Assessing Time to Metastatic Disease as a Proxy for Overall Survival in a Real-World Pan-Tumor Cohort

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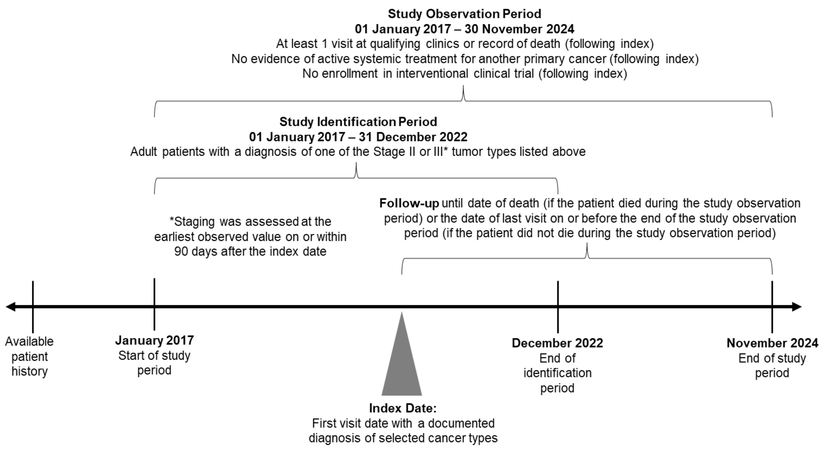
Background

- Overall survival (OS) is often utilized as a primary clinical outcome for oncology clinical trials and real-world evidence (RWE) studies but requires substantial follow-up, particularly in early-stage disease.
- Intermediate endpoints based on response assessments often require access to unstructured electronic health record (EHR) data. Alternatively, time from initial diagnosis to metastatic disease or death (TTMd) is widely available using structured EHR fields.
- To understand the potential of TTMd as a proxy endpoint, we assessed the relationship between TTMd and OS among patients with several solid tumor types in the community oncology setting.

Methods

- This was a retrospective cohort study of structured EHR data among patients diagnosed with Stage II or III disease of any of the following (**Figure 1**):
  1. Head & neck squamous cell carcinoma (HNSCC)
  2. Non-small cell lung cancer (NSCLC)
  3. Triple-negative breast cancer (TNBC)
  4. Hormone receptor-positive breast cancer (HR+BC)
  5. Gastric or gastroesophageal (GEJ) cancer
  6. Bladder cancer
  7. Renal cell carcinoma (RCC)
  8. Melanoma

Figure 1. Study design



- TTMd was defined as the interval between the index date (**Figure 1**) and the date of metastatic disease or death, censoring patients without evidence of an event at the last record date during the observation period.
- The relationship between TTMd and OS from index was assessed using:
  1. Kendall τ rank correlation, overall and by tumor type, with sensitivity analysis among patients with metastatic disease events
  2. Cox proportional hazards model of OS with metastatic disease as a time-dependent covariate, overall and by tumor type
  3. Landmark analysis of OS at 12 and 24 months from the index date by metastatic disease status, overall

Results

- Overall, 31,455 patients were included in the study (34%, HR+BC; 26% NSCLC, 13% TNBC, 9% bladder cancer, 8% melanoma, 5% HNSCC, 3% RCC, 2% gastric/GEJ cancer).
- In the cohort, 7,925 OS events were observed, and 8,808 TTMd events, of which 25% (n=2,241) were metastatic disease events.
- Median TTMd and OS ranged from 22–74 and 25–83 months, respectively, excluding BC where the median was not reached (**Figure 2**).
- Kendall's τ was 0.98 overall and ranged from 0.96 to 0.99 depending on the tumor type (**Table 1**). Among patients with metastatic disease events (n=2,241), Kendall's τ was 0.68 overall (range: 0.54–0.76 by tumor type).
- Metastatic disease events were associated with a significantly higher likelihood of death relative to no documentation of an event overall (HR: 3.91, 95% CI: 3.69–4.15, *P*<0.0001) and by tumor type (**Table 1**).

Figure 2. Kaplan-Meier analysis of (a) TTMd, and (b) OS by tumor type

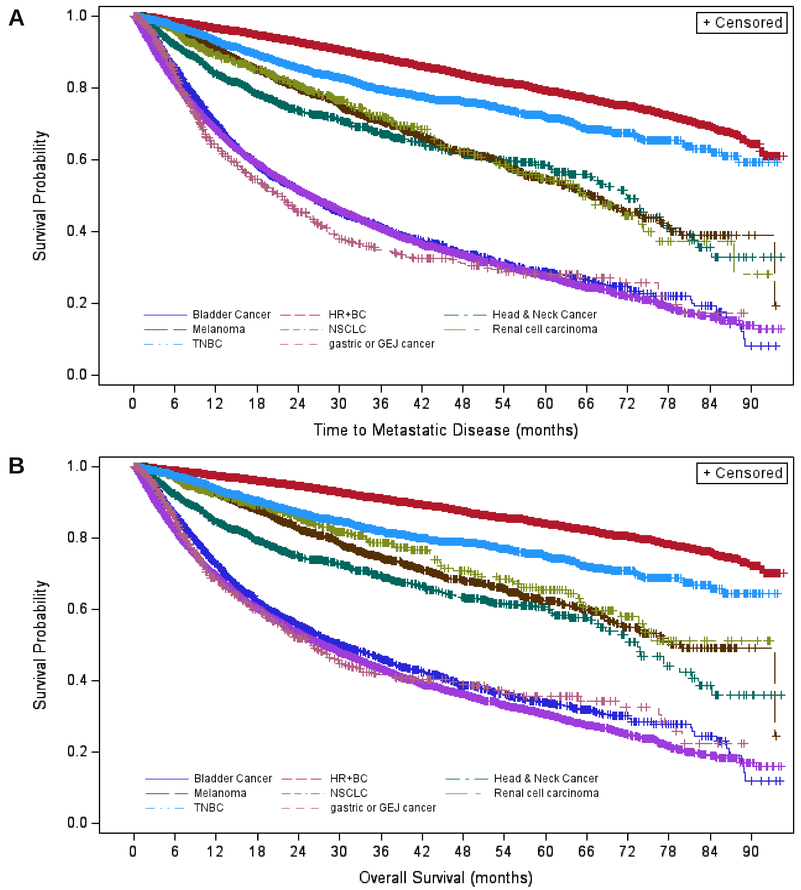
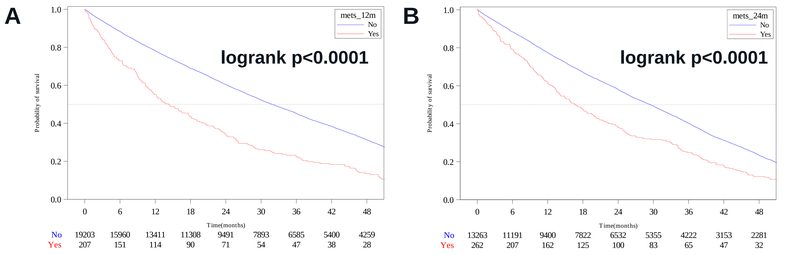


Table 1. Associations between TTMd and OS (months) by tumor type

Tumor Type	Median (95% CI) TTMd	Median (95% CI) OS	τ	HR (95% CI, P-value)
HNSCC	64.9 (59.5–68.1)	68.5 (65.0–72.0)	0.993	3.33 (2.13–5.20), *P*<0.0001)
NSCLC	31.3 (30.4–32.3)	34.6 (33.5–35.7)	0.985	2.09 (1.90–2.30), *P*<0.0001)
TNBC	NR (not reached)	NR	0.988	8.77 (7.36–10.45), *P*<0.0001)
HR+ BC	NR	NR	0.977	5.84 (5.07–6.73), *P*<0.0001)
Gastric/GEJ	21.9 (19.9–23.7)	25.2 (22.4–27.9)	0.958	2.25 (1.70–2.98), *P*<0.0001)
Bladder	35.2 (33.1–36.9)	40.5 (37.9–42.9)	0.968	2.58 (2.22–3.00), *P*<0.0001)
RCC	68.2 (65.2–73.1)	80.6 (75.7–NR)	0.965	3.30 (2.15–5.09), *P*<0.0001)
Melanoma	74.2 (71.4–77.7)	83.4 (79.4–93.4)	0.971	3.41 (2.72–4.28), *P*<0.0001)

- Median (95% CI) landmark OS at 12 & 24 months were 14.3 (11.4–18.1) & 16.7 (13.8–19.9) months in patients with a metastatic disease event and 31.9 (31.2–32.6) & 29.5 (28.8–30.1) months in patients without an event, respectively (**Figure 3**).

Figure 3. Landmark analysis of OS from (a) 12 months, and (b) 24 months post-index by TTMd (metastatic disease) event status



Limitations

- The study was limited to patients with evidence of Stage II or III disease within structured fields of the EHR. A longer duration of follow-up is needed to assess TTMd in patients with Stage 0 or I disease and/or early-stage breast cancer.
- Patients may have developed metastatic disease but did not have documentation in the database.

Conclusions

TTMd was nearly perfectly correlated with OS across multiple solid tumors and remained very strongly associated when limited to only metastatic disease events.

TTMd can be considered in RWE studies of early-stage cancer to advance an earlier understanding of patient prognosis.

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