A Comparison of Radiotherapy with Radiotherapy plus Surgery for Brain Metastases from Urinary Bladder Cancer

Analysis of 62 Patients

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Purpose: To evaluate the role of radiotherapy (RT) and prognostic factors in 62 patients with brain metastases from transitional cell carcinoma (TCC) of the urinary bladder.
Patients and Methods: 62 patients received either RT (n = 49), including whole-brain radiotherapy (WBRT) and/or stereotactic radiosurgery (SRS), or surgery (OP) combined with WBRT (n = 13). Overall survival (OS), intracerebral control (ICC) and local control (LC) were retrospectively analyzed. Six potential prognostic factors were assessed: age, gender, number of brain metastases, extracerebral metastases, recursive partitioning analysis (RPA) class, and interval from tumor diagnosis to RT.
Results: Median OS and ICC for the entire cohort were 9 and 7 months. No significant difference between RT and OP + RT was found for OS ($p = 0.696$) and ICC ($p = 0.996$). On multivariate analysis, improved OS was associated with lack of extracerebral metastases ($p < 0.001$) and RPA class ($p < 0.001$), and ICC with the latter ($p < 0.001$). SRS-incorporating RT resulted in 1-, 2-, and 3-year LC probability of 78%, 66%, and 51%. No association between LC and any of the potential prognostic factors was observed. The results of the subgroup RPA class analyses were similar to the entire cohort.
Conclusion: Patient outcome for the RT-alone arm was not significantly different from OP + RT. SRS-incorporating treatment offers excellent LC rates. RPA class and the presence of extracerebral metastases demonstrated a significant prognostic role for survival. The latter should be used as stratification factors in randomized trials and can help define the cohort of patients that may benefit from more aggressive therapies.

Key Words: Brain metastases · Radiosurgery · Bladder cancer · Prognostic factors

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Vergleich von Strahlentherapie und Strahlentherapie plus Chirurgie bei Gehirnmetastasen eines Harnblasenkarzinoms. Analyse von 62 Patienten

Ziel: Die Rolle der Strahlentherapie (RT) von Patienten (n = 62) mit Gehirnmetastasen eines Urothelkarzinoms der Harnblase sowie prognostische Faktoren wurden ermittelt.
Patienten und Methodik: Von 62 Patienten erhielten 49 eine Ganzhirnbestrahlung (WBRT), gefolgt von einem stereotaktischen Boost oder einer alleinigen stereotaktischen Radiochirurgie (SRS). 13 Patienten erhielten eine Resektion (OP), gefolgt von einer WBRT. Gesamtüberleben sowie intrazerebrale und lokale Kontrolle wurden retrospektiv analysiert. Alter, Geschlecht, Metastasenanzahl, extrazerebrale Metastasierung, RPA-Klassifizierung (rekursive Partitionsanalyse) und Zeitintervall zwischen Diagnosestellung und RT wurden als potentielle prognostische Faktoren untersucht.
Ergebnisse: Medianes Gesamtüberleben und intrazerebrale Kontrolle betrugen 9 und 7 Monate. Ein signifikanter Unterschied zwischen RT und RT + OP hinsichtlich des Gesamtüberlebens ($p = 0,696$) und der intrazerebralen Kontrolle ($p=0,996$) konnte nicht festgestellt werden. In der multivariaten Analyse war ein verlängertes Gesamtüberleben mit fehlender extrazerebraler Metastasierung ($p < 0,001$) und der RPA-Klassenzugehörigkeit ($p < 0,001$) assoziiert. Die intrazerebrale Kontrolle ($p < 0,001$) war mit der RPA-Klassenzugehörigkeit ($p < 0,001$) assoziiert. Die lokalen 1-, 2- und 3-Jahres-Kontrollraten betrugen 78%, 66% und 51%; ein prognostischer Faktor dafür konnte nicht ermittelt werden.

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Schlussfolgerung: Es fanden sich keine signifikanten Unterschiede zwischen alleiniger RT (WBRT ± SRS) und OP + WBRT. Sah das therapeutische Konzept eine SRS vor, waren hervorragende Kontrollraten zu erzielen. RPA-Klassifizierung und das Fehlen von extrazerebralen Metastasen haben prognostische Auswirkung auf das Gesamtüberleben. Weitergehende Studien sollten eruieren, wer von einer aggressiveren Therapie profitiert.

Schlüsselwörter: Gehirnmetastasen · Radiochirurgie · Harnblasenkarzinom · Prognostische Faktoren

Introduction

Brain metastases occur in up to 50% of patients with transitional cell carcinoma (TCC), especially muscle-invasive, and account for approximately 1% of the 170,000 new cases diagnosed each year [6, 22, 33], even though detailed epidemiologic data are lacking. It is estimated that in the USA, 12,500 deaths a year occur due to metastatic bladder cancer [1]. Previous studies have reported a median survival of 2–7 months, whereby whole-brain radiotherapy (WBRT) constituted the main palliative treatment [3, 11, 32, 33]. Importantly, scarce reports on survival times > 7–8 months included mainly patients with single lesions [3, 33].

Several groups have indicated that stereotactic radiosurgery (SRS) can be a useful alternative approach for the treatment of patients with brain metastases, with local control (LC) and overall survival (OS) rates comparable to those of surgery (OP), in certain cases [4, 5, 25, 29]. In TCC patients with cerebral lesions, the role of SRS remains unknown. Furthermore, the majority of the cases reported in the literature were based on a small number of patients (Table 1). The latter poses a barrier in getting a better understanding of the precise role of RT and prognostic factors and whether optimization of the current protocols is needed.

Considering its malignant nature and poor outcome [21], an aggressive therapeutic approach for TCC brain metastases would be reasonable. Identifying certain subgroups of patients who may benefit from a multimodal treatment seems a meaningful approach. In the present study, we investigated the correlation of recursive partitioning analysis (RPA) class with the different therapeutic approaches (RT vs. RT + OP) for OS and intracerebral control (ICC) in 62 patients with TCC who developed brain metastases. Furthermore, six important clinical parameters for outcome were analyzed with the aim to detect potential clinical factors for the selection of the appropriate therapy.

Patients and Methods

Patient Characteristics

Between 1996 and 2007, 62 patients were treated with either (1) radiotherapy (RT, n = 49), including WBRT (n = 32) and/or SRS (n = 17), or (2) OP combined with WBRT (n = 13). SRS was performed for lesions with a diameter of ≤ 3 cm [4, 35]. Further inclusion criteria were: diagnosis of metastases by computed tomography (CT) and/or magnetic resonance imaging (MRI), no prior therapy to the brain and administration of steroids.

The development of new cerebral lesions constitutes the primary reason of treatment failure in the majority of brain metastases. We, therefore, focused on whether the therapeutic modality could increase ICC and prolong survival. OS was measured from the initial diagnosis of brain metastases. Follow-up was based on clinical and MRI and/or CT scan (initially 3 months after RT, then every 6 months) data. Details of the patient characteristics are summarized in Table 2.

Additionally, we evaluated the following potential prognostic factors for OS and ICC: age (< 61 vs. ≥ 61 years), gender, number of brain metastases (up to three vs. more than

Table 1. Treatment of brain metastases in urinary bladder cancer patients: literature overview. OP: surgical resection; RT: radiotherapy.

Tabelle 1. Literaturübersicht über die Behandlung von Gehirnmetastasen bei Patienten mit Harnblasenkarzinomen. OP: Operation; RT: Bestrahlung.

Authors	Patients (n)	Brain lesions (n)	Previous treatment	Treatment for brain lesions	Median survival (months)
Anderson et al. [3]	9	Single: 7 Multiple: 2	RT + chemotherapy	OP + RT vs. RT (vs. steroid: 1 patient)	27 vs. 2 (vs. 1)
Dhote et al. [11]	8	Single: 6 Multiple: 2	Chemotherapy (MVAC)	OP + RT vs. RT	7 vs. 2.8
Bloch et al. [9]	2	Single	RT	OP + RT	8
Salvati et al. [34]	6	Single	RT ± chemotherapy	OP + RT	5.5
Kabalin et al. [18]	4	Single	Chemotherapy (CMV)	OP + RT vs. RT	4 vs. 4
Rosenstein et al. [33]	19	Single: 13 Multiple: 6	Chemotherapy (MVAC)	OP + RT vs. RT	19 vs. 6
Protzel et al. [26]	1	Multiple	Chemotherapy	OP + RT + gemcitabine	15
Reddy et al. [32]	7	Not specified	Not specified	OP + RT (2 patients) vs. RT	Not specified
Lehmann et al. [22]	1	Single	Chemotherapy	OP	Not specified

Table 2. Patient characteristics of the treatment groups. OP: surgical resection; RPA: recursive partitioning analysis; RT: radiotherapy.

Tabelle 2. Patientencharakteristika der Behandlungsgruppen. OP: Operation; RPA: rekursive Partitionsanalyse; RT: Bestrahlung.

	Entire cohort n = 62 n (%)	RT n = 49 n (%)	OP + RT n = 13 n (%)
Age			
• < 61 years	31 (50)	22 (45)	9 (70)
• ≥ 61 years	31 (50)	27 (55)	4 (30)
Gender			
• Female	31 (50)	25 (51)	6 (46)
• Male	31 (50)	24 (49)	7 (54)
Number of brain metastases			
• ≤ 3	16 (25)	14 (28)	6 (46)
• > 3	46 (75)	35 (72)	7 (54)
Extracerebral metastases			
• Yes	53 (85)	37 (75)	6 (46)
• No	9 (15)	12 (25)	7 (54)
RPA class			
• I	11 (17)	8 (16)	5 (39)
• II–III	51 (83)	41 (84)	8 (61)
Interval from tumor diagnosis to radiotherapy			
• > 16 months	27 (43)	18 (37)	7 (54)
• ≤ 16 months	35 (57)	31 (63)	6 (46)
Chemotherapy			
• Yes	50 (80)	38 (77)	8 (61)
• No	12 (20)	11 (23)	5 (39)

three), extracerebral metastases (yes vs. no), RPA class (I vs. II–III), and interval from tumor diagnosis to RT (≤ 16 vs. > 16 months; Table 2). LC rates were analyzed as well. We performed a separate subgroup analysis to compare the different treatments for OS and ICC in regard to RPA.

Radiotherapy Planning and Treatment

SRS technique was performed as previously described [16, 17] and the dose prescribed was according to the RTOG criteria [4, 35]. The doses to the organs at risk were taken into consideration accordingly [13]. WBRT regimen and dose have been also described before [12].

Patients received their first follow-up 3 months post-RT and thereafter based on their clinical symptomatology to exclude recurrence and radiation side effects. The toxicity was evaluated using the Common Toxicity Criteria 2.0 (National Cancer Institute, Bethesda, MD, USA) for early toxicity [37], and the RTOG criteria for late toxicity [10].

Statistical Analysis

Statistical analysis of the data was performed as recently described [12].

Results

The median OS times for RT and OP + RT were 8.9 and 9.6 months, respectively. The median OS for the entire cohort amounted to 9 months. The 1-year, 2-year, and 3-year survival rates from the onset of brain metastases were 17%, 11%, and 8%, respectively.

The impact of potential prognostic factors on survival is shown in Table 3 (univariate analysis). Improved OS was significantly associated with age < 61 years ($p = 0.025$), lack of extracranial metastases ($p < 0.001$), and RPA class I ($p < 0.001$). No difference between RT and OP + RT was noted ($p = 0.696$; Figure 1). Similarly, the WBRT schedule had no significant impact on OS. In the RT-only arm, a trend toward better survival was noted for those patients (n = 17) who received SRS ($p = 0.051$). The factors that were significant in the univariate analysis were included in multivariate analyses. Of those, lack of extracerebral metastases (risk ratio [RR]: 1.90; 95% confidence interval [CI]:

Table 3. Results of the univariate analysis of survival. OP: surgical resection; RPA: recursive partitioning analysis; RT: radiotherapy.

Tabelle 3. Ergebnisse der univariaten Analyse für das Gesamtüberleben. OP: Operation; RPA: rekursive Partitionsanalyse; RT: Bestrahlung.

At	6 months (%)	12 months (%)	18 months (%)	24 months (%)	p-value
Therapeutic regimen					
• RT (n = 49)	32	16	12	12	0.696
• RT + OP (n = 13)	39	24	23	8	
Age					
• < 61 years	48	22	19	16	0.025
• ≥ 61 years	20	13	10	6	
Gender					
• Female	33	16	13	10	
• Male	41	23	16	13	0.730
Number of brain metastases					
• ≤ 3	50	19	15	12	
• > 3	26	18	3	2	0.880
Extracerebral metastases					
• Yes	23	2	0	0	
• No	68	53	47	37	< 0.001
RPA class					
• I	90	81	73	64	
• II–III	20	2	1	0	< 0.001
Interval from tumor diagnosis to radiotherapy					
• > 16 months	51	40	22	17	
• ≤ 16 months	40	31	23	11	0.189
Chemotherapy					
• Yes	36	22	15	14	
• No	29	12	12	12	0.689

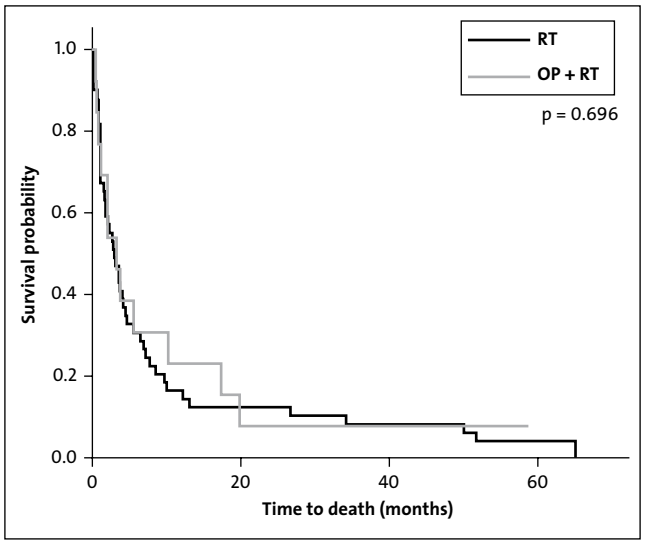

Figure 1. Comparison of radiotherapy, including whole-brain radiotherapy (WBRT) and/or stereotactic radiosurgery (SRS), with surgery (OP) plus WBRT regarding overall survival.

Abbildung 1. Vergleich zwischen Ganzhirnbestrahlung (WBRT) und/oder stereotaktischer Radiochirurgie (SRS) und Resektion (OP) plus WBRT hinsichtlich des Gesamtüberlebens.

1.09–3.29; $p < 0.001$) and RPA class (RR: 15.3; 95% CI: 4.0–5.7; $p < 0.001$) remained significant, while age < 61 years lost significance ($p = 0.396$).

Recurrence anywhere in the brain after treatment was observed in 18 patients (29%) after a median interval of 7 months. The 1-year, 2-year and 3-year ICC rates from the onset of brain metastases were 11%, 10%, and 8%, respectively. On univariate analysis, no significant difference ($p = 0.996$) in ICC was detected between RT and OP + RT (Table 4, Figure 2). Similarly, in the RT-only arm, SRS did not provide any ICC advantage ($p = 0.357$). Again, lack of extracerebral metastases and RPA class I significantly affected ICC (both $p < 0.001$) on univariate analysis. However, on multivariate analysis, only RPA class I showed statistical significance (RR: 7.45; 95% CI: 2.27–24.41; $p = 0.001$).

16 patients (26%) were diagnosed with a local recurrence after a median of 7 months. Of this group, twelve (19% of total) were treated with SRS and four (6% of total) received WBRT. Of the patients that developed a recurrence, four received 24 Gy (including two that underwent SRS in two and three different regions, respectively), seven 18 Gy, and one patients 15 Gy, while three patients and one patient received 10×3 Gy and 20×2 Gy WBRT, respectively.

Patients treated only with RT incorporating SRS had a 1-, 2-, and 3-year LC probability of 78%, 66%, and 51%.

No significant association between LC and any of the potential prognostic factors was noted.

Results of univariate subgroup analyses performed separately for RPA class I and II–II patients are shown in Table 5.

Table 4. Results of the univariate analysis of intracerebral control. OP: surgical resection; RPA: recursive partitioning analysis; RT: radiotherapy.

Tabelle 4. Ergebnisse der univariaten Analyse für die intrazerebrale Kontrolle. OP: Operation; RPA: rekursive Partitionsanalyse; RT: Bestrahlung.

At	6 months (%)	12 months (%)	18 months (%)	24 months (%)	p-value
Therapeutic regimen					
• RT (n = 49)	27	12	12	12	0.996
• RT + OP (n = 13)	23	15	8	8	
Age					
• < 61 years	39	16	13	13	0.036
• ≥ 61 years	13	6	6	6	
Gender					
• Female	23	10	7	7	
• Male	26	13	13	13	0.614
Number of brain metastases					
• ≤ 3	25	6	0	0	
• > 3	26	13	13	10	0.503
Extracerebral metastases					
• Yes	13	0	0	0	
• No	89	89	67	56	< 0.001
RPA class					
• I	72	64	54	54	
• II–III	13	0	0	0	< 0.001
Interval from tumor diagnosis to radiotherapy					
• > 16 months	47	37	21	16	
• ≤ 16 months	39	30	21	12	0.543
Chemotherapy					
• Yes	26	10	8	8	
• No	25	17	17	17	0.551

Regarding OS, the results of the subgroup analyses were similar to the results of the entire cohort. OS was not affected by any of the two arms investigated, neither in RPA class I ($p = 0.728$) nor in RPA class II–III patients ($p = 0.861$). Similar results were revealed for ICC, both in RPA class I ($p = 0.276$) and RPA class II–III patients ($p = 0.539$).

Grade 3 acute toxicities (alopecia, nausea, vomiting, headache) occurred in 3% of patients treated with RT only and in 4–5% of the OP + RT arm. Grade 3 late toxicities (headache, neurocognitive deficits, visual/hearing impairment) were observed in 4% of patients treated with RT and in 5–6% of the OP + RT group.

Discussion

Despite the previous underestimation, brain metastases represent an important sequel of TCC [21]. Even though a radioresistant role for brain metastases has not been clearly defined

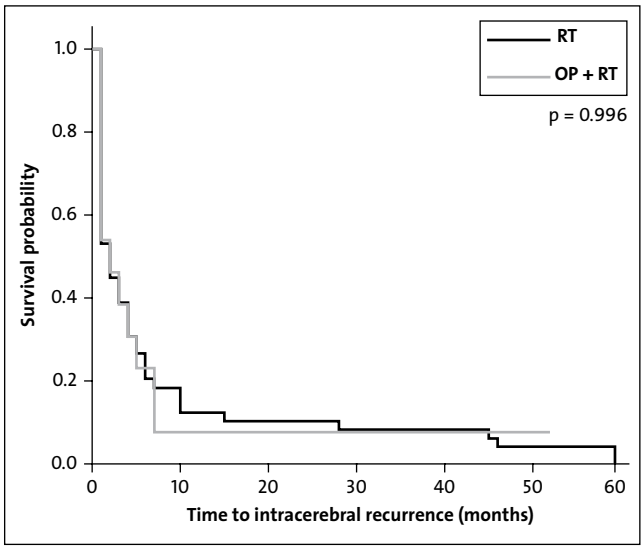

Figure 2. Comparison of radiotherapy, including whole-brain radiotherapy (WBRT) and/or stereotactic radiosurgery (SRS), with surgery (OP) plus WBRT regarding intracerebral control.

Abbildung 2. Vergleich zwischen Ganzhirnbestrahlung (WBRT) und/oder stereotaktischer Radiochirurgie (SRS) und Resektion (OP) plus WBRT hinsichtlich der intrazerebralen Kontrolle.

in metastatic TCC, patients with multiple metastases receiving only WBRT have a survival of 2–4 months [9, 11, 33]. In our study, only five of the 32 patients that were treated with WBRT alone for multiple cerebral secondaries were alive 12 months after RT. The median OS for the entire cohort was 9 months, and the 1-, 2-, and 3-year survival rates from the onset of brain metastases were 17%, 11%, and 8%, respectively. OS rates between RT (WBRT and/or SRS) and RT + OP were not statistically different, indicating the potential of SRS in treatment of brain lesions.

The advent of new chemotherapy agents and the implementation of SRS in the treatment of brain metastases have stressed the importance of identifying prognostic factor [4, 23, 25, 27, 29]. In TCC patients with cerebral secondaries, however, and to the authors' best knowledge, no data exist regarding this issue, probably due to the small number of patients previously studied (Table 1).

RPA class has been shown by many authors to be of prognostic significance in patients with secondary brain tumors [4, 5, 14, 29]. In line with this, RPA class I was the major determinant of survival in our series. OS was associated with age < 61 years and lack of extracranial metastases, which is in accordance with other reports [4, 29–31]. Notably, an important retrospective study has previously identified Karnofsky performance status and lack of visceral secondaries as prognostic factors for survival in TCC patients with systemic metastases, but individuals with known brain metastases were excluded from this work [7].

Table 5. Subgroup analyses of the different RPA classes for survival and intracerebral control of treated metastase(s) in regard to the impact of the therapeutic regimen. OP: surgical resection; RPA: recursive partitioning analysis; RT: radiotherapy.

Tabelle 5. Subgruppenanalysen beider RPA-Klassen für das Gesamtüberleben und die intrazerebrale Kontrolle der behandelten Metastase(n) in Bezug auf den Einfluss des Behandlungsregimes. OP: Operation; RPA: rekursive Partitionsanalyse; RT: Bestrahlung.

Survival at	**6 months (%)**	**12 months (%)**	**18 months (%)**	**24 months (%)**	**p-value**
RPA class I					
• RT (n = 8)	100	88	75	75	0.728
• RT + OP alone (n = 3)	100	33	33	33	
RPA class II–III					
• RT (n = 41)	19	3	0	0	0.861
• RT + OP (n = 10)	20	10	10	0	
Intracerebral control at	**6 months (%)**	**12 months (%)**	**18 months (%)**	**24 months (%)**	**p-value**
RPA class I					
• RT (n = 8)	88	75	62	62	0.276
• RT + OP alone (n = 3)	33	33	33	33	
RPA class II–III					
• RT (n = 41)	14	0	0	0	0.539
• RT + OP (n = 10)	20	0	0	0	

WBRT has been applied mainly for palliative purposes, while the exact role of SRS in the treatment of brain metastases from TCC remains unknown. In the present work, a trend toward better survival was noted for the 17 patients who received SRS, in the RT-only arm (p = 0.051). This is probably due to the fact that SRS was applied in individuals with both limited and multiple cerebral lesions (the latter in combination with WBRT). Additionally, SRS-incorporating RT resulted in 1-year LC probability of 78%. Therefore, SRS represents a valuable alternative choice in certain patients [25, 35] characterized by a high LC response rate and low morbidity, as in our present work. Previous analyses have demonstrated a clear LC and, in some cases, OS benefit for SRS in patients with a limited number of brain metastases [2, 23, 25, 28–30]. Whether SRS would demonstrate a survival advantage if only applied in TCC patients with few brain secondaries (up to three) in our institute, remains a speculation and a higher number of patients are required to clarify this issue.

The RPA parameter is a key determinant of patient survival [15, 28, 29]. Our subgroup analysis of RPA for OS revealed findings similar to our entire cohort. Neither RT nor RT + OP improved OS or ICC in RPA class I and II–III patients. This is the first time that a subgroup analysis of the dif-

ferent RPA classes is performed in TCC patients with brain metastases.

The OP-incorporating arm did not show any benefit regarding OS, ICC, or LC. Nevertheless, one should bear in mind that SRS cannot be applied for bulky lesions [35]. Therefore, the value of surgical resection for the treatment of large metastases or those causing mass effects with > 1 cm midline shift and severe acute neurological deficits should not be underestimated [19].

TCC of the bladder is a chemosensitive malignancy [8]. The widely applied regimen of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) during the 1980s prolonged patients' survival up to 14 months and resulted in a slight increase in the reported cases of patients with brain secondaries [36]. In recent years, gemcitabine combined with cisplatin has substituted the older MVAC and it is now considered the chemotherapy of choice, because it provided similar response rates associated with less hematologic and mucous toxicity [20, 21, 38]. Notably, in the majority of prospective or retrospective analyses that assessed the efficacy of chemotherapy in metastatic TCC, patients with brain metastases were either not reported or excluded from the studies [8, 20–22, 38]. In consequence, the role of chemotherapy remains unclear. In our retrospective study, chemotherapy did not show any benefit for OS ($p = 0.689$) nor for ICC ($p = 0.551$). This is in line with the majority of previous studies, with non-small cell lung cancer comprising the only exception [24]. However, the retrospective nature of the present study limits the ability to draw firm conclusions.

Grade 3 acute toxicities were found in 3% of patients treated with RT only and in 4–5% of the OP + RT arm. Grade 3 late toxicities occurred in 4% of patients treated with RT and in 5–6% of OP + RT group, which is in line with previous reports [4, 5, 19, 28, 29].

We acknowledge that different factors could potentially influence the present analysis of this retrospective study and bias cannot be excluded.

Conclusion

Cerebral metastases in TCC patients remain a lethal disease. No difference in OS or ICC was noted between the RT-alone arm in comparison with OP + RT. The results were confirmed in a subgroup analysis for the different RPA classes. SRS is a valuable, effective tool and offers excellent LC. RPA I class and the lack of extracerebral metastases were identified as the most useful independent prognostic factors for TCC patients with brain metastases. The identification factors can help stratify patients for more aggressive therapy in selected trials.

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