Health Resource Utilization Associated with Locoregional and Distant Recurrence in Patients with Non-metastatic Melanoma

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Background

- The mainstay treatment for non-metastatic melanoma is local excision of the tumor with wide margins, or lymph node surgery (i.e., dissection or lymphadenectomy) if regional lymph nodes are involved).[1]
- However, up to half of patients with non-metastatic melanoma will have a recurrence in their lifetime[2,3], with approximately 50% in regional lymph nodes, 20% local recurrences and 30% distant recurrences.[4]
- While a few studies analyzed HRU in patients with advanced/metastatic melanoma[5-9], there is a paucity of data on HRU related to recurrences, particularly locoregional ones.
- With the adjuvant treatment landscape likely to change dramatically this year with the approval of new therapies with better efficacy and safety,[10,11] payers need up-to-date information on HRU associated with locoregional and distant recurrences to guide their decisions.

Objective

- The study aimed to quantify HRU associated with locoregional (including node metastasis) and distant recurrence in patients with non-metastatic melanoma who underwent lymph node surgery.

Methods

Data Source

- The study used the Truven Health Analytics MarketScan® Commercial Claims and Encounters, and Medicare Supplemental databases (Truven) from January 1, 2008 to July 31, 2017
- Truven has data on more than 240 million unique patients since 1995 from approximately 100 employers and several health plans, and includes enrollment history, demographic variables, and claims for medical (provider and institutional) and pharmacy services
- Data are de-identified and comply with the confidentiality requirements of the Health Insurance Portability and Accountability Act

Sample Selection

- From January 2008 to July 2017, there were 265,421 patients with a melanoma diagnosis in the Truven database, of which 68,032 adult patients did not have an indicator of other primary cancer, and had >15 months of continuous healthcare coverage.
- Patients with a melanoma-related surgery (lymph node surgery; for a minority of cases, with a diagnosis of secondary malignancy in the lymph nodes surgical excision was also allowed) were selected, and patients with indicators of metastatic melanoma excluded.
- The study sample included 6,400 patients with non-metastatic melanoma who underwent surgery.

Study Design

- The study used a retrospective claims design. The study period spanned from the index surgery until the earliest date between end of eligibility (due to disenrollment or death), or end of data availability (Jul 31, 2017).
- Locoregional and distant recurrence episodes
  - Recurrences were identified based on post-surgery recurrence indicators derived from patterns of melanoma therapy (i.e., initiation of new pharmacotherapy, radiotherapy, or new skin excision/lymph node surgery) and secondary malignancy diagnoses.
  - Distant recurrences were distinguished from locoregional recurrences based on indicators that were specific to metastatic disease (e.g., new secondary malignancy codes; stereotactic radiotherapy; antineoplastic agents and regimens not listed as adjuvant therapies in the NCCN melanoma guidelines, including systemic therapies and ipilimumab before 2015)
  - Recurrence episodes were defined from 30 days prior to first indicator of a locoregional/distant recurrence to 30 days after last indicator for recurrence (locoregional recurrences) or end of follow-up (distant recurrences).
- HRU was (a) reported during episodes of locoregional/distant recurrence and (b) compared in the year post-recurrence between
  - patients with locoregional/distant recurrence(s) and
  - recurrence-free matched controls (1:1 matching on propensity scores percentiles,[12] insurance coverage with Medicare supplemental, and time between index lymph node surgery and beginning of first recurrence; among patients with at least 3 months of insurance coverage after the beginning of the first recurrence, a matched control was found for 950/977 patients with locoregional recurrence and 87/90 patients with distant recurrence)
- Patient baseline characteristics were measured in the six months before the index surgery and included demographics, melanoma tumor site, baseline HRU, the Quan-Charlson comorbidity index[13] (excluding cancer diagnosis) and a cancer-specific index[14] (excluding melanoma diagnosis).

Outcomes

- HRU outcomes, reported per 100 person-months, included:
  - All-cause HRU, by component: inpatient admission, inpatient days, emergency department admission), and outpatient visits including medication administration.
  - Melanoma-specific HRU in real world, defined as HRU associated with medical services for melanoma, including treatments (pharmacological: antineoplastic whether in NCCN guidelines or not, and other including injection of steroid, pain control medication, anesthesia [for surgery], surgery, radiotherapy) and disease monitoring.
- For the description of all-cause and melanoma-specific HRU during episodes of recurrence, all episodes were included (1,524 locoregional and 102 distant recurrence episodes) and a patient could contribute more than one locoregional recurrence episode. HRU was measured between the start and end date of the episodes of recurrence
- For the comparison of all-cause HRU between recurrence and recurrence-free cohorts, only the first recurrence episode was included for the recurrence cohorts. HRU was measured in the year after the first recurrence for the patients in the recurrence cohorts and in the year following a randomly selected index date for the recurrence-free cohorts

Statistical Analyses

- Descriptive analyses relied on frequencies and proportions for categorical variables and means (standard deviations) for continuous variables.
- For the comparison of the matched recurrence and recurrence-free cohorts non-parametric bootstrap procedure methods (B=549 resamples) were used to obtain the 95% confidence interval (CI) of the difference in HRU between cohorts, and the p-value.

Results

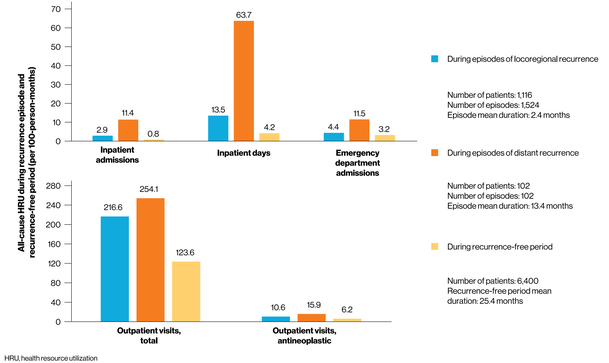
Table 1. Baseline Characteristics: Study Sample and Matched Recurrence and Recurrence-free Cohorts

	Study sample	Matched cohorts: locoregional recurrence		Matched cohorts: distant recurrence	
Variable	**N = 6,400**	**Recurrence N=950**	**Recurrence-free N=950**	**Recurrence N=87**	**Recurrence-free N=87**
BASELINE CHARACTERISTICS					
Age (years), Mean ± SD	53.8 ± 13.5	59.6 ± 13.2	59.6 ± 12.7	62.1 ± 12.9	61.0 ± 13.6
Females, N (%)	2,924 (45.7%)	370 (38.9%)	377 (39.7%)	32 (36.8%)	29 (33.3%)
Insurance plan type, N (%)					
Commercial insurance only	5,354 (83.7%)	689 (72.5%)	689 (72.5%)	55 (63.2%)	55 (63.2%)
Commercial insurance + Medicare supplemental	1,046 (16.3%)	261 (27.5%)	261 (27.5%)	32 (36.8%)	32 (36.8%)
All-cause HRU (per 100 person-months), Mean ± SD					
Number of inpatient admissions	0.7 ± 3.8	1.2 ± 4.7	1.0 ± 4.3	1.7 ± 5.7	1.5 ± 4.8
Number of inpatient days	3.2 ± 22.5	4.4 ± 21.9	3.5 ± 17.4	6.7 ± 24.8	7.3 ± 24.6
Number of emergency department admissions	3.0 ± 10.9	2.8 ± 9.3	3.1 ± 9.4	3.4 ± 10.2	3.1 ± 9.0
Number of outpatient visits	146.9 ± 111.1	158.2 ± 156.4	160.5 ± 155.9	185.4 ± 151.9	140.0 ± 123.2*
Melanoma tumor site, N (%)					
Face	473 (7.4%)	78 (8.2%)	89 (9.4%)	8 (9.2%)	10 (11.5%)
Neck	346 (5.4%)	48 (5.1%)	51 (5.4%)	11 (12.6%)	4 (4.6%)*
Trunk	2,232 (34.9%)	338 (35.6%)	329 (34.6%)	27 (31.0%)	33 (37.9%)†
Limb	2,873 (44.9%)	414 (43.6%)	403 (42.4%)	33 (37.9%)	38 (43.7%)†
Other	133 (2.1%)	19 (2.0%)	19 (2.0%)	2 (2.3%)	0 (0.0%)*
Unspecified	774 (12.1%)	115 (12.1%)	124 (13.1%)	18 (20.7%)	5 (5.7%)*
Quan-Charlson comorbidity index[13,a], Mean ± SD	0.2 ± 0.6	0.2 ± 0.6	0.2 ± 0.6	0.4 ± 0.8	0.4 ± 0.7
Cancer-specific comorbidity index[14], Mean ± SD	1.2 ± 1.5	1.0 ± 1.3	1.0 ± 1.3	1.2 ± 1.4	1.0 ± 1.0†
Comorbidities					
Hypertension	2,405 (37.6%)	344 (36.2%)	365 (38.4%)	31 (35.6%)	31 (35.6%)
Actinic keratosis	960 (15%)	238 (25.1%)	245 (25.8%)	16 (18.4%)	12 (13.8%)†
Diabetes, uncomplicated	745 (11.6%)	124 (13.1%)	127 (13.4%)	5 (5.7%)	19 (21.8%)*
Cardiac arrhythmias	615 (9.6%)	69 (7.3%)	76 (8.0%)	13 (14.9%)	11 (12.6%)
OTHER COVARIATES					
Study period (months), Mean ± SD	29.8 ± 23.1	-	-	-	-
Index lymph node surgery to first recurrence (months), Mean ± SD	-	15.3 ± 16.6	16.0 ± 16.6	19.3 ± 14.4	18.6 ± 15.3

HRU, health resource use; SD,standard deviation
*Standardized difference >|20%| between recurrence group within cohort after matching; †Standardized difference >|10%| between recurrence group within cohort after matching.
[a]The index excluded cancer diagnoses.

- Mean age in the study sample (N=6,400) was 53.8 years and approximately 46% were women; mean duration of the study period was 29.8 months.
- Most baseline covariates were balanced after matching between the recurrence and recurrence-free cohorts (i.e., standardized differences <|20%|), with a few exceptions for the distant recurrence versus recurrence-free cohorts, where some melanoma sites, number of outpatient visits and diabetes presented a standardized difference superior to |20%|, and some comorbidities a standardized difference superior to |10%|.

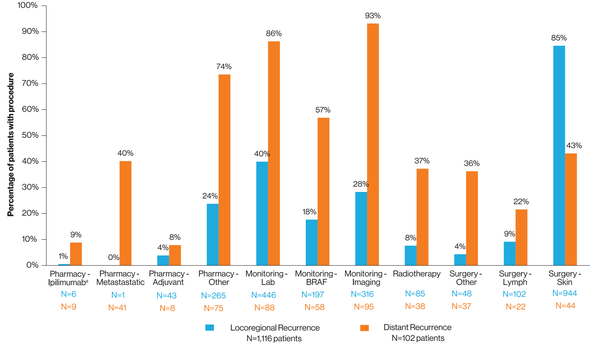
Figure 1. All-cause HRU During Episodes of Recurrence and During Recurrence-free Period[a]



HRU, health resource utilization
[a]The recurrence-free period included the time between the index surgery date and the first recurrence for patients with a recurrence, or the time between the index surgery date and the end data of data availability or end of insurance coverage/death for those patients with no recurrence.
[b]Outpatient visits associated with administration of antineoplastic treatments, whether in the NCCN guidelines for melanoma or not (of note, a few agents such as methotrexate can also be used for non-cancer indications).

- The HRU were numerically superior during the recurrence episode, especially during distant recurrence episodes, compared to the recurrence-free period. For instance, the number of inpatient admissions was approximately 14 times larger during episodes of distant recurrence compared to the recurrence-free period.
- The number of outpatient visits associated with antineoplastic treatment administration was relatively low, especially during distant recurrence episodes. This may be explained by several factors: some distant episodes were identified based on new codes for secondary malignancy and stereotactic radiotherapy only; others were identified based on pharmacotherapies that did not require an OP for administration (e.g., most targeted regimens); finally, distant episodes lasted until disenrollment/death and use of antineoplastic pharmacotherapy may be infrequent towards the end of life.

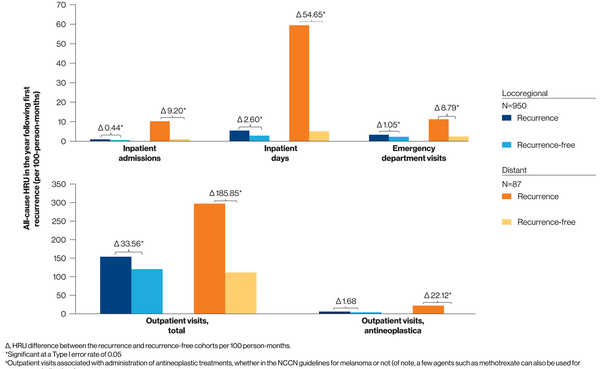
Figure 2. Use of Melanoma-specific Procedures During Episodes of Locoregional and Distant Recurrence



*Ipilimumab presented separately as it was used in metastatic setting only between 2011 and 2015, and then used in metastatic and adjuvant settings from 2015.

- Surgery to the skin and monitoring (e.g., laboratory tests) were the most commonly used melanoma-specific procedures during an episode of locoregional recurrence (used by 944/1,116 [84.6%] and 446/1,116 [40.0%] of the patients, respectively).
- Monitoring (e.g., imaging) and pharmacological treatments were the most commonly used melanoma-specific procedures during episodes of distant recurrences (used by 95/102 [93.1%] and 75/102 [73.5%] of the patients, respectively).

Figure 3. All-cause HRU in the Year Following First Recurrence Between Matched Cohorts



Δ, HRU difference between the recurrence and recurrence-free cohorts per 100 person-months.
*Significant at a Type I error rate of 0.05
[a]Outpatient visits associated with administration of antineoplastic treatments, whether in the NCCN guidelines for melanoma or not (of note, a few agents such as methotrexate can also be used for non-cancer indications).

- Patients with recurrences, in particular distant recurrences, incurred significantly higher HRU compared to recurrence-free matched controls in the year following the start of the first episode of recurrence.

Limitations

- Potential inaccuracies in the database, common to studies based on healthcare claims, are expected to affect cohorts to a similar extent. Residual confounding due to factors unobserved in claims data cannot be ruled out.
- The recurrence algorithm used treatment pattern indicators to detect recurrences; although previous published studies have shown that claims-based algorithms may be used to identify cancer recurrences[15-17], misclassifications may have occurred.
- The first melanoma diagnosis captured in the current study could have corresponded to the locoregional after an earlier melanoma diagnosis. A 12-month washout period was applied to minimize the chance of capturing recurrences at the first melanoma diagnosis in the data.

Conclusion

- Recurrences are associated with significant increases in HRU. The majority of recurrences were locoregional in this real-world study, with episode associated with nearly a doubling of inpatient admissions as compared to matched recurrence-free controls (1.00 vs. 0.57 inpatient admissions per 100 person-months in the year following the recurrence).
- While distant recurrences were comparatively rare, the inpatient admissions in patients with distant recurrences were approximately 10 times higher relative to a recurrence-free cohort (from 1.05 to 10.25 inpatient admissions per 100 person-months in the year following the recurrence).
- New generations of adjuvant melanoma therapies such as immune-checkpoint inhibitors and targeted agents[10,11] are likely to change the treatment landscape. Future studies following the introduction of novel therapies are needed to determine whether use of adjuvant therapies for non-metastatic melanoma will reduce risk of recurrences and whether this in turn may translate to reduced HRU.

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