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Brief Correspondence

The Prognostic Importance of Metastatic Site in Men with Metastatic Castration-resistant Prostate Cancer

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Abstract

The presence of visceral metastases is adversely prognostic in men with metastatic castration-resistant prostate cancer (mCRPC), but the prognostic impact of the site of visceral metastasis is unclear. Men with mCRPC in the TAX 327 phase 3 trial receiving docetaxel or mitoxantrone every 3 wk or weekly docetaxel, each with prednisone, were analyzed retrospectively to study the impact of the site of visceral metastasis on overall survival (OS). Patients were assessed for OS by site of metastases: liver with or without other sites, lung with or without bone or lymph nodes, bone plus lymph nodes, bone only, and lymph nodes only. Cox proportional hazards regression, adjusted for treatment and stratification factors, was performed. Men with liver metastases with or without other metastases had shorter median OS (10.0 mo; 95% confidence interval [CI], 5.4–11.5) than men with lung metastases with or without bone or nodal metastases (median OS: 14.4 mo; 95% CI, 11.5–22.4). Men with lymph node-only disease had the best median OS (26.7 mo; 95% CI, 22.3–34.2), followed by men with bone-only metastases (median OS: 19.0 mo; 95% CI, 18.2–20.7) and bone-plus-node disease (median OS: 15.7 mo; 95% CI, 14.4–17.2). Thus, pattern of spread including site of visceral metastasis confers a differential prognostic impact. These data require validation and may inform trial design and therapy.

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Prognostic classifications assist in the estimation of survival in patients with metastatic castration-resistant prostate cancer (mCRPC) [1,2]. The Prostate Cancer Working Group 2 guidelines advocate reporting of outcomes based on the presence of bone, lymph node or soft tissue, or visceral metastases [3]. However, the relative survival of men stratified by metastatic site, including specific visceral metastatic sites, has not been reported. Visceral metastasis has assumed greater importance because some phase 3 clinical trials (investigating sipuleucel-T, radium-223, and abiraterone acetate in docetaxel-naïve men) have excluded such patients.

A CRPC nomogram and additional retrospective analyses in the context of first-line chemotherapy and recent risk stratifications in the context of postdocetaxel abiraterone acetate or enzalutamide specify liver metastasis as a poor prognostic factor, whereas other prognostic classifications have grouped all sites of visceral disease [1,4–6]. In this paper, we analyzed the TAX 327 trial to investigate the differential impact of site of metastasis on overall survival (OS).

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Table 1 – Overall survival and secondary outcomes

	Liver with or without other sites	Lung with or without bone/node	Bone plus node	Bone only	Node only
All patients					
Deaths, no. (%)	59 (88.1)	45 (90.0)	263 (92.0)	442 (83.7)	48 (75.0)
OS, median (95% CI), mo	10.0 (5.4–11.5)	14.4 (11.5–22.4)	15.7 (14.4–17.2)	19.0 (18.2–20.7)	26.7 (22.3–34.2)
1-yr OS (95% CI)	37.3 (25.9–48.7)	62.0 (47.1–73.8)	65.4 (59.6–70.6)	73.4 (69.4–77.0)	81.0 (68.9–88.7)
OS, HR (95% CI)	2.60 (1.97–3.44)	1.37 (1.00–1.86)	1.37 (1.17–1.60)	Reference	0.69 (0.51–0.93)
Patients receiving docetaxel every 3 wk					
Deaths, no. (%)	13 (76.5)	12 (80.0)	87 (93.6)	150 (82.9)	16 (72.7)
OS, median (95% CI), mo	13.8 (2.7–19.1)	16.7 (7.2–22.4)	18.3 (15.1–20.4)	20.8 (18.3–22.9)	26.1 (19.7–40.9)
1-yr OS (95% CI)	52.9 (27.6–73.0)	66.7 (37.5–84.6)	75.3 (65.2–82.8)	74.5 (67.4–80.2)	86.4 (63.4–95.4)
OS, HR (95% CI)	2.08 (1.15–3.75)	1.50 (0.82–2.73)	1.48 (1.13–1.93)	Reference	0.77 (0.46–1.30)
Secondary outcomes (all patients)					
≥50% PSA reduction	13/58 (22.4)	12/39 (30.8)	113/264 (42.8)	192/456 (42.1)	29/49 (59.2)
Pain response	7/31 (22.6)	3/23 (13.0)	38/129 (29.5)	78/261 (29.9)	8/17 (47.1)
WHO tumor response	3/51 (5.9)	2/27 (7.4)	18/215 (8.4)	2/57 (3.5)	12/55 (21.8)

CI = confidence interval; HR = hazard ratio; OS = overall survival; PSA = prostate-specific antigen; WHO = World Health Organization.

Primary results of the TAX 327 study were published previously [7]. Briefly, the TAX 327 study was a phase 3 clinical trial of 1006 men with mCRPC randomized to receive prednisone with either 75 mg/m^2 docetaxel every 3 wk (DP3), 30 mg/m^2 docetaxel weekly, or 12 mg/m^2 mitoxantrone every 3 wk. Treatment continued for up to 30 wk or until toxicity, progression, or death occurred.

Patient characteristics were summarized using descriptive statistics and grouped by site of metastases identified radiographically: liver with or without other sites, lung with or without bone or lymph nodes, bone plus nodes, bone only, and lymph node only. The Kaplan-Meier method was used to calculate the median and 1-yr OS estimates with 95% confidence intervals (CIs). Cox proportional hazards regression, adjusted for treatment received and trial stratum of baseline pain and Karnofsky performance status (KPS) ≥80% versus ≤70%, was performed to estimate the increased risk of death due to site of metastasis, along with the predefined subgroups. A multivariate analysis was also performed after adjusting for factors in the nomogram derived from the TAX 327 trial (other than liver metastasis, number of metastatic sites, and prostate-specific antigen [PSA] doubling time, which was available on only about two-thirds of patients), namely, treatment received, baseline pain, KPS, prior progression type (measurable disease, bone scan), PSA, tumor grade, alkaline phosphatase, and hemoglobin [1]. A secondary analysis was performed with patients who received DP3. Additional outcomes examined across metastatic groups were PSA response (≥50% decline), pain response, and radiographic response (among those evaluable per World Health Organization criteria). All tests were two-sided, and a p value of ≤0.05 was considered statistically significant by SAS v.9.2 (SAS Institute, Cary, NC, USA). No corrections were made for multiple significance testing.

Eleven patients without liver, lung, bone, or nodal metastases were excluded from all analyses. Sixty-seven patients had liver metastases with or without other sites, whereas 50 men had lung but not liver metastases with or without bone or nodes (Supplemental Table 1). Patients with lung metastases with or without bone or node metastases were significantly more likely ($p < 0.05$) to have a KPS ≥80% and a lower PSA than those with liver metastases with or without other sites. Patients with node-only metastasis tended to have less pain, lower PSA, and favorable alkaline phosphatase and hemoglobin.

Among all patients, men with liver metastases with or without other metastases had the worst median OS (10.0 mo; 95% CI, 5.4–11.5), followed by men with lung with or without bone or node metastases (median OS: 14.4 mo; 95% CI, 11.5–22.4) (Table 1). Men with node-only disease had the best median OS (26.7 mo; 95% CI, 22.3–34.2), followed by men with bone-only metastases (median OS: 19.0 mo; 95% CI, 18.2–20.7) and men with bone-plus-node disease (median OS: 15.7 mo; 95% CI, 14.4–17.2) (Fig. 1). One-year survival levels in relation to metastatic spread and hazard ratios (HRs) for death compared with the largest group (bone only) are also shown in Table 1: Those with liver metastases had a HR of 2.6 compared with 1.37 for

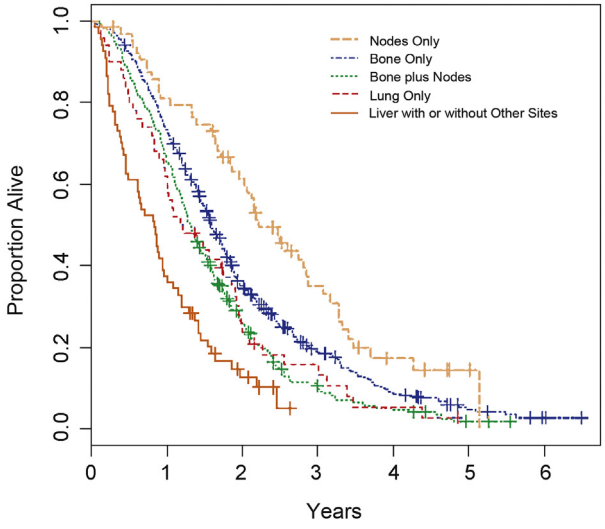

Fig. 1 – Kaplan Meier plot for overall survival for all patients, based on patterns of metastatic spread.