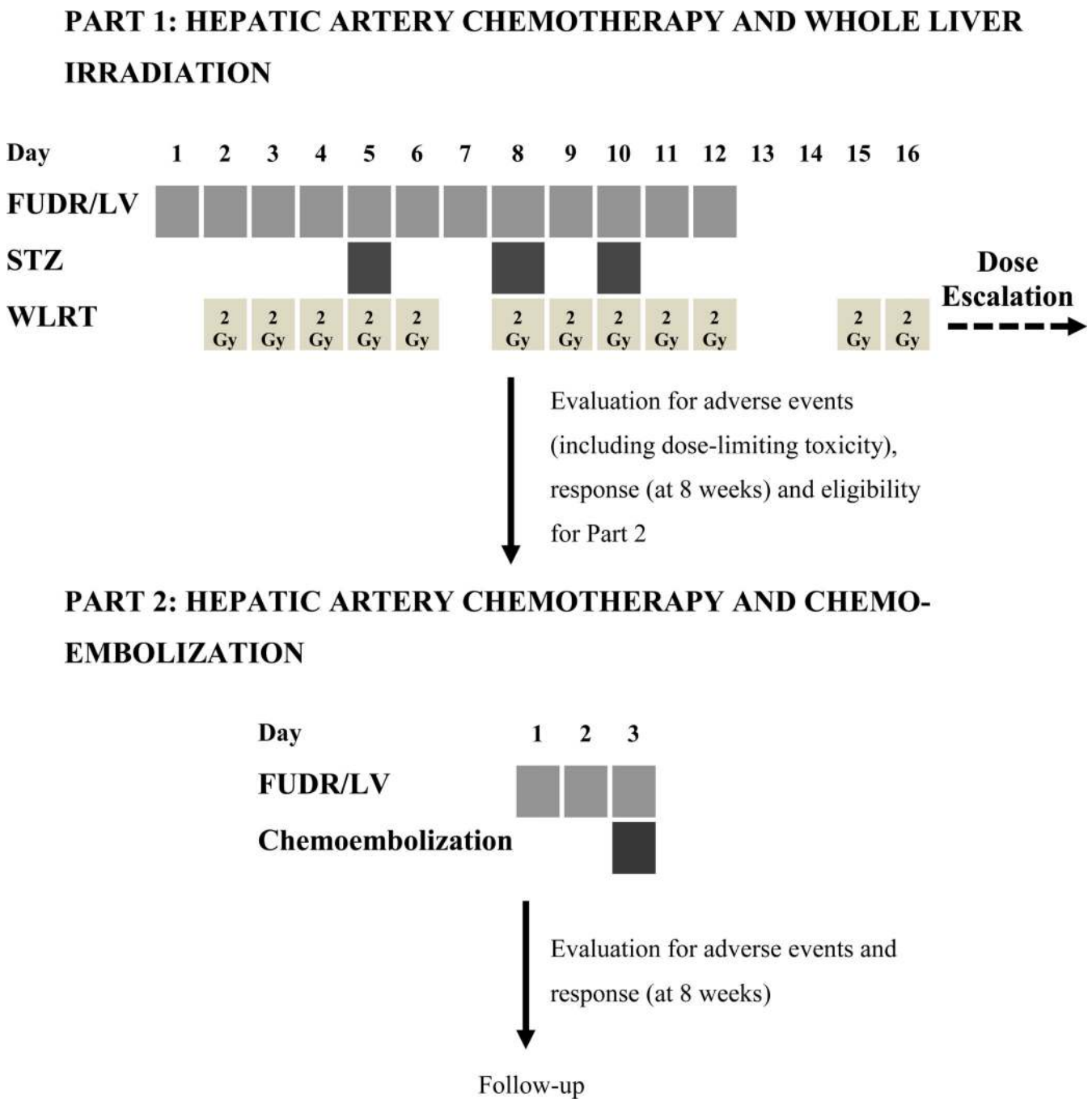

Figure 1.

Treatment scheme. WLRT was delivered daily starting on day 2 (generally Monday-Friday), until the prescribed dose was completed. Patients were allowed to begin mid-week if necessary due to scheduling constraints, and to receive radiation on Saturdays during their treatment. The two parts were at least 8 weeks apart to allow time for detection of RILD. Initial protocol laboratory eligibility criteria were to be met prior to the second part being initiated.

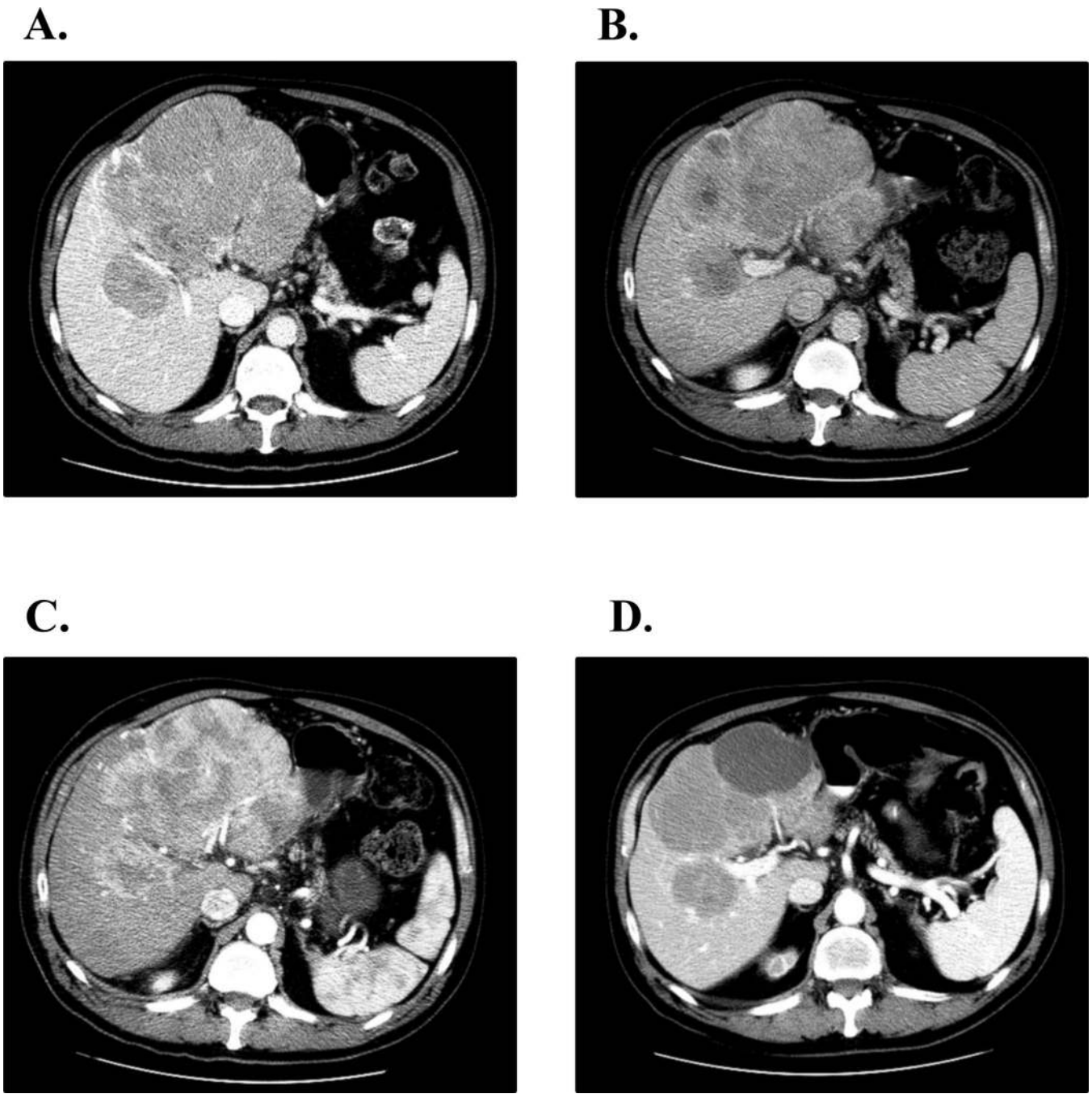

Figure 2.
Response of liver metastases to treatment (WLRT dose of 32 Gy/2 Gy fractions). Computed tomography images before the treatment (A), 2 months after the first part of the treatment (B), 2 months after the second part of the treatment (C), and 24 months after the second part of the treatment.

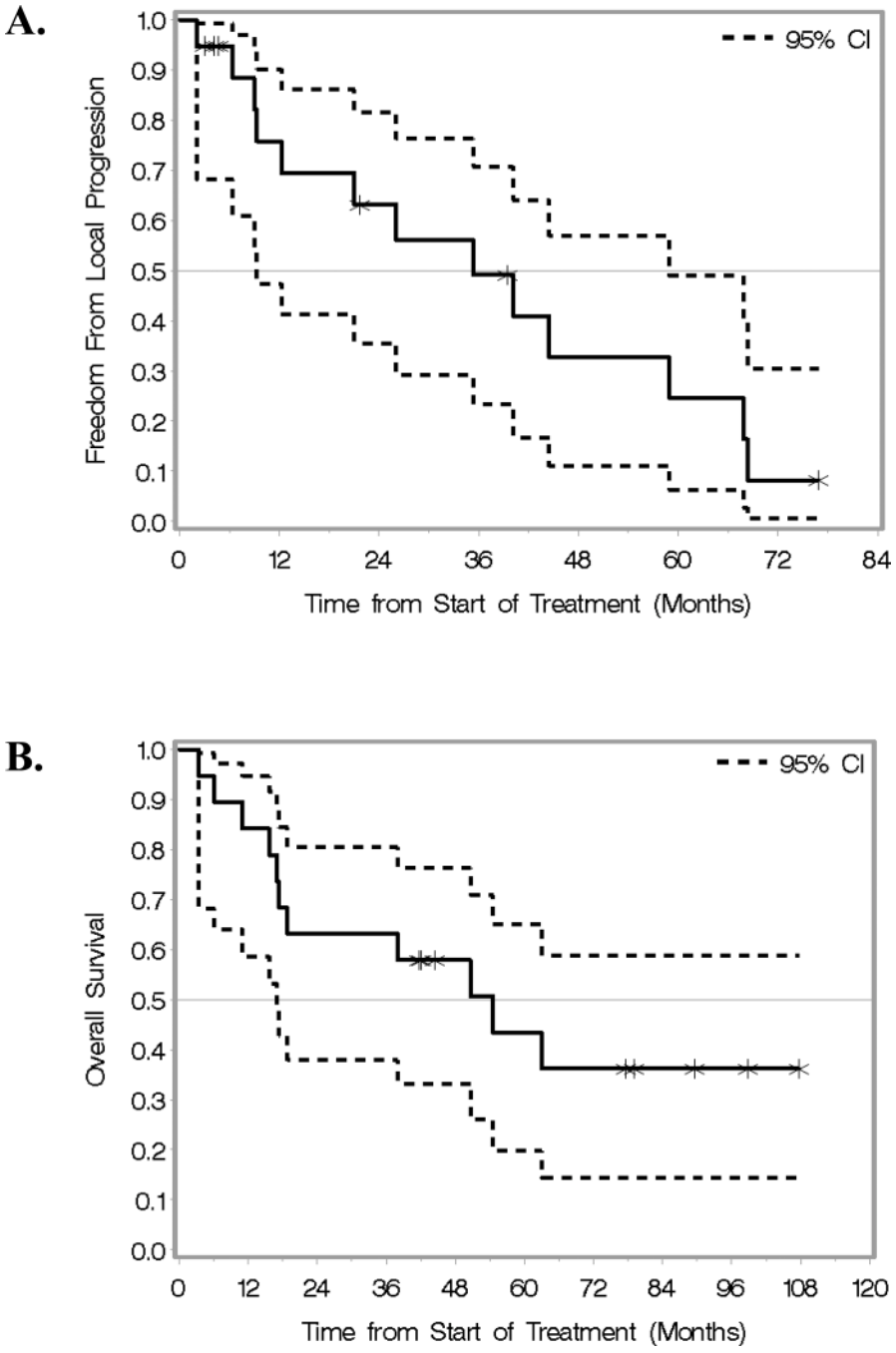

Figure 3.

Kaplan-Meyer survival analysis curves of freedom from local progression (FFLP) (A) and overall survival (OS) (B) probabilities in all patients. CI –confidence interval.

Table 1

Clinical characteristics of patients

Characteristic	Value
Total patients, n	19
Age, years (IQR)	52 (47–9)
Histology	
Carcinoid	11
Neuroendocrine carcinoma NOS	3
Neuroendocrine tumor NOS	2
Islet cell tumor NOS	2
Insulinoma	1
Gastrinoma	1
Origin of the primary tumor	
Small bowel	6
Cecum or appendix	2
Pancreas	3
Lung	1
Unknown	7
Secretory status of the tumor	
Secreting	13
Non-secreting	6
Presence of extrahepatic metastases	4
Previous surgical resection, RFA or RT	7
Previous systemic chemotherapy	11

Abbreviations: IQR – interquartile range, NOS – not otherwise specified, MEN – multiple endocrine neoplasia, RFA – radiofrequency ablation, RT – radiotherapy.

Table 2

Initial (π_0) and posterior (π) estimates of probabilities of DLT, by dose of WLRT

Dose, Gy	π_0	DLTs (n)/ Patients (n)	π	90% Confidence Interval
24	0.01	0/8	0.0016	(0.00008,0.016)
26	0.02	0/2	0.0039	(0.0003,0.031)
28	0.05	0/1	0.0124	(0.0124,0.071)
30	0.10	0/2	0.0309	(0,0042,0.134)
32	0.15	0/6	0.0535	(0.0089,0.192)

Abbreviations: DLT – dose-limiting toxicity, WLRT - whole-liver radiotherapy