Bias Characterization of Real-World Patients with and without Imaging in a Community Oncology Electronic Health Record-derived Database

Xinye Li[1], Benjamin Ackerman[1], Kelly Magee[1], Jonathan Kern[1], Katherine Tan[1]

[1] Flatiron Health, New York, NY

Background

Radiology imaging is critical to diagnose and monitor response to treatment for patients with cancer. Assessment of real-world response from electronic health record (EHR) documentation alone is reliant upon clinician documentation [1], which limits the ability to apply standardized measurements such as RECIST criteria. With the addition of real-world imaging, a more quantifiable assessment of changes in tumor burden may be possible [2]. However, real-world radiographic imaging data availability and timing for patients may vary due to facility capabilities, institutional standards, etc., and selecting real-world patients based on imaging availability may introduce biases, potentially impacting generalizability of results. Therefore, this study aimed to assess the representativeness of imaging-derived cohorts relative to a broader real-world oncology target population based on available patient baseline characteristics and endpoints.

Methods

Data source

- This study used the nationwide Flatiron Health EHR-derived de-identified Research Database (FHRD), a longitudinal database comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction [3&4].
- During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care).
- De-identified imaging metadata were retrospectively retrieved from the Picture Archiving and Communication System (PACS), available for selected practices from the FHRD.

Cohort selection, target population, and imaging samples

- Patients with advanced non-small cell lung cancer (aNCLC) and diffuse large B-cell lymphoma (DLBCL) were selected and further categorized as one of the three study samples. Please see Figure 1 for detailed definitions of target populations and imaging samples.

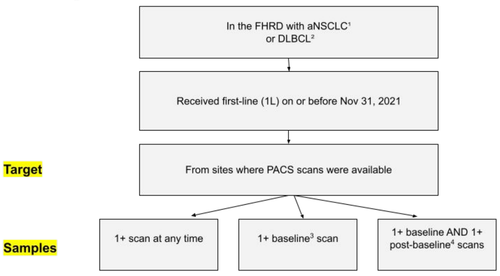
Patient characteristics

- Baseline characteristics: Demographics, biomarker status, clinical characteristics, treatment patterns, follow-up time
- Endpoints (using 1L initiation as index date)
  - Real-world overall survival (rwOS) for both aNSCLC and DLBCL cohorts
  - Real-world progression free survival (rwPFS) for aNSCLC cohort

Statistical analysis

- For each disease cohort (target from Figure 1), our comparisons were based on imaging availability at various time points (samples from Figure 1): any time point, baseline (pre-1L initiation), and post-baseline (during 1L duration).
- Differences in baseline demographic, clinical, and treatment characteristics between groups were measured through the absolute standardized mean difference (ASMD), with a threshold of 0.1 denoting a notable difference [5&6].
- Real-world Overall Survival (rwOS) and real-world Progression-Free Survival (rwPFS) endpoints between groups were compared through Kaplan-Meier estimates. Median survival estimates along with the 95% confidence intervals (CI) were reported.

Figure 1. Illustration of cohort selection



Disease-specific FHRD clinical I/E criteria

[1] aNSCLC:

- Inclusion
  - Diagnosed with with lung cancer (ICD-9 162.x or ICD-10 C34x or C39.9)
  - At least two documented clinical visits, on different days, occurring on or after January 1, 2011
  - Pathology consistent with NSCLC. Diagnosed with Stage IIIB, IIIC, IVA or IVB NSCLC on or after 1/1/2011, or diagnosed with early-stage NSCLC and subsequently develops recurrent or progressive disease on or after 1/1/2011.
- Exclusion
  - Lacking relevant unstructured documents in the FHRD for review by the abstraction team.

[2] DLBCL:

- Inclusion
  - Diagnosed with Non-Hodgkin's Lymphoma (ICD 9: 200x, 202x; ICD 10: C82x, C83x, C84x, C85x, C86x, C88x, C96x)
  - At least two documented clinical visits, on different days, occurring on or after January 1, 2011
  - Has evidence of DLBCL with an initial diagnosis date on or after January 1, 2011
- Exclusion
  - Lacking relevant unstructured documents in the FHRD for review by the abstraction team.

Scan timing definition

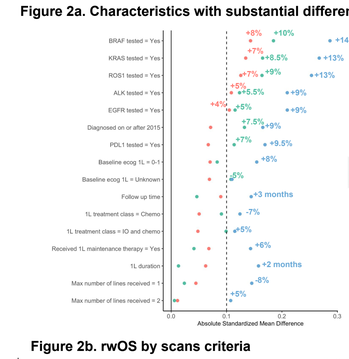
[3] Defined as a CT or PET-CT scan for aNSCLC patients, or PET-CT scan for DLBCL patients within 6 weeks prior to first line (i.e. 1L) initiation.

[4] Defined as a CT or PET-CT scan for aNSCLC patients, or PET-CT scan for DLBCL patients during 1L (non-maintenance portion only).

Results - aNSCLC

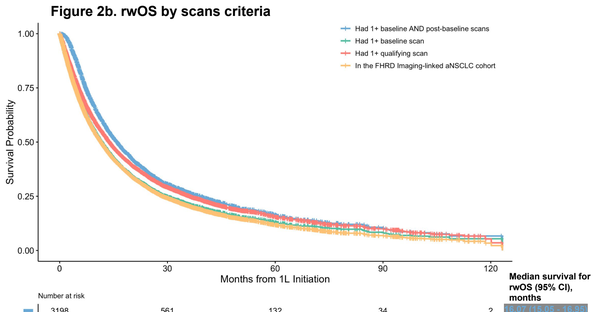
- A total of 11,056 patients met clinical IE criteria and were included in the FHRD imaging-linked aNSCLC target cohort. Of those, 7,493 patients had 1+ scan at any time, 4,619 patients had 1+ baseline scan, and 3,199 patients had 1+ baseline and 1+ post-baseline scans.
- Baseline characteristics compared to the aNSCLC target population
  - Higher biomarker testing rates and better data completeness in **all scans samples**
  - More recent diagnosis, a higher proportion of patients with lower ECOG performance scores among those **with a baseline scan (w/ or w/o a post-baseline scan)**
  - Longer follow-up time, longer 1L duration, more LOT received **if patients had both baseline and post-baseline scans**
- Real-world endpoints were similar between patients with 1+ baseline scan and the target population. The median survivals for both endpoints were slightly longer among patients with a scan at any time point (+2 months for rwOS, +0.5 months for rwPFS), and were significantly longer once post-baseline scans were required (+4.5 months for rwOS, +1 month for rwPFS).

Figure 2a. Characteristics with substantial differences (ASMD > 0.1)



Differences are provided when ASMD is > 0.1

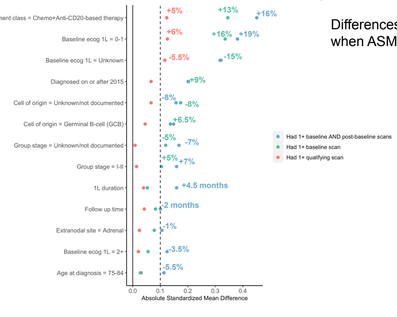
Figure 2b. rwOS by scans criteria



Results - DLBCL

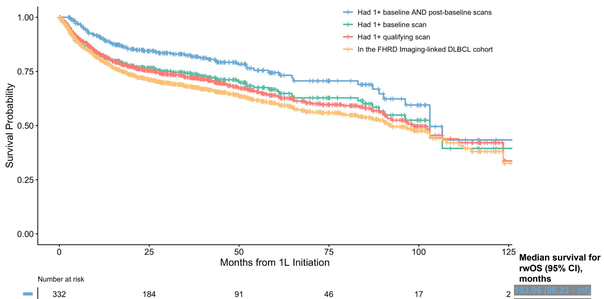
- A total of 1,323 patients met the clinical IE criteria and were included in the FHRD imaging-linked DLBCL target cohort. Of those, 932 patients had 1+ scan at any time, 454 patients had 1+ baseline scan, and 332 patients had 1+ baseline and 1+ post-baseline scans.
- Baseline Characteristics compared to the DLBCL target population
  - Less unknown and more patients with lower ECOG performance scores, more chemo and anti-cd20 therapy in 1L observed in **all scans samples**
  - More recent diagnosis, more with lower stage at diagnosis, more with germinal center B-cell-like (GCB) cell of origin for **patients with a baseline scan (w/ or w/o a post-baseline scan)**
- Patients with 1+ scan at any time point had similar median survival for rwOS compared to the target population. Longer median survivals were observed for patients with 1+ baseline scan (+10 months) or 1+ baseline and post-baseline scans (+10 months).

Figure 3a. Characteristics with substantial differences (ASMD > 0.1)



Differences are provided when ASMD is > 0.1

Figure 3b. rwOS by scans criteria



Conclusion

- Requiring scans at any time point or in the baseline window resulted in the cohort being similar to the broader real-world cohort with respect to baseline characteristics; however, median survival times trended longer for both rwOS and rwPFS endpoints.
- Requiring scans in the post-baseline window may introduce selection and immortal time bias. Patients with post-baseline scans appear healthier, as seen in the baseline characteristics and rwOS and rwPFS estimates.
- Effectively integrating real-world imaging into research studies requires an understanding of the representativeness of imaging-derived cohorts.
- Further work is needed to assess the application of existing methods to account for such selection and immortal bias in this context.

Reference

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