Cardiovasc Intervent Radiol (2024) 47:60–68
https://doi.org/10.1007/s00270-023-03614-8

CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Integrated Capecitabine–Temozolomide with Radioembolization for Liver-Dominant G2 NETs: Long-Term Outcomes of a Single-Institution Retrospective Study

Michael C. Soulen[1,6] · Ursina R. Teitelbaum[2] · Rosemarie Mick[3] · Jennifer Eads[2] · Jeffrey I. Mondschein[1] · Mandeep Dagli[1] · Diana van Houten[1] · Nevena Damjanov[2] · Charles Schneider[2] · Keith Cengel[4] · David C. Metz[5]

Received: 4 August 2023 / Accepted: 31 October 2023 / Published online: 6 December 2023

Abstract

Purpose Capecitabine–Temozolomide (CapTem) is an oral chemotherapy regimen for NETs. Both drugs are radiosensitizers. Integrating CapTem and Y90 transarterial radioembolization (TARE) in patients with grade 2 neuroendocrine tumor (NET) liver metastases achieved an encouraging objective response rate (ORR) and progression-free survival (PFS) in a feasibility study. This study expands that report to a larger cohort with longer follow-up.

Methods Therapy consisted of monthly cycles of capecitabine 600 mg/m^2 twice daily for 14 days and temozolomide 150–200 mg/m2 on day 10–14. Simulation angiography was performed during the initial cycle. The dominant lobe was treated with ^{90}Y-resin microspheres using BSA dosimetry on day 7 of the second cycle of CapTem. Patients with bilobar disease had the other lobe treated on day 7 of the third or fourth cycle. CapTem was continued until progression or intolerance. Clinical and laboratory assessment was done monthly and imaging every 3 months.

Results 35/37 patients completed the prescribed regimen. Primary sites of disease were pancreas (16), lung (10), gut (7) and unknown (4). Mean duration of CapTem was 12 months (range, 4–32 months). ORR in the liver was 72% with a disease control rate of 100%. Median PFS was 36 months (95% CI, 25–45 months). Median overall survival was 41 months (95% CI, 24–87 months) from initiation of CapTemY90 therapy and 130 months (95% CI, 56–172 months) from initial diagnosis.

Conclusion Chemoradiation with CapTem and TARE provided durable control of G2 NET liver metastases for substantially longer than expectations for embolotherapy or chemotherapy alone.

✉ Michael C. Soulen
Michael.soulen@pennmedicine.upenn.edu

1 Neuroendocrine Tumor Program, Division of Interventional Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

2 Neuroendocrine Tumor Program, Division of Medical Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

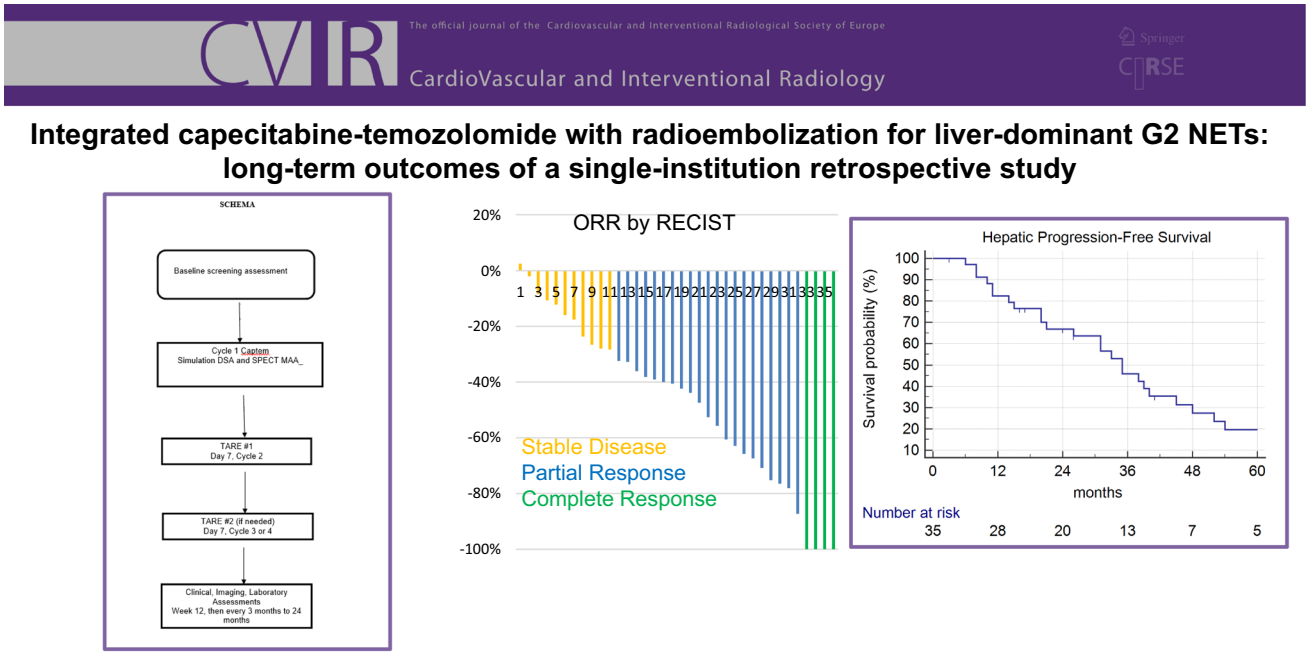
3 Department of Biostatistics, Epidemiology and Informatics, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

4 Neuroendocrine Tumor Program, Division of Radiation Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

5 Neuroendocrine Tumor Program, Division of Gastroenterology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

6 Neuroendocrine Tumor Program, Department of Radiology, Abramson Cancer Center, University of Pennsylvania, 1 Silverstein, 3400 Spruce Street, Philadelphia, PA 19104, USA

Graphical Abstract



Keywords Neuroendocrine tumor · Radioembolization · Chemotherapy

Introduction

Guidelines from the National Comprehensive Cancer Network, North American Neuroendocrine Tumor Society, and European Neuroendocrine Tumor Society endorse embolotherapy for symptomatic or progressive liver-dominant metastases [1–3]. Embolic techniques include bland embolization, chemoembolization, and radioembolization which have reported similar oncologic outcomes [4]. Transarterial radioembolization (TARE) is appealing because of its low acute toxicity compared to bland or chemoembolization [5]. Postembolization syndrome is minimal and almost all patients are treated on an outpatient basis [5].

A multicenter analysis of 155 patients from 7 US cancer centers reported hepatic progression free survival of 86% at 1 year and 69% at 2 years for Grade 1 NETs and 57% and 19% for Grade 2 NETs, with a median PFS of 13 months for Grade 2 [6]. PFS was the same irrespective of primary tumor site (pancreas vs. intestinal vs. lung) for both chemoembolization and radioembolization. These data suggest that patients with Grade 2 NETs might benefit from a more aggressive approach than liver-directed therapy alone.

The regimen of capecitabine for 14 days with temozolomide on days 10 to 14 of a 2-week cycle was first described by Fine et al. [7]. A retrospective series of 143 patients had 54% partial response (PR) and 35% stable disease (SD) by Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 [8]. Median PFS was 14.5 months (95% CI, 10–14.5) for G2 tumors. The ECOG-ACRIN 2211 trial randomized patients with pancreatic NET to CapTem versus temozolomide alone [9]. CapTem was statistically superior with an ORR of 30% and median PFS of 23 months.

Capecitabine and temozolomide are both radiosensitizers. In hopes of improving disease control over systemic or liver-directed therapy alone with no more than additive toxicities, an integrated treatment protocol combining capecitabine–temozolomide with yttrium-90 radioembolization (CapTemY90) for liver-dominant G2 metastases was inaugurated. In the feasibility and safety cohort of this integrated regimen, 19/21 patients completed the prescribed regimen [10]. Toxicities were as expected from each therapy alone, ORR 74%, and median PFS 31 months. This report details long-term clinical follow-up of an expanded cohort including the original 21 patients.

Methods

Institutional Review Board approval was obtained for this Health Insurance Portability and Accountability Act-compliant retrospective analysis. Patient selection and procedural methodology were as previously reported [10]. In brief, patients with metastatic NETs were evaluated by the Neuroendocrine Tumor Board. Patients with unresectable G2 NET liver-dominant metastases without contraindications to radioembolization or to CapTem were offered therapy with the CapTemY90 regimen. Liver dominance was defined as more than 50% of the total body tumor burden confined to the liver by consensus imaging review. Relevant criteria for this regimen included a liver tumor burden of less than 75%, patent portal vein, preserved organ function (total bilirubin level, < 2 mg/dL, creatinine level < 2 mg/dL, platelet count, $\geq$ 100,000/cL, international normalized ratio, < 1.6), and ability to undergo triple phase contrast-enhanced magnetic resonance imaging or computed tomography imaging.

Chemotherapy was initiated with capecitabine 750 mg/m^2 twice daily for 14 days and temozolomide 150–200 mg/m^2 in 2 divided doses on days 10–14, with 14 days between cycles. During the first cycle of CapTem, simulation angiography and technetium-99m-labeled macroaggregated albumin SPECT/CT were performed. Once the patient had completed the first cycle of CapTem with tolerable toxicity and undergone simulation demonstrating eligibility for TARE, the dominant lobe was radioembolized on day 7 of the second cycle of CapTem. Resin Y90 microspheres (SIR-Spheres; Sirtex Medical, Woburn, Mass) were prescribed according to the body surface area method (BSA) using visual estimates of liver and tumor fractions. For patients with bilobar disease, the other lobe was treated on day 7 of the third or fourth cycle of CapTem. CapTem was continued in 4-week cycles until progression or intolerance. Clinical assessment and laboratory tests (complete blood cell count, comprehensive metabolic panel, international normalized ratio, chromogranin A) were performed monthly. Triple phase contrast-enhanced abdominal magnetic resonance imaging or computed tomography imaging was performed 3 months after TARE, then every 3 months for 1 year. Patients without progression were imaged every 4 months the second year and every 6 months thereafter. Toxicities were graded using Common Terminology Criteria for Adverse Events v5. Tumor response and progression were categorized according to RECIST, with measurement of the longest diameter of up to 5 metastases in the liver to assess hepatic PFS and up to two metastases per extrahepatic site for overall PFS by RECIST 1.1. Progression-free survival was defined as the time from initiation of CapTem to documented disease progression or death due to any cause. Patients who were alive and progression-free at last contact were censored for PFS. Overall survival (OS) was defined as the time from initiation of CapTem to death due to any cause or last contact alive. PFS and OS were estimated using the Kaplan–Meier method. Differences among subgroups were evaluated by log rank test, with $P < 0.05$ considered significant.

Results

Primary sites of disease were pancreas (16), lung (10), gut (7) and unknown (4). Baseline characteristics are summarized in Table 1. The mean Ki-67 was 9.8%; range, 3–20%.

35/37 patients (18 female) completed the prescribed regimen between 2013 and 2020. Two patients did not receive a planned second lobar TARE due to post-embolization toxicities (pain, G1 elevated bilirubin) and were included in the analysis. Fifty-nine Y90 instillations were performed including 23 bilobar administrations in 23 patients, eight unilobar only, and five single whole liver instillations. Reasons for unilobar only treatment included prior hepatectomy, unilobar disease, or post-embolization toxicity. Median lung shunt fraction was 3% (mean, 4.5%; range, 0.5–14%). No dose reductions for excessive lung shunting were required. Mean prescribed activity was 1.78 GBq, range 0.81–2.85 GBq, and mean administered activity was 1.77 GBq, range 0.78–2.74 GBq. Three administrations were stopped for stasis after delivery of 71%, 74%, and 94% of the prescribed activity, respectively. These three procedures occurred prior to the change in the SIR-Spheres Instructions for Use from sterile water to 5% dextrose for delivery. For the remaining instillations, mean delivery was 100% (range, 96–106%). There were no procedure-related complications.

A total of 460 cycles of CapTem were administered, median 9 per patient (mean, 12; range, 4–32). Nine patients had dose reduction or interruptions for cytopenias [5], fatigue [4], nausea [3], and/or hand-foot skin reaction [2]. CapTem therapy was finally stopped due to chronic clinical toxicity (fatigue/nausea) in eight patients, thrombocytopenia in 5, elevated liver function tests in 3, hand-foot skin reaction in 3, tumor progression in 3, and sustained response beyond 2 years in 2, with three patients having more than 1 indicator.

Toxicity of the Integrated Regimen

Toxicities are summarized in Table 2 and were typical for CapTem and radioembolization individually. The most common were thrombocytopenia, fatigue, and nausea. One patient developed radioembolization-induced chronic

Table 1 Patient Characteristics

	N (%)
Age, mean, range, years	59 (35–78)
Sex, female	18 (49%)
ECOG Performance Status 0/1	21/16
Site of primary tumor	
Pancreas	16 (43%)
Lung	10 (27%)
Midgut	4 (11%)
Gastroduodenal	2 (5%)
Rectum	1 (3%)
Unknown	4 (11%)
Primary resected	17 (46%)
Sites of extrahepatic disease	
Unresected primary	11 (30%)
Lymph nodes	19 (51%)
Osseus	10 (27%)
peritoneum	1 (3%)
other	8 (22%)
Liver tumor burden	
$< 25\%$	19 (51%)
25–50%	10 (27%)
$> 50\%$	8 (22%)
Months from primary diagnosis, median, range	22.6 (0.6–153)
Months from diagnosis of liver metastases, median, range	15.5 (1–101)
Prior therapy	
Somatostatin analog	30 (81%)
Everolimus	7 (19%)
Cytotoxic chemotherapy	7 (19%)
Resection/ablation	1 (3%)
Embolization	10 (27%)
Baseline chromogranin A, mean, range	5030 (30–70000)
Prior whipple or biliary stent	7 (19%)
Post-progression therapies (13 had > 1)	26 (70%)
PRRT	7 (19%)
Chemotherapy	6 (16%)
Embolization	6 (16%)
Resection/ablation	5 (14%)
2nd course of CapTemY90	4 (11%)
Targeted agent	4 (11%)
Radiation therapy	4 (11%)

hepatic toxicity [11] and succumbed to spontaneous bacterial peritonitis 17 months after TARE with sustained control of his tumor.

Tumor Response

Thirty-two patients had images evaluable for response. Three had unmeasurable diffuse disease and two lacked source images for retrospective analysis. Median reduction in the sum of longest diameters of index hepatic metastases was 42% (mean, 48%; range, − 2 to 100%). By RECIST, there were 4 complete responses in the liver, 19 partial responses (PR), and 9 with stable disease (SD), for an objective response rate (ORR) of 72% and disease control rate of 100%. Median reduction in CgA level was 77%. Figure 1 shows waterfall plots for hepatic tumor and CgA

Table 2 Toxicities according to CTCAE v5

	Platelets	Fatigue	N/V	Pain	HFSR	Liver
G1	6	13	9	5	1	1
G2	2	4			2	1
G3	3	1	1	2	1	
G4	4					
G5						1

N/V nausea/vomiting, *HFSR* hand-foot skin reaction

response. Eighteen patients had evaluable disease outside the liver. Median reduction in sum of longest tumor diameters was 28% (mean, 33%; range, − 16 to 63%). By RECIST, the ORR for extrahepatic disease was 55%.

Disease Control and Survival

Median follow-up from initiation of CapTemY90 was 32 months (mean, 46 months; range, 10–113 months). Twenty-seven patients developed intrahepatic progression of disease by RECIST. Median hepatic PFS was 35 months (95% CI 21–45 months). Twenty-two patients develop tumor progression outside of the liver; among these 22, only 3 had extrahepatic progression only without liver progression. Median extrahepatic PFS was 41 months (95% CI 21–52 months). Median overall PFS was 36 months (95% CI 20–39 months) (Fig. 2).

Comparing the 16 pancreatic NETs with the 21 non-pancreatic primary tumors, median hepatic PFS for pancreatic NETs was 31 months (95% CI, 37.5–56.3 months) versus 28 months for other histologies (95% CI, 28.0–48.4 months), $P = 0.77$. Median overall PFS was 31 months

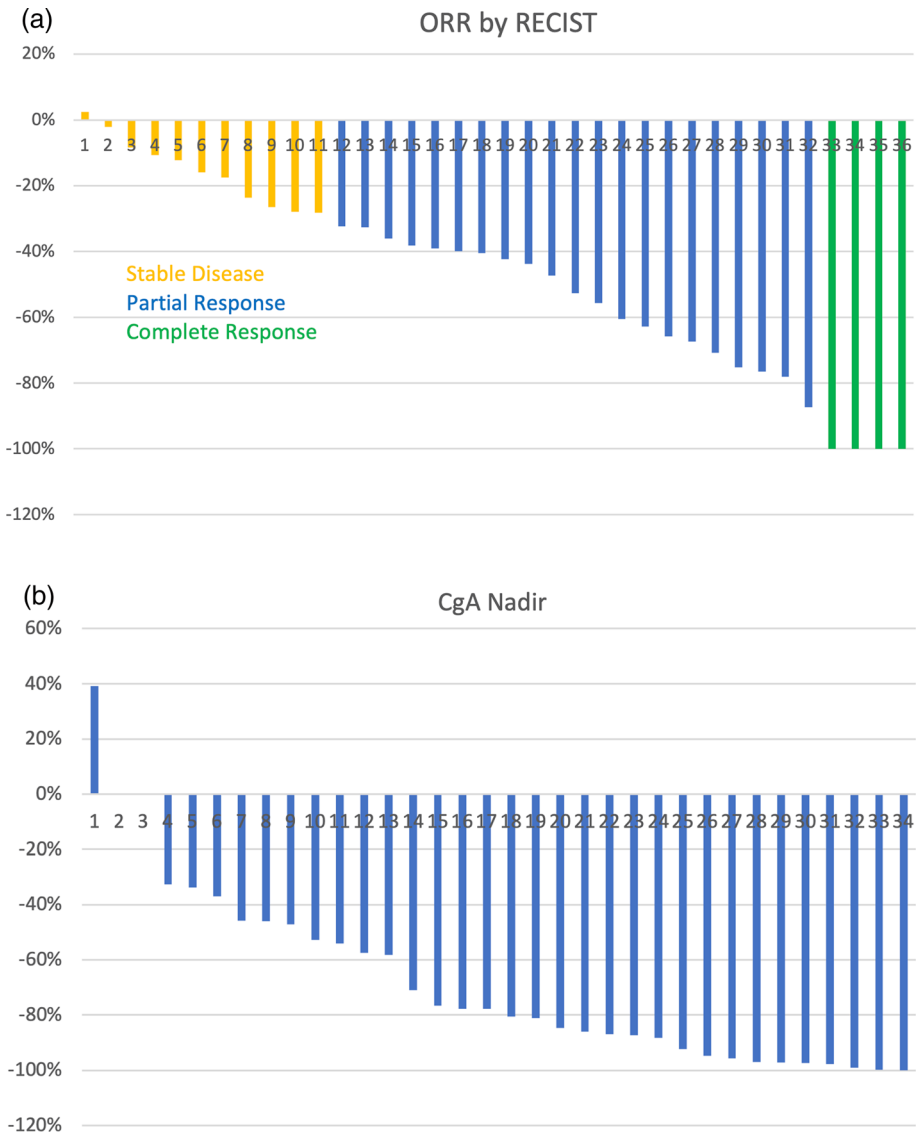


Fig. 1 **A** Tumor response by RECIST. ORR was 72%. **B** Chromogranin A nadir following CapTemY90

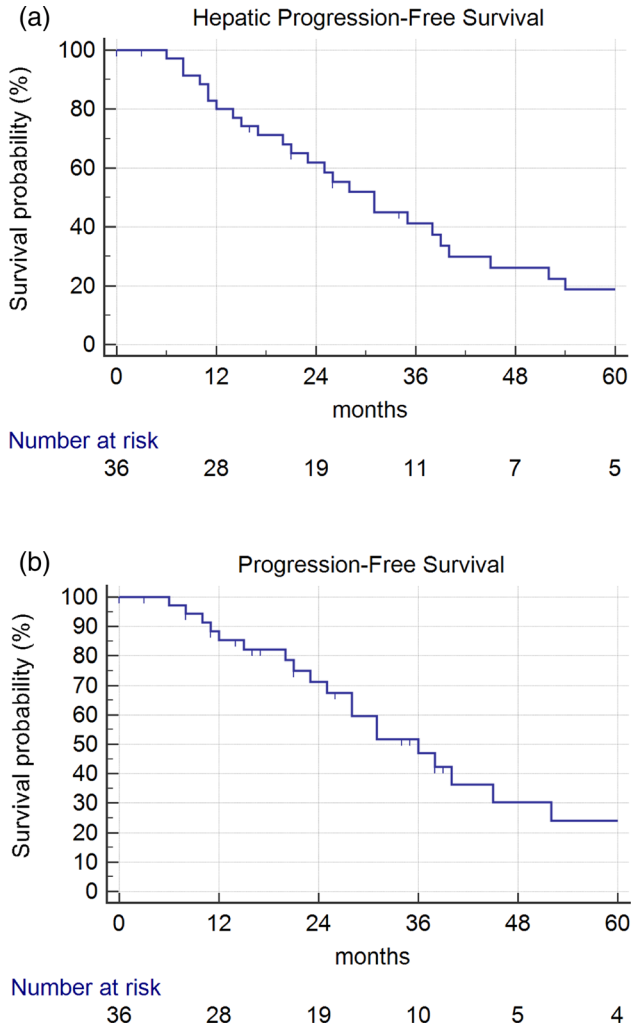


Fig. 2 **A** Kaplan–Meier estimate of hepatic progression-free survival. Median is 31 months. **B** Kaplan–Meier estimate of overall progression-free survival. Median is 36 months

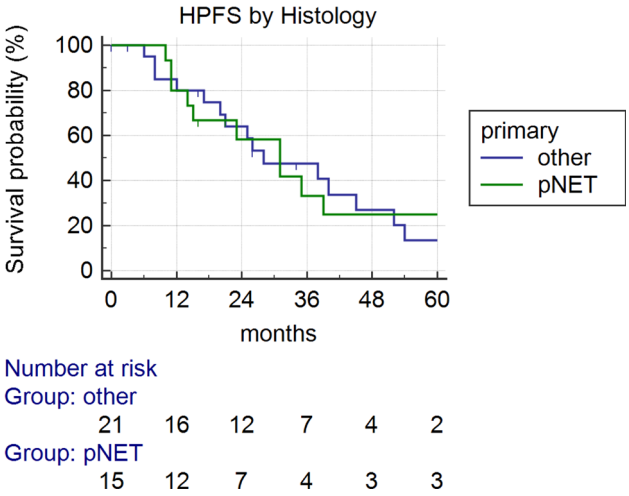


Fig. 3 Kaplan–Meier estimates of hepatic progression-free survival following CapTemY90 according to primary histology. The difference between pancreatic neuroendocrine tumors (pNET) and other histologies (lung, gut, unknown) is not significant. HPFS = hepatic progression-free survival

(95% CI, 37.5–56.3 months) for pancreatic NETS versus 36 months (95% CI, 21.5–41.8 months) for other histologies, $P = 0.36$ (Fig. 3).

Survival rates at 1, 2 and 3 years were 92%, 69%, and 55% after start of CapTem, and 92%, 86%, and 75% from initial diagnosis (Fig. 4).

Kaplan–Meier estimates of PFS for the 25 patients with "low" Grade 2 (Ki67 3%-11%) versus the 12 with "high" Grade 2 (Ki67 12–20%) were not significantly different (27 months vs. 35 months, $p = 0.71$).

Duration of CapTem and PFS

Ten subjects were on CapTem for 3–6 months, 15 for 7–12 months, and 12 for 13–32 months. 14/36 (39%) stopped CapTem due to toxicities prior to disease progression. Median PFS was > 36 months in the 3–6-month chemo group; 23 months for the 7–12-month chemo group, and 30 months for those on chemo > 12 months.

Discussion

Liver metastases occur in up to 90% of patients with NETs and are the major risk factor for worse prognosis. Integration of systemic chemotherapy and liver-directed therapy to enhance control in the liver and simultaneously treat extrahepatic disease is an attractive goal. To add value, an integrated regimen needs to be tolerable and improve oncologic outcomes over those expected for the individual therapies without worse toxicity. The combination of TARE with various chemotherapeutic drugs including capecitabine, 5-fluorouracil, floxuridine, oxaliplatin, and irinotecan has proven feasible and safe for treating metastatic colorectal cancer [12–15]. The integration of CapTem and TARE for NET liver metastases is feasible, with only 2 of 37 patients unable to complete the full cycle of radioembolization due to postembolization toxicities unrelated to the chemotherapy. Tolerance for CapTem therapy was similar to the report of Cives et al. in which 143 patients received a median of nine cycles of CapTem (range, 1–28) [8]. The most common grade 3–4 toxicities were thrombocytopenia, as expected with CapTem therapy. Nausea and fatigue were common adverse events which can be seen with either radioembolization and/or CapTem. Pain and hepatic toxicity were expected adverse events after radioembolization. Overall adverse events appear

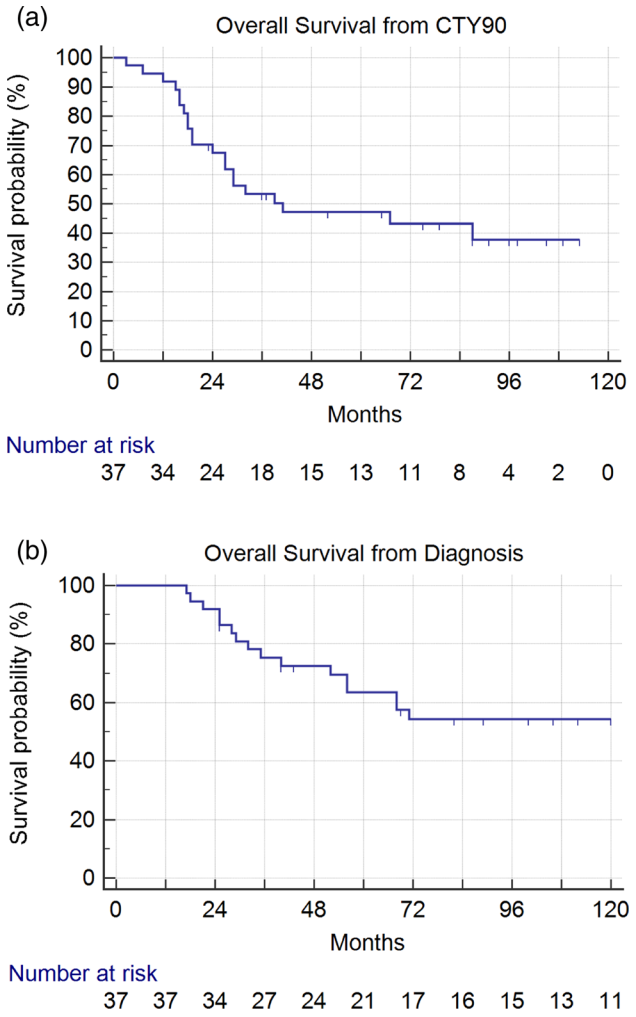


Fig. 4 Kaplan–Meier estimates of overall survival from **A** initiation of CapTemY90 and **B** diagnosis

similar to expectations from each therapy alone, without toxic synergy.

The ORR in the liver was 72%. A meta-analysis of 12 TARE series reported a range from 12 to 100% (mean, 61%) [16]. A recent international multicenter retrospective study reported an ORR of 41% among 210 patients [17]. The ORR to CapTem alone has been reported to be 54% to 60% in retrospective studies [7, 8] and only 30% in the recent ECOG-ACRIN trial [9]. The ORR for measurable extrahepatic disease in this cohort was 55%, in line with expectations for the effect of CapTem alone, whereas the better than expected response in the liver suggests the possibility of synergy. The mechanism for this synergy might involve direct cellular radiosensitization but could also involve additional modes of radiation cytotoxicity enhancement by chemotherapy or even radiotherapeutic enhancement of chemotherapy through altered perfusion or local drug metabolism. These results are particularly encouraging since the study cohort consisted entirely of patients with G2 tumors. In the Cives et al. series, only 50% of G2 NETs had an objective response to CapTem alone. The biochemical response rate was also better than expected, with 80% achieving a $> 50\%$ reduction in CgA level after chemoradioembolization versus 61% reported with CapTem alone.

Pancreatic NETs are more responsive to cytotoxic chemotherapy than midgut tumors [18], whereas response to embolotherapy is independent of histology [6]. In this cohort, there was no difference in PFS comparing pancreatic to lung or gut primaries, suggesting that the liver-directed therapy is the primary driver of outcome. Furthermore, PFS appeared to be independent of duration of chemotherapy, suggesting that a short course for radiosensitization may be sufficient and patients could be spared subsequent months of chemotherapy-related toxicities without sacrificing oncologic benefit. This would need to be evaluated prospectively in a larger trial.

Most important is the durability of disease control because prevention of intrahepatic progression is the major determinant of survival. The liver is the first and often only site of disease progression even when extrahepatic disease is present. Among a group of 123 patients with extrahepatic disease treated with chemoembolization, 70% progressed at 2 years, 68% in the liver, and 55% in the liver only [19]. After CapTemY90 in the current study, median PFS was 35 months in the liver and 41 months outside the liver. This appears to exceed the expected PFS of 12–14 months for G2 tumors following liver-directed therapy alone and the PFS reported in prospective trials of systemic therapies such as CapTem alone and PRRT [9, 20].

Limitations of this study include the retrospective analysis, single-center source of patients, and accrual period pre-dating recent improvements in dosimetry and delivery technology. The PFS exceeds prior reports of other liver-directed and systemic therapies to an extent that invites skepticism. Nonetheless, the data are encouraging that synergy between TARE and radiosensitizing chemotherapy may exist and provided the basis for the design of an ongoing multicenter phase 2 trial (NCT04339036).

Other important concerns about this regimen include the Y90 prescription methodology and the whole-liver treatment employed in most patients. BSA prescriptions were created based on estimates of liver and tumor fractions per the SIRSpheres Instructions for Use. Partition models or voxel-based dosimetry provide more precise dose calculations for tumor and liver. A dose–response relationship has been reported for neuroendocrine tumor liver metastases with both TheraSpheres and SIRSpheres [21, 22]. The clinical relevance of this is unknown since no association with PFS or OS has been documented. Neuroendocrine liver metastases are typically diffuse, numerous and ill-

suited to segmentation of the tumor vs. liver compartment, making more precise dosimetry difficult. Compromise methods include segmenting only up to five metastases [21]. It is possible that more precise dosimetry methods could improve on the outcomes reported in this series.

Late radiation-induced liver failure is a particular concern in NET patients due to their long life expectancy. Clinical hepatic decompensation has been reported in 10–20% of patients surviving 2–10 years after radioembolization, particularly when the whole liver was treated [11, 23, 24]. Current practice is evolving to spare two segments or 30% of liver volume when doing TARE. This would eliminate the opportunity for synergy in the excluded liver volume and possibly limit the benefit of chemoradioembolization.

In summary, chemoradioembolization with capecitabine and temozolomide combined with TARE was safe and effective in this cohort of patients with Grade 2 NET metastases. A prospective multicenter trial of this regimen is underway. Opportunities to improve dosimetry and mitigate the risk of radioembolization-induced chronic hepatic toxicity are important considerations for refinement of this approach.

Funding This study was not supported by any funding.

Declarations

Conflict of interest Dr. Soulen reports grants and personal fees from Guerbet LLC, personal fees from Genetech, grants from Pfizer, grants from Sirtex, personal fees from AstraZeneca, personal fees from Varian, outside the submitted work. Dr. Eads reports grants from Oncolys, Genentech, Merck, Seagen, Medimmune, AstraZeneca, Arcus, Amgen, Gilead, and Hutchmed and personal fees from Advanced Accelerator Applications, outside the reported work. The remaining authors report no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study has obtained IRB approval from the University of Pennsylvania and the need for informed consent was waived. For this type of study, consent for publication is not required.

References

1. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
2. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The north American neuroendocrine tumor society consensus guidelines for surveillance and medical management of midgut neuroendocrine tumors. Pancreas. 2017;46:707–14.
3. Pavel M, Baudin E, Couvelard A, et al. ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2012;95:157–76.
4. Gaba RC. Chemoembolization practice patterns and technical methods among interventional radiologists: results of an online survey. AJR Am J Roentgenol. 2012;198:692–9.
5. Salem R, Gilbertsen M, Butt Z, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization compared with chemoembolization. Clin Gastroenterol Hepatol. 2013;11:1358-1365.e1.
6. Chen JX, Rose S, White SB, El-Haddad G, Fidelman N, Yarmohammadi H, Hwang W, Sze DY, Kothary N, Stashek K, Wileyto EP, Salem R, Metz DC, Soulen MC. Embolotherapy for neuroendocrine tumor liver metastases: prognostic factors for hepatic progression-free survival and overall survival. Cardiovasc Intervent Radiol. 2017;40:69–80.
7. Fine RL, Gulati AP, Krantz BA, Moss RA, Schreibman S, Tsushima DA, Mowatt KB, Dinnen RD, Mao Y, Stevens PD, Schrope B, Allendorf J, Lee JA, Sherman WH, Cabot JA. Capecitabine and temozolomide (CAPTEM) for metastatic well-differentiated neuroendocrine cancers. Cancer Chemother Pharmacol. 2013;71:663–70.
8. Cives M, Ghayouri M, Morse B, Brelsford M, Black M, Rizzo A, Meeker A, Stroberg J. Analysis of potential response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors. Endocr Relat Cancer. 2016;23:759–67.
9. Kunz PL, Graham NT, Catalano PJ, Nimeiri HS, Fisher GA, Longacre TA, Suarez CJ, Martin BA, Yao JC, Kulke MH, Hendifar AE, Shanks JC, Shah MH, Zalupski MM, Schmulbach EL, Reidy-Lagunes DL, Strosberg JR, O'Dwyer PJ, Benson AB 3rd. 2022 A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). J Clin Oncol. 2023;41(7):1359–69.
10. Soulen MC, van Houten D, Teitelbaum UR, et al. Safety and feasibility of integrating Yttrium-90 radioembolization with capecitabine–temozolomide for grade 2 liver-dominant metastatic neuroendocrine tumors. Pancreas. 2018;47(8):980–4.
11. Currie BM, Hoteit M, Ben-Josef E, Nadolski GJ, Soulen MC. Radioembolization-induced chronic hepatotoxicity: a single-center cohort analysis. J Vasc Intervent Radiol. 2019;30:1915–23.
12. Hickey R, Mulcahy MF, Lewandowski RJ, et al. Chemoradiation of hepatic malignancies: prospective, phase 1 study of full-dose capecitabine with escalating doses of yttrium-90 radioembolization. Int J Radiat Oncol Biol Phys. 2014;88:1025–31.
13. Cohen SJ, Konski AA, Putnam S, Ball DS, Meyer JE, Yu JQ, Astsaturov I, Marlow C, Dickens A, Cade DN, Merepol NJ. Phase I study of capecitabine combined with radioembolization using yttrium-90 resin microspheres (SIR-Spheres) in patients with advanced cancer. Br J Cancer. 2014;111:265–71.
14. Sharma RA, Van Hazel GA, Morgan B, et al. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. J Clin Oncol. 2007;25:1099–106.
15. van Hazel GA, Pavlakis N, Goldstein D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol. 2009;27:4089–95.
16. Yang TX, Chua TC, Morris DL. Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases—a systematic review. Surg Oncol. 2012;21:299–308.
17. Schaarschmidt BM, Wildgruber M, Kloeckner R, et al. ^{90}Y radioembolization in the treatment of neuroendocrine neoplasms: results of an international multicenter study. J Nucl Med. 2022;63:679–85.

18. Al-Toubah T, Morse B, Strosberg J. Efficacy of capecitabine and temozolomide in small bowel (midgut) neuroendocrine tumors. Curr Oncol. 2022;29:510–5.
19. Arrese D, Mcnally ME, Chokshi R, Feria-Arias E, Schmidt C, Klemanski D, Gregory G, Khabiri H, Shah M, Bloomston M. Extrahepatic disease should not preclude transarterial chemoembolization for metastatic neuroendocrine carcinoma. Ann Surg Oncol. 2013;20:1114–20.
20. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A, Mittra E, Wolin EM, Yao JC, Pavel ME, Grande E, Van Cutsem E, Seregni E, Duarte H, Gericke G, Bartalotta A, Mariani MF, Demange A, Mutevelic S, Krenning EP. Lancet Oncol. 2021;22(12):1752–63.
21. Ebbers SC, van Roekel C, Braat MNGJA, Barentsz MW, Lam MGEH, Braat AJAT. Dose-response relationship after yttrium-90-radioembolization with glass microspheres in patients with neuroendocrine tumor liver metastases. Eur J Nucl Med Mol Imaging. 2022;49(5):1700–10.
22. Chansanti O, Jahangiri Y, Matsui Y, Adachi A, Geeratikun Y, Kaufman JA, Kolbeck KJ, Stevens JS, Farsad K. Tumor dose response in Yttrium-90 resin microsphere embolization for neuroendocrine liver metastases: a tumor-specific analysis with dose estimation using SPECT-CT. J Vasc Interv Radiol. 2017;28(11):1528–35.
23. Su Y-K, Mackey RV, Riaz A, et al. Long-term hepatotoxicity of yttrium-90 radioembolization as treatment of metastatic neuroendocrine tumor to the liver. J Vasc Interv Radiol. 2017;28:1520–6.
24. Tomozawa Y, Jahangiri Y, Pathak P, et al. Long-term toxicity after transarterial radioembolization with yttrium-90 using resin microspheres for neuroendocrine tumor liver metastases. J Vasc Interv Radiol. 2018;29:858–65.