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Cranial Radiotherapy for Prostate Cancer Patients With Brain Metastases Inaccessible to Stereotactic Radiotherapy

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Abstract. *Background/Aim: To evaluate patients and treatment characteristics as well as clinical outcome in patients with intracranial metastases from prostate cancer (PCA) treated with palliative radiotherapy. Patients and Methods: Fifteen patients treated for intracranial metastases of PCA were identified. The median age of patients was 69 years. 80% of patients received whole brain radiotherapy and 20% received partial brain radiotherapy. Clinical outcome was assessed. Univariate analysis was performed to analyze the impact of patient specific parameters on survival. Results: There was no >G2 acute or any late toxicity. Median time from the first diagnosis of PCA to first diagnosis of intracranial metastases was 62 months (range=15-160 months). Median survival from first diagnosis of intracranial metastases was 14 weeks (range=0-126 weeks) and 6 weeks (range=0-47 weeks) from the start of radiotherapy. In univariate analysis, survival was significantly better for patients with an Eastern Cooperative Oncology Group (ECOG) performance status 1 compared to ECOG 2-3 [18 weeks (range=5-47 weeks) vs. 3 weeks (range=0-21 weeks), p=0.030] and Recursive Partitioning Analysis (RPA) class 2 compared to RPA class 3 [18 weeks (range=5-47 weeks) vs. 6 weeks (range=0-21 weeks), p=0.045]. Conclusion: Overall survival of the patients with wide-spread intracranial metastases from PCA was poor. The decision for a radiotherapy should be done on individual patient basis.*

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Prostate cancer is one of the most common types of cancer with almost 1,500,000 new cases worldwide (1). Cranial metastases are rare with an estimated 0.16-0.7% of all prostate cancer patients developing parenchymal or meningeal metastases during the course of their disease (2, 3). Brain metastases occur late in the course of treatment with an estimated median time from first diagnosis of prostate cancer to the first diagnosis of brain metastases of 29-82 months (3-6).

Survival after the diagnosis of brain metastases is poor with a median survival from radiotherapy of 1-4 months (2, 3, 7) and only few case series of selected patients reporting a longer median survival of 10-16 months (4, 8, 9). In those case series, patients were treated with stereotactic radiotherapy or a combination of whole brain radiotherapy, stereotactic radiotherapy, surgery or further systemic therapy. With improved survival of castration resistant metastatic prostate cancer patients due to effective systemic treatments (10-14), the question remains, whether there will be an increase in prostate cancer patients presenting with advanced disease and intracranial metastases requiring effective local treatment.

Radiotherapy with palliative intent is an established local treatment option in patients with brain metastases but outcome data regarding toxicity and survival is scarce in prostate cancer patients with brain metastases due to the low incidence (2-9, 15-17). We therefore conducted this retrospective analysis of prostate cancer patients treated with palliative radiotherapy for intracranial metastases.

Patients and Methods

Patient characteristics. We retrospectively reviewed patient records of all patients treated with palliative radiotherapy for intracranial metastases in our department from 02/2010 until 02/2021 (*n*=716). We identified 15 patients that were treated for intracranial metastases from prostate cancer between 06/2014 and 02/2021. The median age of the patients was 63 years at first diagnosis and 69 years at the time of cranial radiotherapy. All but one patient presented with a high-risk (according to the D'Amico classification)

Table I. *Patient characteristics (n=15).*

	Median	Range
Age at first diagnosis (years)	63	51-90
Age at cranial RT (years)	69	55-91
	N	%
Histology		
Adenocarcinoma	13	86.7
Neuroendocrine carcinoma	1	6.7
Unknown	1	6.7
Initial D'Amico risk group		
Low risk	1	6.7
Intermediate risk	0	0
High risk	14	93.3
Gleason score		
≤7	3	20
8	5	33.3
≥9	6	40
Unknown	1	6.7
Initial M status		
M0	7	46.7
M1	7	46.7
Unknown	1	6.7
Initial local treatment of primary		
RPE with LND	5	33.3
Palliative Radiotherapy	3	20
No local treatment (ADT)	7	46.7
Other sites of metastases at diagnosis of brain metastases		
Bone only	5	33.3
Bone and visceral	10	66.7
Pattern of cranial metastases		
≥10 parenchymal metastases	4	26.7
Meningeosis carcinomatosa	11	73.3
ECOG at RT		
1	6	40
≥2	8	53.3
Unknown	1	6.7
RPA class at RT		
2	6	40
3	7	46.7
Unknown	2	13.3

Table II. *Treatment characteristics.*

	N	%
Target volume		
Partial brain RT	3	20
WBRT	12	80
Fractionation (planned)		
3 Gy×10	11	73.3
4 Gy×5	4	26.7
RT completed		
Yes	13	86.7
No	2	13.3
Steroid use at RT		
Yes	10	66.7
No	5	33.3
Lines of systemic therapy at intracranial RT		
1-2	2	13.3
3-4	4	26.7
≥5	9	60

tumor at first diagnosis. The vast majority of patients had adenocarcinoma (86.7%), one patient had a neuroendocrine carcinoma in the prostate and the histological subtype of one patient with prostate carcinoma was unknown. The 80% of patients had a tumor with a Gleason score of 8 or higher.

Upon cranial radiotherapy, 73.3% of patients presented with meningeosis carcinomatosa, the other 26.7% had multiple parenchymal metastases inaccessible to stereotactic radiotherapy. The 66.7% of patients had very advanced disease with visceral metastases at the time of diagnosis of cranial metastases and 53.3% had an Eastern Cooperative Oncology Group (ECOG) performance status 2 to 3. Recursive partitioning analysis (RPA) class was also rather unfavorable with all patients having a RPA class of 2 to 3. All but one patient were symptomatic from their cranial metastases. Common symptoms at diagnosis of intracranial metastases included sensory deficits (*n*=3), cranial nerve paresis (*n*=3), dizziness (*n*=3), gait disturbance (*n*=3), motor deficits (*n*=3), nausea (*n*=3) and headache (*n*=3). Further patient characteristics are shown in Table I.

Treatment characteristics. All patients referred for cranial radiotherapy had received at least one line of systemic therapy. The 93.3% of patients had received ADT as first systemic treatment and at least one line of chemotherapy in the later disease course. The 6.7% received several lines of chemotherapy. The 80% of patients had also received a second-line ADT (abiraterone acetate or enzalutamide) during the course of their disease. Three patients (20%) received enzalutamide within three months of the cranial radiotherapy. Another three patients (20%) received abiraterone acetate within three months of cranial radiotherapy. Overall, patients had received multiple lines of systemic therapy at the time of cranial radiotherapy with a median of five lines of systemic therapy (range=1-8).

Unfortunately, all patients were inaccessible to stereotactic radiotherapy. In 80% of patients whole brain radiotherapy (WBRT) was conducted and in 20% partial cranial radiotherapy was attempted to avoid WBRT. The majority (73.3%) had a fractionation of 3 Gy×10, the remaining 26.7% received 4 Gy×5. Only 86.7% of patients were able to complete the intracranial radiotherapy. In 13.3% treatment had to be stopped prematurely due to a rapid decline in performance status. Treatment related information is summarized in Table II.

Endpoints and statistical analysis. Toxicity was scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Toxicity was defined as either acute (<12 weeks after RT) or late (>12 weeks after RT) toxicity. Overall survival was calculated according to the Kaplan-Meier method calculated from the first day of irradiation until death or last follow-up. Univariate analysis using the log-rank test was performed to

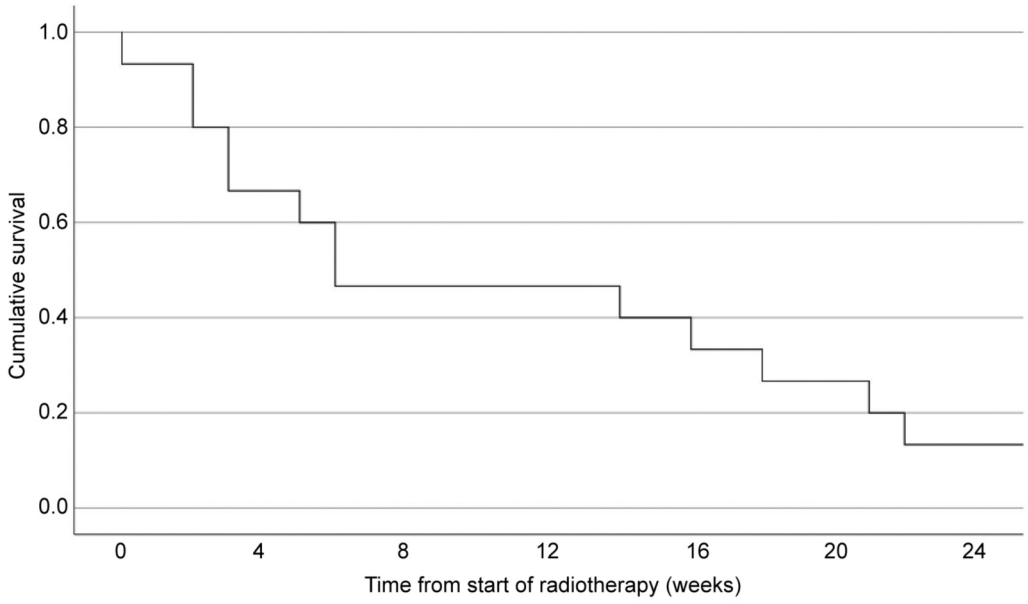

Figure 1. *Survival from the start of cranial radiotherapy (n=15).*

evaluate the influence of the presence of meningeosis carcinomatosa, ECOG performance status score (1 *vs*. 2-3), recursive partitioning analysis (RPA) class and the time from first diagnosis of prostate cancer to the first diagnosis of brain metastases (≤62 months *vs*. >62 months). This analysis was approved by the responsible ethics committee of the Canton of Zurich. Statistical analyses were performed with IBM SPSS statistics 25 (Statistical Package for Social Sciences, International Business Machines Corp., Armonk, NY, USA).

Results

Toxicity. Overall, the intracranial radiation therapy was well tolerated. No >G2 acute toxicity events were reported. Low grade acute toxicity was reported in nine patients. Six patients reported low grade treatment related fatigue, one of them grade 2. Alopecia ≤grade 2 was reported by four patients and four patients reported radiation dermatitis, one of them grade 2 in the ear canal. There was no reported late toxicity.

Survival. Median time from first diagnosis of prostate cancer to first diagnosis of intracranial metastases was 62 months (range=15-160 months). Median survival from first diagnosis of intracranial metastases was 14 weeks (range=0-126 weeks). Median survival from start of radiotherapy was 6 weeks (range=0-47 weeks). At 3 months after radiotherapy, seven patients were still alive. At 6 months after therapy, only two patients remained alive. Figure 1 shows the survival from the start of radiotherapy for all patients.

Univariate analysis. There was no significant difference in survival for patients with or without meningeosis carcinomatosa [6 weeks (range=0-47 weeks) *vs*. 6 weeks (range=3-29 weeks), p=0.900] or regarding the time from prostate cancer diagnosis to the diagnosis of intracranial metastases [14 weeks (range=3-29 weeks) *vs*. 3 weeks (range=0-47 weeks), p=0.421]. Survival was significantly better for patients with an ECOG score of 1 compared to an ECOG score of 2-3 [18 weeks (range=5-47 weeks) *vs*. 3 weeks (range=0-21 weeks), p=0.030] and RPA class 2 compared to RPA class 3 [18 weeks (range=5-47 weeks) *vs*. 6 weeks (range=0-21 weeks), p=0.045].

Discussion

Intracranial metastases in prostate cancer patients are rare and associated with a poor prognosis (2, 3, 7). The largest case series with 103 patients from the M. D. Anderson Cancer Center published by Tremont-Lukats *et al*. reported a median survival of patients of 4 months if treated with cranial radiotherapy and only 1 month in untreated patients (3).

Also in our analysis, survival was very poor with a median survival from first diagnosis of cranial metastases of 14 weeks and just 6 weeks from the start of radiotherapy. Only 47% of patients lived longer than 3 months after the start of treatment. In two patients (13.3%), palliative radiotherapy had to be terminated early due to a decline in performance status. This survival is quite poor compared to published data with a median survival of up to 16 months (3-6, 8, 9).

Data on patients treated with surgical resection and WBRT or stereotactic radiotherapy show longer survival but there is likely a selection bias regarding performance status and number of cranial metastases. In our analysis, the patients had a high parenchymal or meningeal tumor load as well as visceral metastases, thus none were accessible for stereotactic radiotherapy. The majority of patients had an ECOG performance status of 2-3 (53.3%). 80% received WBRT and the remaining 20% received partial brain irradiation with a palliative dose for symptomatic metastases in attempt to avoid WBRT. Therefore, survival in this cohort with a very advanced disease is likely to be worse than in selected patients with few cranial metastases. Another aspect might be the high amount of patients with adenocarcinoma in this analysis (86.7%). Tremont-Lukats *et al*. suggested poorer outcome for brain metastases of adenocarcinoma with a median survival of 1 month compared to prostate cancer of other histological subtypes with a median survival of 6 months (3).

Further factors that were associated with survival were performance status, RPA class, the use of cranial radiotherapy in cohorts including untreated patients and the time from prostate cancer diagnosis to diagnosis of brain metastases or WBRT (3, 18, 19). Better performance status and lower RPA class were also associated with improved survival in this analysis. However, the time from prostate cancer diagnosis to diagnosis of intracranial metastases did not significantly affect survival.

Another aspect to discuss in this context is the applied treatment dose for cranial radiotherapy. Prostate cancer is considered rather radioresistant with 2-Gy equivalent treatment doses to the primary in the curative setting of up to 79.2 Gy for normofractionated treatment or greater than 80 Gy when treated with stereotactic body radiotherapy (SBRT) (20-22). A treatment dose of 4 Gy×5 fractions or even 3 Gy×10 fractions might not be sufficient to achieve local control of the cranial metastases. Stereotactic radiotherapy with the advantage to deliver a high local treatment dose very precisely might be beneficial in this case. However, not all patients qualify for stereotactic cranial radiotherapy. In the present cohort, all patients were inaccessible due to the size of individual lesions or the overall cranial tumor load.

Overall, patient selection for palliative radiation treatment seems to be of the essence in this cohort. While treatment was overall well tolerated with no >G2 treatment related toxicities, median survival after palliative radiotherapy was short with only half of the patients surviving more than 3 months. Therefore, many patients were under treatment or even hospitalized for a relevant part of their remaining lifetime. In symptomatic patients, conventional cranial radiotherapy might still be warranted for symptom relieve but an impact on overall survival is at least questionable. Unfortunately, due to the short survival and loss of close follow up, as many patients received best supportive care after RT, a comprehensive analysis of possible beneficial effects of cranial radiotherapy was not possible in this cohort. For patients with brain metastases from non-small cell lung cancer (NSCLC), the phase III QUARTZ trial suggests that WBRT provides little clinically significant benefit in patients unsuitable for surgical resection or stereotactic radiotherapy (23). As no study has compared best supportive care and WBRT for patients with brain metastases from prostate cancer, the decision for conventional cranial radiotherapy should be done individually based on the patient's prognosis, symptoms and treatment goals.

The limitations of this analysis lie within its retrospective nature and the limited patient number resulting in limited statistical power to detect associations between outcome and the examined factors. Also, due to the short overall survival the follow-up in this cohort is short, which limits for example the possibility to analyze treatment related late toxicity. Still, this retrospective analysis may offer clinical guidance for the challenging care of these patients.

In conclusion, overall survival of patients with cranial metastases from prostate cancer was poor in this analysis. Patients with a worse performance status and higher RPA class had a significantly shorter survival. Notably, patients in this analysis had very advanced disease with a high cranial tumor load. The decision for conventional cranial radiotherapy with palliative intent should be performed on individual patient basis and within a multidisciplinary team, ideally including a specialized palliative care team.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conceptualization, C.S. and R.F.; methodology, C.S.; formal analysis, C.S.; investigation, C.S.; resources, D.Z.; data curation, C.S, J.L..; writing—original draft preparation, C.S.; writing—review and editing, P.W.; visualization, C.S.; supervision, R.F.; project administration, D.Z. All Authors have read and agreed to the published version of the manuscript.

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References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *71(3)*: 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660

2 Hatzoglou V, Patel GV, Morris MJ, Curtis K, Zhang Z, Shi W, Huse J, Rosenblum M, Holodny AI and Young RJ: Brain metastases from prostate cancer: an 11-year analysis in the MRI era with emphasis on imaging characteristics, incidence, and prognosis. J Neuroimaging *24(2)*: 161-166, 2014. PMID: 23279641. DOI: 10.1111/j.1552-6569.2012.00767.x

3 Tremont-Lukats IW, Bobustuc G, Lagos GK, Lolas K, Kyritsis AP and Puduvalli VK: Brain metastasis from prostate carcinoma: The M. D. Anderson Cancer Center experience. Cancer *98(2)*: 363-368, 2003. PMID: 12872358. DOI: 10.1002/cncr.11522

4 Kim SH, Chao ST, Toms SA, Vogelbaum MA, Barnett GH, Suh JH and Weil RJ: Stereotactic radiosurgical treatment of parenchymal brain metastases from prostate adenocarcinoma. Surg Neurol *69(6)*: 641-6; discussion 646, 2008. PMID: 18262258. DOI: 10.1016/j.surneu.2007.05.035

5 Lawton A, Sudakoff G, Dezelan LC and Davis N: Presentation, treatment, and outcomes of dural metastases in men with metastatic castrate-resistant prostate cancer: a case series. J Palliat Med *13(9)*: 1125-1129, 2010. PMID: 20836637. DOI: 10.1089/jpm.2009.0416

6 McCutcheon IE, Eng DY and Logothetis CJ: Brain metastasis from prostate carcinoma: antemortem recognition and outcome after treatment. Cancer *86(11)*: 2301-2311, 1999. PMID: 10590371. DOI: 10.1002/(sici)1097-0142(19991201)86:11<2301::aid-cncr18>3.0.co;2-d

7 Bhambhvani HP, Greenberg DR, Srinivas S and Hayden Gephart M: Prostate cancer brain metastases: a single-institution experience. World Neurosurg *138*: e445-e449, 2020. PMID: 32147556. DOI: 10.1016/j.wneu.2020.02.152

8 De Placido S, Rescigno P, Federico P, Buonerba C, Bosso D, Puglia L, Izzo M, Policastro T and Di Lorenzo G: Cabazitaxel in castration resistant prostate cancer with brain metastases: 3 case reports. World J Clin Cases *2(6)*: 228-231, 2014. PMID: 24945013. DOI: 10.12998/wjcc.v2.i6.228

9 Flannery T, Kano H, Niranjan A, Monaco EA 3rd, Flickinger JC, Lunsford LD and Kondziolka D: Stereotactic radiosurgery as a therapeutic strategy for intracranial metastatic prostate carcinoma. J Neurooncol *96(3)*: 369-374, 2010. PMID: 19609490. DOI: 10.1007/s11060-009-9966-5

10 de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI and COU-AA-301 Investigators: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med *364(21)*: 1995-2005, 2011. PMID: 21612468. DOI: 10.1056/NEJMoa1014618

11 de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, Kramer G, Eymard JC, Bamias A, Carles J, Iacovelli R, Melichar B, Sverrisdóttir Á, Theodore C, Feyerabend S, Helissey C, Ozatilgan A, Geffriaud-Ricouard C, Castellano D and CARD Investigators: Cabazitaxel *versus* abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med *381(26)*: 2506-2518, 2019. PMID: 31566937. DOI: 10.1056/NEJMoa1911206

12 Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, Ivashchenko P, Demirhan E, Modelska K, Phung, Krivoshik A and Sternberg CN: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med *378(26)*: 2465-2474, 2018. PMID: 29949494. DOI: 10.1056/NEJMoa1800536

13 Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen DC, Hoskin P, Bottomley D, James ND, Solberg A, Syndikus I, Kliment J, Wedel S, Boehmer S, Dall'Oglio M, Franzén L, Coleman R, Vogelzang NJ, O'Bryan-Tear CG, Staudacher K, Garcia-Vargas J, Shan M, Bruland ØS, Sartor O and ALSYMPCA Investigators: Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med *369(3)*: 213-223, 2013. PMID: 23863050. DOI: 10.1056/NEJMoa1213755

14 Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin ME, Higano CS, de Souza P, de Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A, Rathkopf DE and COU-AA-302 Investigators: Abiraterone acetate plus prednisone *versus* placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol *16(2)*: 152-160, 2015. PMID: 25601341. DOI: 10.1016/S1470-2045(14)71205-7

15 Bartscht T and Rades D: Predicting survival after whole-brain irradiation for cerebral metastases from prostate cancer. Anticancer Res *34(8)*: 4357-4360, 2014. PMID: 25075071.

16 Gzell CE, Kench JG, Stockler MR and Hruby G: Biopsy-proven brain metastases from prostate cancer: a series of four cases with review of the literature. Int Urol Nephrol *45(3)*: 735-742, 2013. PMID: 23666549. DOI: 10.1007/s11255-013-0462-7

17 Salvati M, Frati A, Russo N, Brogna C, Piccirilli M, D'Andrea G, Occhiogrosso G, Pichierri A and Caroli E: Brain metastasis from prostate cancer. Report of 13 cases and critical analysis of the literature. J Exp Clin Cancer Res *24(2)*: 203-207, 2005. PMID: 16110752.

18 Dziggel L, Schild SE, Veninga T, Bajrovic A and Rades D: Clinical factors asssociated with treatment outcomes following whole-brain irradiation in patients with prostate cancer. In Vivo *31(1)*: 35-38, 2017. PMID: 28064217. DOI: 10.21873/invivo.11021

19 Nguyen T, Bartscht T, Schild SE and Rades D: Performance status is associated with survival in elderly patients irradiated for cerebral metastases from prostate cancer. Anticancer Res *40(3)*: 1665-1668, 2020. PMID: 32132072. DOI: 10.21873/anticanres.14117

20 Chen LN, Suy S, Uhm S, Oermann EK, Ju AW, Chen V, Hanscom HN, Laing S, Kim JS, Lei S, Batipps GP, Kowalczyk K, Bandi G, Pahira J, McGeagh KG, Collins BT, Krishnan P, Dawson NA, Taylor KL, Dritschilo A, Lynch JH and Collins SP: Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. Radiat Oncol *8*: 58, 2013. PMID: 23497695. DOI: 10.1186/1748-717X-8-58

21 King CR, Brooks JD, Gill H and Presti JC Jr: Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys *82(2)*: 877-882, 2012. PMID: 21300474. DOI: 10.1016/j.ijrobp.2010.11.054

22 Michalski JM, Moughan J, Purdy J, Bosch W, Bruner DW, Bahary JP, Lau H, Duclos M, Parliament M, Morton G, Hamstra D, Seider M, Lock MI, Patel M, Gay H, Vigneault E, Winter K and Sandler H: Effect of standard *vs*. dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: The NRG Oncology RTOG 0126 randomized clinical trial. JAMA Oncol *4(6)*: e180039, 2018. PMID: 29543933. DOI: 10.1001/jamaoncol.2018.0039

23 Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, Moore B, Brisbane I, Ardron D, Holt T, Morgan S, Lee C, Waite K, Bayman N, Pugh C, Sydes B, Stephens R, Parmar MK and Langley RE: Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet *388(10055)*: 2004-2014, 2016. PMID: 27604504. DOI: 10.1016/S0140-6736(16)30825-X

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