Oncology Research and Treatment

Research Article

Oncol Res Treat 2023;46:466–474
DOI: 10.1159/000533983

Received: May 12, 2023
Accepted: September 1, 2023
Published online: October 12, 2023

Concomitant Irradiation to Checkpoint Inhibitor Therapy of Hepatocellular Carcinoma Patients: A Systematic Retrospective, Single-Center Analysis

Stefan Munker[a, b] Daniel Rossler[a, b] Osman Öcal[c] Najib Ben-Khaled[a, b] Kathrin Bernhart[a, b] Liangtao Ye[a, b] Ignazio Piseddu[a, b] Jakob Vielhauer[a, b] Florian P. Reiter[a, b, d] Isaac Rodriguez[e] Jens Ricke[c] Andreas Teufel[e, f] Enrico De Toni[a, b] Max Seidensticker[c] Maximilian Niyazi[g, h, i] Stefanie Corradini[g, h, i]

[a]Department of Medicine II, University Hospital, LMU Munich, Munich, Germany; [b]Liver Center Munich, University Hospital, LMU Munich, Munich, Germany; [c]Department of Radiology, University Hospital, LMU Munich, Munich, Germany; [d]Division of Hepatology, Department of Medicine II, University Hospital Würzburg, Würzburg, Germany; [e]Department of Medicine II, Division of Hepatology, Division of Bioinformatics, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [f]Clinical Cooperation Unit Healthy Metabolism, Center for Preventive Medicine and Digital Health Baden-Württemberg (CPDBW), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [g]Bavarian Cancer Research Center (BZKF), Munich, Germany; [h]German Cancer Consortium (DKTK), partner site Munich, Munich, Germany; [i]Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany

Keywords

Immunotherapy · Hepatocellular carcinoma · Checkpoint inhibitor · Radiotherapy · Locoregional therapy

Abstract

Introduction: Immunotherapy has been established as the standard treatment option for patients with advanced hepatocellular carcinoma (aHCC). Despite the increased efficacy, disease progression occurs in a relevant proportion of patients even after an objective response. Combination concepts with locoregional therapy are currently under investigation for hepatic disease but are also in discussion for the control of distant metastasis. Radiotherapy is a highly effective treatment modality for local tumor control. It is also thought to increase the efficacy of checkpoint inhibition and sensitize distant lesions to the effects of immunotherapy, but may potentially increase adverse effects. In our center, few patients with aHCC treated with immune checkpoint inhibitors (ICIs) received concomitant radiotherapy for symptom or disease control. The aim of this study was to retrospectively analyze adverse effects and efficacy of concomitant radiotherapy in patients with aHCC treated with checkpoint inhibition. ***Methods:*** To this aim, patients who received a combination of ICI and radiotherapy in our institution were retrospectively considered for analysis. The predefined inclusion criterion was radiotherapy after initiated checkpoint inhibition and continuation of ICI therapy for at least 8 weeks. Adverse effects and efficacy measurements were performed according to local standards. ***Results:*** The database search of 2016–2021 revealed six consecutive patients fulfilling the predefined criteria for concomitant ICI and radiotherapy. Three patients received

The study was conducted at the gastrointestinal cancer unit of the University Hospital LMU Munich, Germany.

karger@karger.com
www.karger.com/ort

Correspondence to:
Stefan Munker, stefan.munker@med.uni-muenchen.de

Karger

high-dose-rate brachytherapy (15 Gy) to treat progredient hepatic lesions. Two patients received stereotactic body radiotherapy (SBRT) (25–30 Gy) for symptom control, and 1 patient received brachytherapy and SBRT to treat metastases. No severe adverse events were reported in the period (<6 months) after concomitant radiotherapy. In 5 out of 6 cases, long-term tumor control could be achieved by this therapeutic combination. ***Conclusion:*** A good efficacy of concomitant radiotherapy and checkpoint inhibition has been achieved with no safety concerns. Further investigations should evaluate the safety, appropriate clinical context, and efficacy of this promising approach.

Introduction

The treatment landscape for hepatocellular carcinoma (HCC) is observing an enormous paradigm shift toward immune checkpoint inhibitor (ICI) treatments, which have emerged as a promising therapeutic option [1]. ICI, in combination with anti-VEGF antibody therapy, became standard of care in the first-line treatment of advanced hepatocellular carcinoma (aHCC) [2]. In the case of a systemic progress, escalation strategies are currently developed by combining, for example, ICI with tyrosine kinase inhibitors in a second-line setting [3]. In the case of progressive disease limited to the liver, an additive locoregional approach might be feasible and is currently tested in the DEMAND trial [4]. However, in case of limited progression of extrahepatic disease, new multimodal treatment concepts are urgently needed [5]. Radiotherapy (RT) may increase efficacy of checkpoint inhibition through additional immune sensitization, as shown in preclinical models [6] and clinical studies of malignant melanoma [7, 8]. With high-dose-rate brachytherapy (HDRBT) and stereotactic body radiation therapy (SBRT), two effective radiotherapeutic modalities are available for the treatment of HCC.

HDRBT is used for minimally invasive tumor ablation, to achieve local tumor control and support systemic therapies. It can also be used as a bridging therapy prior to liver transplantation [9]. HDRBT enables the administration of high-dose radiation to the tumor region while maintaining a low radiation dose to the remaining healthy hepatic tissue. It has also enabled us to overcome the limitations associated with thermal ablation techniques. Such limitations included tumor size, proximity to adjacent thermosensitive structures, and vascular cooling effects [10]. Besides local tumor ablation, using the destructive alpha radiation-based brachytherapy induces a lasting local immune response and a systemic anti-tumor response [11]. When used with immunomodulators, this anti-tumor response is further potentiated [12].

External beam RT is a well-characterized therapeutic modality for HCC and remains an essential treatment option, especially in patients with hepatic lesions not amenable to locoregional treatment due to size, anatomical reasons, or other accompanying circumstances such as ascites or an impaired coagulation status [13]. In the past, irradiation of hepatic lesions could lead to hepatic decompensation in up to 5% of the cases [14, 15] because radiation has the potential to harm surrounding healthy liver parenchyma. Therefore, its utilization as a treatment option has historically been limited [16, 17]. However, new technological improvements such as intensity-modulated and image-guided SBRT allow administering the dose safely in carefully selected patients, thereby protecting the proper functioning of liver parenchyma [18, 19]. Previous studies have supported the utilization of SBRT as a therapeutic approach for treating liver cancer with the aim of achieving a favorable toxicity profile [20, 21]. Moreover, SBRT can be used in combination with locoregionary therapies as a bridging therapy before transplantation to efficiently control the spread of the tumor in pre-transplant conditions [9, 22].

RT may increase efficacy of checkpoint inhibition through additional immune sensitization, as shown in preclinical models [6] and clinical studies of malignant melanoma [7, 8]. The combination enhances the expression of MHC-I and CD8 cells ultimately leading to the major improvements in the cytotoxic activity and overall efficacy of ICI [23]. RT may be an effective additive immune sensitizing therapy, but in the context of checkpoint inhibition, it is quite plausible that radiation may trigger immunogenic off-target effects [24, 25]. Only few data are currently available, characterizing tolerance and efficacy of concomitant RT in ICI-treated HCC patients. To this aim, we systematically evaluated HCC cases in our center that received RT in the context of checkpoint inhibition.

Methods

Study Design

A retrospective analysis was performed based on clinical data obtained from our gastrointestinal cancer unit at the University Hospital LMU Munich, Germany. All consecutive patients between 2016 and 2021 with the diagnosis C22.0 were retrospectively screened for receiving RT at our outpatient clinic at the University Medical Center Großhadern LMU. The only inclusion criterion was that RT was begun after initiated checkpoint inhibition and continuation of ICI therapy for at least 2 months after RT, including efficacy measurements. Due to the low number, the individual patient cases are presented each as separate case vignettes. Data collection and retrospective analysis of patient information were anonymized in accordance with the Declaration of Helsinki. Ethics approval from the Local Institutional Review Board was obtained (18–604).

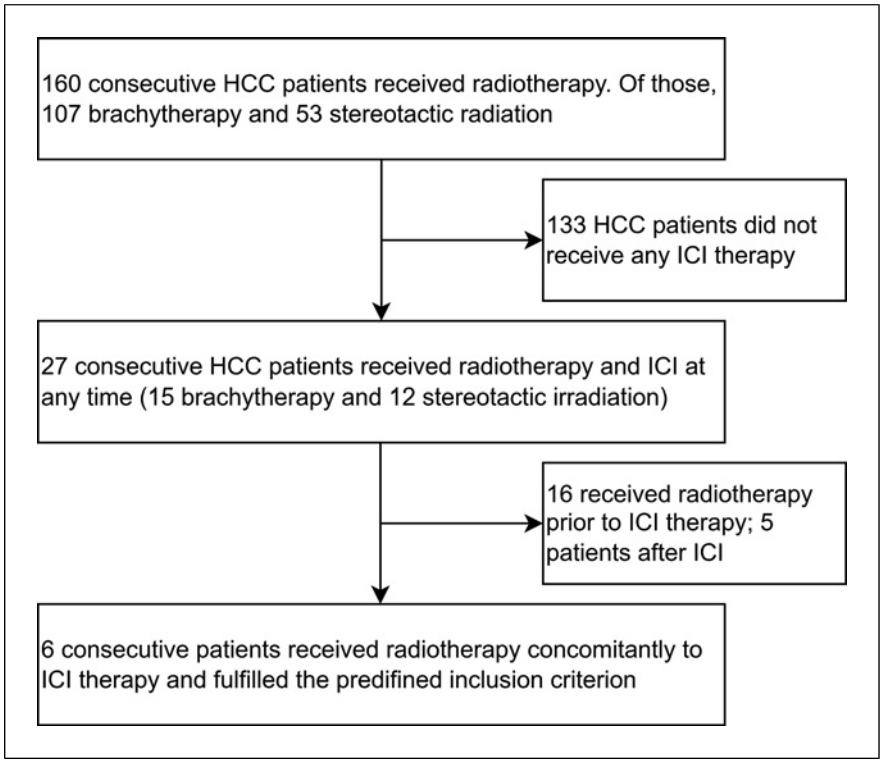

Fig. 1. Flowchart depicting results of the database search.

Treatment Schedule

One patient with HCC received nivolumab and ipilimumab according to the established protocol (1 mg/kg nivolumab followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, followed by 240 mg nivolumab monotherapy maintenance 2-weekly) [26]. Three patients received full-dose (240 mg) nivolumab monotherapy 2-weekly [27]. Another patient received pembrolizumab in combination with local treatment as part of a study treatment [28]. One patient received durvalumab and tremelimumab treatments (single dose treme 300 mg, durva 1,500 mg every 4 weeks) as part of a study treatment.

Regarding external beam RT, different techniques were applied. For bone metastases, a 3D conformal technique was used, while for other metastases SBRT techniques were used. Therefore, various fractionation schemes were used (10 × 3 Gy, 5 × 4 Gy, 5 × 5 Gy).

The brachytherapy procedure was conducted under conscious sedation under sterile conditions. Under CT fluoroscopy, the HCC was punctured with a 17G needle which was exchanged over a stiff wire to a 6-French sheath that can hold a brachytherapy catheter. The number of catheters was dependent on size and number of target lesions. A tumor surrounding prescription dose of 15 Gy was aimed at as a single fraction using high-dose brachytherapy with an iridium-192 afterloading unit. Organ at risk constraints were as follows: bowel/colon and stomach D1 ccm: 12 Gy, D0.1 ccm: 15 Gy; esophagus D1 ccm: 12 Gy, D0.01 ccm: 15 Gy; spinal cord D0.01 ccm: 10 Gy; skin D0.01 ccm: 10 Gy. One-third of the uninvolved liver was irradiated with less than 5 Gy [9].

Assessments

Routine efficacy assessments were conducted by computed tomography of the chest, abdomen, and pelvis or magnetic resonance imaging of the abdomen in every 3 months. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 and modified RECIST for hepatocellular cancer (mRECIST) retrospectively by two experienced hepatobiliary radiologists.

Results

Database Search

A database search showed a total of 27 consecutive HCC patients receiving RT and checkpoint inhibition at any time. Of those, only six patients fulfilled the predefined inclusion criterion with concomitant RT. Another 16 patients received ICI before and 5 patients after RT (Fig. 1).

Patient characteristics of the six patients receiving concomitant RT and checkpoint inhibition are depicted in Table 1. The age range was from 42 to 80 years old.

Case Vignettes

Patient 1 was diagnosed with poorly differentiated HCC (verified by histology) and renal carcinoma with suspected lymph node metastasis of the renal cell carcinoma (RCC). Treatment with nivolumab and ipilimumab for metastasized RCC was initiated (Fig. 2a). One of two HCC lesions responded to the initiated treatment with shrinkage, while the second lesion showed isolated tumor growth. The progressive lesion was treated with brachytherapy. Afterward, the HCC and the lymph node metastasis showed sustained

Table 1. Patient characteristics with the corresponding checkpoint inhibitor, radiotherapeutic modality, coincidental adverse effects, and treatment outcomes

Pat. No.	BCLC	Cirrhosis	ICI therapy	RT modality	RT target	Number of fractions × single dose	Indication	Coincidental adverse effect	Best response in-field	Best overall response	Time to best response after ICI	Time to best response after RTX	Duration of the best response
1	C	Child A	Nivolumab and ipilimumab	Brachytherapy	Seg VIII and VII	1 × 15 Gy	Local tumor control	No AE	CR	CR	12	3	15
2	C	Child A	Nivolumab	SBRT	Lymph node metastases	5 × 5 Gy (80% isodose)	Local tumor control	No AE	CR	CR	35	8	12
				Brachytherapy	Seg III and V	1 × 15 Gy	Local tumor control	No AE	CR				
				SBRT	Cerebral metastasis	5 × 5 Gy	Local tumor control		CR				
3	B	Child A	Pembrolizumab (Immulab)	Brachytherapy	Seg VI/VIII	1 × 15 Gy	Local tumor control	No AE	PR	PR	3	2	11
4	C	No	Durvalumab and tremelimumab (Himalaya)	3D conformal EBRT	Bone metastasis T11-L1	10 × 3 Gy	Palliative	Hypothyreosis	SD	SD	4	3	14
				3D conformal EBRT	Bone metastasis B6-B10	10 × 3 Gy	Palliative		SD				
5	B	Child A	Nivolumab	Brachytherapy	3 lesions, seg IVb/a and V	1 × 15 Gy	Local tumor control	Nummulary eczema	CR	CR	37	3	20
				Brachytherapy	2 lesions, seg VI/VII	1 × 15 Gy	Local tumor control	Xerosis cutis	CR				
				Brachytherapy	1 lesion, seg V/VIII	1 × 15 Gy	Local tumor control; tumor-control		CR				
6	C	Child B	Nivolumab	3D conformal EBRT	T12-L1, popliteal fossa right, tibia li, B6-8, pelvis/right os ischii	10 × 3 Gy	Palliative	No AE	SD	PD	?	?	?

SBRT, stereotactic body radiation therapy; EBRT, external beam radiation therapy; PD, progressive disease; PR, partial response; CR, complete response.

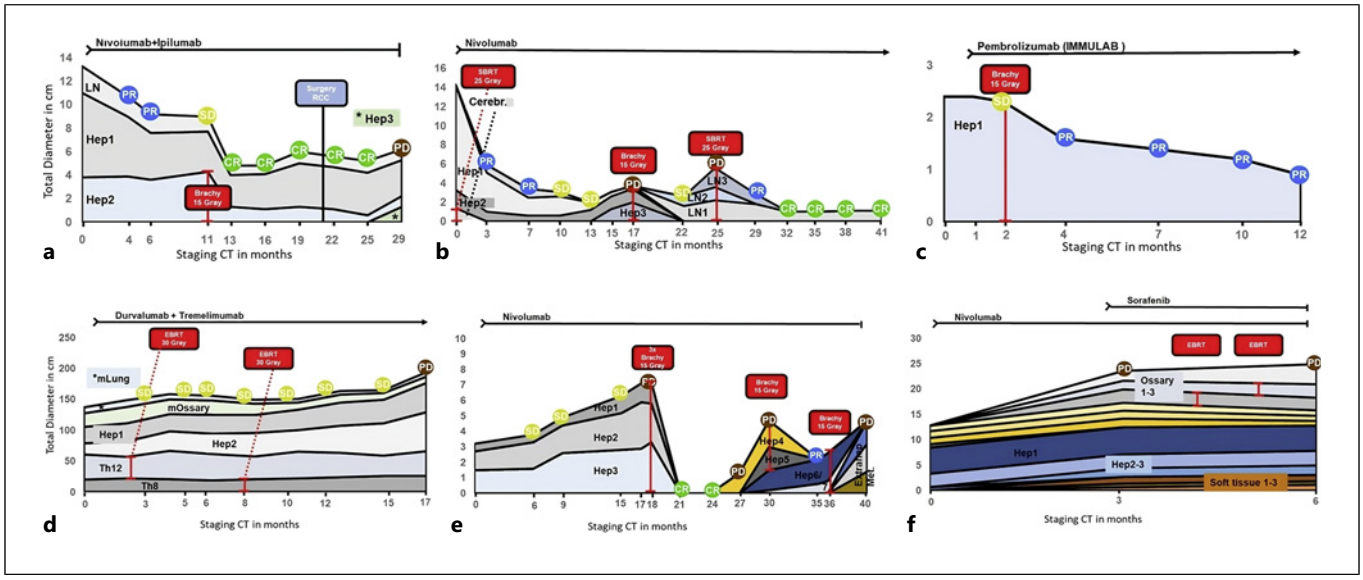

Fig. 2. a–f Schematic representation of the 6 patient courses. The longest tumor axis was used for diameter measurements. Hep, hepatic metastasis; LN, lymph node metastasis; SBRT, stereotactic intensity-modulated radiotherapy; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

complete remission. Due to good tumor control and sustained good performance status, nephrectomy of the RCC was performed (histologically confirmed RCC R0 resection), whereas histology of the lymph nodes showed HCC metastasis with a good regression status. Due to the good efficacy of ICI therapy, it was further continued. Eight months later, a new hepatic tumor nodule developed, and ICI therapy was discontinued.

Patient 2 was diagnosed with metastatic HCC in 2017 with cerebral metastasis. Upon initiation with sorafenib, he developed an intracerebral hemorrhage originating from a cerebral metastasis. The bleeding lesion was evacuated surgically. Treatment was switched to nivolumab, and the patient received postoperative SBRT of the surgical cavity (Fig. 2b). The hepatic tumor had an excellent response. Seventeen months later, two new hepatic nodules developed and local brachytherapy was administered, and reasonable local tumor control was achieved. Eight months later, progressive retroperitoneal lymph node metastasis was evident, which was treated by stereotactic irradiation. Sustained, complete response was achieved, and so far, no treatment-related adverse effects have been reported. The patient is still doing well after 41 months of treatment.

Patient 3 had a singular HCC lesion and received pembrolizumab as a study treatment additive to locoregional treatment (Fig. 2c). Brachytherapy was performed. The staging CT showed tumor devascularization indicating good local tumor control and no adverse effects were reported.

Patient 4 was diagnosed with HCC with bone, pulmonary, and hepatic metastases. He received durvalumab and tremelimumab (Fig. 2d). Due to symptomatic vertebral metastasis, he received palliative RT for symptom control. Other than hypothyreosis, no additional adverse effects were evident. However, he had an intrahepatic progress after 17 months, and the study medication was discontinued.

Patient 5 presented with intrahepatic disseminated HCC. Initial therapies consisted of selective internal RT, transarterial chemo embolization, and radiofrequency thermal ablation. A therapy with sorafenib was initiated upon intrahepatic progression and evidence of peritoneal carcinosis. Due to the progression of the hepatic lesion, the patient was included in a trial and entered the placebo arm. Due to hepatic progression, therapy with nivolumab was initiated (Fig. 2e). Progressive lesions were treated with brachytherapy and local control was achieved. Except for nummulary eczema and xerosis cutis, no adverse events occurred. After 40 months, extrahepatic metastasis was diagnosed, and nivolumab treatment was discontinued.

Patient 6 was diagnosed with HCC in 2012. He received orthotopic liver transplantation in February 2014 and had an intrahepatic HCC recurrence in January 2015. He received local ablative treatments. When extrahepatic disease (bone, lymph nodes) was evident, a treatment with nivolumab was started (Fig. 2f). Due to symptomatic vertebral (B12-L2 and C6-B3) metastases, a palliative RT treatment for symptom control was performed and sorafenib was added. As he progressed, systemic treatment with nivolumab was discontinued.

Table 2. Ongoing clinical trials using checkpoint inhibitors with RT for HCC (www.ClinicalTrials.gov)

Clinical trial identification	Study start date	Phase	Type of radiative intervention	Type of CPI	Est. enrollment	Primary endpoint
NCT04167293	November 16, 2019	II/III	SBRT	Sintilimab	116	6-month PFS
NCT03482102	May 14, 2018	II	RT (not specified)	Durvalumab and tremelimumab	70	Best ORR
NCT03817736	March 1, 2019	II	TACE+ SBRT	Not specified	33	No. of patients eligible to curative surgical intervention
NCT03316872	February 15, 2018	II	SBRT	Pembrolizumab	30	ORR
NCT04611165	November 15, 2019	II	EBRT	Nivolumab	50	PFS
NCT04547452	July 1, 2020	II	SBRT	Sintilimab	84	PFS
NCT02608385	December 2015	I	SBRT	Pembrolizumab	130	Recommended SBRT dose
NCT04547452	July 1, 2020	II	SBRT	Sintilimab	84	PFS
NCT04193696	January 10, 2020	II	RT	Anti-PD-1 agent	39	ORR
NCT03817736 (START-FIT)	March 1, 2019	II	TACE + SBRT	Not specified	33	No. of patients eligible to curative surgical intervention
NCT05286320	March 28, 2022	Ib/II	SBRT	Lenvatinib/ pembrolizumab	27	Safety rate ORR PFS OS
NCT03753659 (IMMULAB)	May 9, 2019		RFA MWA Brachytherapy TACE	Pembrolizumab	30	ORR OS TTR Incidence and severity of adverse events

RT, radiotherapy; RE, radioembolization; SBRT, stereotactic body radiation therapy; PR, pathological response; TACE, transcatheter arterial chemoembolization; RR, response rate; ORR, overall response rate; MW, microwave ablation; MTD, maximum tolerated dose; TTR, time to response; PFS, progression-free survival; AEs, adverse events; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; EBRT, external beam radiotherapy; PDL-1, programmed cell death ligand 1.

Discussion

Current studies have demonstrated the role of RT in potentiating and modulating the tumor immunity. With emerging clinical evidence supporting the use of RT in combination with immunotherapy, there is a need to discuss and analyze their effects from the standpoint of toxicity and safety. Here, we present a systematic retrospective database analysis highlighting six consecutive cases of HCC patients receiving concomitant checkpoint inhibition and RT. Immunotherapy in combination with antiangiogenic therapy is considered the standard first-line treatment choice for treating HCC patients [29]. Locoregional therapies hold numerous potentials to act synergistically or in combination with immunotherapy to produce more efficient results in HCC patients. Although many clinical trials are currently investigating the synergistic combination of RT and ICI, few results have been published. A summary of ongoing clinical trials using this combination is outlined in Table 2.

To our knowledge, this is the first study describing the clinical courses of concomitant checkpoint inhibition and radiation therapy in patients with HCC. The combination therapy did not raise safety concerns, i.e., an increased rate of adverse effects of the respective irradiated tissue, and gave a good efficacy signal for patients with limited disease progression.

Brachytherapy irradiation has a favorable dose deposition with little radiation scattering and minor off-target parenchymal tissue damage. Nevertheless, a small area of irradiation of surrounding hepatic parenchyma occurs. This may provoke local autoimmune phenomena and ultimately induction of checkpoint hepatitis may be plausible. In HCC patients, the liver function is additionally limited due to frequently underlying cirrhosis or fibrosis; therefore, triggering autoimmune hepatitis in the context of liver disease may more frequently lead to worsening of liver function up to liver failure. In 4 patients receiving seven local RT treatments, no autoimmune hepatitis occurred, indicating only a limited immune sensitization due to RT of liver tissue in the context of checkpoint inhibition.

Stereotactic irradiation or intensity-modulated RT of other tissues may similarly provoke autoimmune processes. Few studies have investigated the adverse effects of combination concepts of irradiation and checkpoint inhibition. Welsh et al.'s [7] prospective clinical trial focused on non-melanoma carcinoma patients receiving a combination scheme of concurrent ipilimumab and stereotactic ablative RT with 50 or 60 Gy. In light of the various pretreated cancer entities, an acceptable overall disease control rate (26%) could be achieved. Interestingly, the study found that low-dose (5–10 Gy) irradiated lesions responded in 31% versus 5% of nonirradiated lesions. No grade 4–5 toxicities and only a few grade 3 toxicities were evident. The number of patients with liver diseases was not stated. However, only 1 HCC patient was included.

Various recent trials have also demonstrated the high safety and tolerance levels with little or no toxicity reactions in cancer patients that were treated with this multimodal combination. In a pooled analysis of patient data from prospective trials in the US Food and Drug Administration databases, Anscher et al. [30] found that patients with cancer receiving RT within 90 days prior to the start of ICI treatment did not have an increased risk for severe adverse events compared to those who did not receive RT. Similar results were also found in a multicenter safety analysis by Bang et al. [19] corroborating the safety of the combination. There were no significant differences in adverse events between those receiving RT during/after checkpoint inhibitors and before checkpoint inhibitors ($p = 0.053$), and between those receiving RT within 14 days or outside 14 days of checkpoint blockade ($p = 0.06$). Immune-related adverse events occurred in 39% of patients receiving RT with ICI, compared to 23% of patients who used RT only. All of these adverse events were mild, easily manageable, and were independent of the irradiated site. In a phase I trial recruiting 22 melanoma patients, Victor et al. reported no grade 4 toxicities when treated with ipilimumab in combination with RT (6 Gy × 2–3 or 8 Gy × 2–3 to one site). Grade 3 toxicities were reported in the form of anemia (4/22) and colitis (1/22) [6]. In another study, multiple regimens of RT (8.0–12.5 Gy, administered to 1–2 sites) and ipilimumab were used. There was only one case of grade 4 colitis, one grade 3 hypophysitis, skin rashes (4/22), and no other significant adverse results greater than grade 3 [31]. Tang et al. [32] also conducted a phase I trial in which doses of ipilimumab were administered in combination with SBRT (50 Gy in four fractions or 60 Gy in ten fractions) either sequentially or simultaneously. There were no grade 4 or 5 toxicities found in patients, while 12 patients out of 35 showed grade 3 toxicities.

The scarcity of severe toxicities in these studies mirrors our observations. In our study, 3 patients received in total five radiation treatments. Despite irradiation of abdominal masses, cerebral mass, or bone masses with off-target volumes in either abdominal organs or the lung, no severe colitis, pneumonitis, or other severe adverse effect was triggered. The use of dual ICI with brachytherapy also seems to be well-tolerated (patients 1 and 4).

The manifestation of brain metastasis in HCC patients generally causes severe complications and is associated with poor prognosis and a survival rate of less than 4 weeks. Our patient 2, which has been previously reported by Ye et al. [33] was a proof of concept of the efficacy of sorafenib and nivolumab in combination with RT in aHCC with brain metastasis. After treatment, a profound durable response in terms of shrinkage of metastatic lesions and a major decline in the number of alphafetoprotein was observed in the patient. The patient remained in remission for >5 years until today. Our results therefore favor the utilization of combination therapy for potentially controlling the presence of brain metastasis in aHCC.

An appropriate escalation concept should address the subset of patients with limited systemic progression upon checkpoint inhibition [25]. Our analysis showed that the 2 patients with extensive HCC tumor load (patients 4 and 6) did not show radiologic response after RT treatment, whereas the other 4 patients, who had only few progressive metastases, could be well addressed with local RT, and subsequently showed a good local control.

This analysis has several limitations. First, the numbers of patients are very limited. The HCC patients were heterogeneous, as they had disease limited to the liver or extrahepatic disease. In addition, different RT techniques were used. These data leads to the hypothesis that concomitant radiation therapy may be applied in HCC patients with oligoprogression and that this combination therapy should be evaluated in a prospective clinical study setting.

Further research is needed to validate the best-suited RT regimens and the optimal dose given in conjunction with ICI. It is also of utmost importance to evaluate late toxicity and immune-related responses. Further understanding of the patient factors associated with toxicities is needed for risk stratification, to minimize their effects, and to tailor personalized treatments.

Conclusion

The results of our case series indicate a good efficacy of concomitant RT and checkpoint inhibition with a favorable safety profile. Further investigations should evaluate the safety, the appropriate clinical context, and efficacy of this combination therapy.

Statement of Ethics

Data collection and retrospective analysis of patient information were anonymized in accordance with the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of the Ludwig-Maximilians-University (LMU) Munich, Germany, approval number (18-604). As this was a retrospective study, the need for informed consent was waived by the Ethics Committee of the University Hospital LMU Munich.

Conflict of Interest Statement

M.S. has received travel support from Ipsen, EISAI, and Roche and research funding by Ipsen. D.R. had received advisory fees from Bayer, speaker fees from Ipsen, and travel support from Ipsen and Bayer. F.P.R. has received honoraria for lectures and travel support from the Falk Foundation, Gilead, Ipsen, and Novartis. A.T. received advisory fees and honoraria from Roche. A.T. received grants from the Sino-German Center for Research Promotion (Grant No. GZ-1546 and C-0012), the State Ministry of Baden-Wuerttemberg for Sciences, Research and Arts supporting the Clinical Cooperation Unit Healthy Metabolism at the Center for Preventive Medicine and Digital Health (grant identifier: CCU Healthy Metabolism), the Foundation for Biomedical Alcohol Research (grant identifier: N/A), and the Baden-Wuerttemberg center for digital early disease detection and prevention (grant identifier: BW-ZDFP). E.D.T. has served as a paid consultant for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co., MSD, Mallinckrodt, Omega, Pfizer, IPSEN, Terumo, and Roche. He has received reimbursement of meeting attendance fees and travel expenses from ArQule, AstraZeneca, BMS, Bayer, Celsion, and Roche, and lecture honoraria from BMS and Falk. He has received third-party funding for scientific research from ArQule, AstraZeneca, BMS, Bayer, Eli Lilly, IPSEN, and Roche. M.S., research grants: SIRTEX Medical and Bayer Healthcare; lecture honoraria: Bayer Healthcare, Cook, Balt, Boston Scientific, LIAM, and SIRTEX Medical; and advisory board: Bayer Healthcare, Siemens Healthineers, and AstraZeneca. S.C. has received research grants from Elekta, ViewRay, and Brainlab and speaker fees/travel support from Elekta, ViewRay, C-RAD, Roche, and Brainlab.

Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

Conception and design of the study: Stefan Munker, Osman Öcal, Jens Ricke, Max Seidensticker, and Maximilian Niyazi. Acquisition, analysis, and interpretation of data: Daniel Rössler, Najib Ben-Khaled, Liangtao Ye, Ignazio Piseddu, and Jakob Vielhauer. Drafting of the manuscript: Kathrin Bernhart, Isaac Rodriguez, Florian P. Reiter, and Stefanie Corradini. Critical revision of the manuscript: Liangtao Ye, Ignazio Piseddu, Jakob Vielhauer, Jens Ricke, Andreas Teufel, Enrico N. De Toni, and Maximilian Niyazi. Final approval of the manuscript: Stefan Munker, Daniel Rössler, Osman Öcal, Jakob Vielhauer, Florian P. Reiter, Andreas Teufel, Enrico N. De Toni, Max Seidensticker, Maximilian Niyazi, and Stefanie Corradini. Guarantor of the study: Stefan Munker, Enrico N. De Toni, Max Seidensticker, and Maximilian Niyazi.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282–96.

2 Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. J Clin Oncol. 2020;38(36):4317–45.

3 Onuma AE, Zhang H, Huang H, Williams TM, Noonan A, Tsung A. Immune checkpoint inhibitors in hepatocellular cancer: current understanding on mechanisms of resistance and biomarkers of response to treatment. Gene Expr. 2020;20(1):53–65.

4 De Toni EN. Immune checkpoint inhibitors: use them early, combined and instead of TACE? Gut. 2020;69(10):1887–8.

5 Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021;18(8):525–43.

6 Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520(7547):373–7.

7 Welsh JW, Tang C, de Groot P, Naing A, Hess KR, Heymach JV, et al. Phase II trial of ipilimumab with stereotactic radiation therapy for metastatic disease: outcomes, toxicities, and low-dose radiation–related abscopal responses. Cancer Immunol Res. 2019;7(12):1903–9.

8 Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol. 2016;13(8):516–24.

9 Walter F, Fuchs F, Gerum S, Rottler MC, Erdelkamp R, Neumann J, et al. HDR brachytherapy and SBRT as bridging therapy to liver transplantation in HCC patients: a single-center experience. Front Oncol. 2021;11:717792.

10 Ricke J, Wust P. Computed tomography – guided brachytherapy for liver cancer. in: Seminars in radiation oncology. Elsevier; 2011.

11 Keam SP, Halse H, Nguyen T, Wang M, Van Kooten Losio N, Mitchell C, et al. High dose-rate brachytherapy of localized prostate cancer converts tumors from cold to hot. J Immunother Cancer. 2020;8(1):e000792.

12 Domankevich V, Cohen A, Efrati M, Schmidt M, Rammensee HG, Nair SS, et al. Combining alpha radiation-based brachytherapy with immunomodulators promotes complete tumor regression in mice via tumor-specific long-term immune response. Cancer Immunol Immunother. 2019;68(12):1949–58.

13 Llovet JM, De Baere T, Kulik L, Haber PK, Greten TF, Meyer T, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021;18(5):293–313.

14 Li G, Wang J, Hu W, Zhang Z. Radiation-induced liver injury in three-dimensional conformal radiation therapy (3D-CRT) for postoperative or locoregional recurrent gastric cancer: risk factors and dose limitations. PLoS One. 2015;10(8):e0136288.

15 Schefter TE, Kavanagh BD, Timmerman RD, Cardenes HR, Baron A, Gaspar LE. A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. Int J Radiat Oncol Biol Phys. 2005;62(5):1371–8.
16 Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, et al. Radiation-associated liver injury. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl l):S94–100.
17 Dawson LA, McGinn CJ, Normolle D, Ten Haken RK, Walker S, Ensminger W, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol. 2000;18(11):2210–8.
18 Shanker MD, Liu HY, Lee YY, Stuart KA, Powell EE, Wigg A, et al. Stereotactic radiotherapy for hepatocellular carcinoma: expanding the multidisciplinary armamentarium. J Gastroenterol Hepatol. 2021;36(4):873–84.
19 Bang A, Dawson LA. Radiotherapy for HCC: ready for prime time? JHEP Rep. 2019;1(2):131–7.
20 Feng M, Suresh K, Schipper MJ, Bazzi L, Ben-Josef E, Matuszak MM, et al. Individualized adaptive stereotactic body radiotherapy for liver tumors in patients at high risk for liver damage: a phase 2 clinical trial. JAMA Oncol. 2018;4(1):40–7.
21 Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RKS, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;31(13):1631–9.
22 Bauer U, Gerum S, Roeder F, Münch S, Combs SE, Philipp AB, et al. High rate of complete histopathological response in hepatocellular carcinoma patients after combined transarterial chemoembolization and stereotactic body radiation therapy. World J Gastroenterol. 2021;27(24):3630–42.
23 Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med. 2006;203(5):1259–71.
24 Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS. Safety of combining radiotherapy with immune-checkpoint inhibition. Nat Rev Clin Oncol. 2018;15(8):477–94.
25 Varayathu H, Sarathy V, Thomas BE, Mufti SS, Naik R. Combination strategies to augment immune check point inhibitors efficacy-implications for translational research. Front Oncol. 2021;11:559161.
26 Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–90.
27 El-Khoueiry A, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492–502.
28 Vogel A, Goetze T, Hausner G, Geissler M, Siegler G, Weikersthalet LFV, et al. The IMMULAB trial: a phase II trial of immunotherapy with pembrolizumab in combination wit local ablation for patients with early stage hepatocellular carcinoma (HCC). Wolters Kluwer Health; 2021.
29 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–905.
30 Anscher MS, Arora S, Weinstock C, Amatya A, Bandaru P, Tang C, et al. Association of radiation therapy with risk of adverse events in patients receiving immunotherapy: a pooled analysis of trials in the US Food and drug administration database. JAMA Oncol. 2022;8(2):232–40.
31 Hiniker SM, Reddy SA, Maecker HT, Subrahmanyam PB, Rosenberg-Hasson Y, Swetter SM, et al. A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma. Int J Radiat Oncol Biol Phys. 2016;96(3):578–88.
32 Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, et al. Ipilimumab with stereotactic ablative radiation therapy: phase I results and immunologic correlates from peripheral T cells. Clin Cancer Res. 2017;23(6):1388–96.
33 Ye L, Zhang C, Seidensticker M, Mayerle J, Reiter FP, De Toni EN. Durable Complete Response of Brain Metastasis From Hepatocellular Carcinoma On Treatment With Nivolumab and Radiation Treatment. Am J Gastroenterol. 2020;115(12):2114–2116.