Differences in Time Burden across Local Therapy Strategies for Early-stage Breast Cancer

Background: “Time burden” (time required during treatment) is relevant when choosing a local therapy option for early-stage breast cancer but has not been rigorously studied. We compared the time burden for three common local therapies for breast cancer: (1) lumpectomy plus whole-breast irradiation (Lump+WBI), (2) mastectomy without radiation or reconstruction (Mast alone), and (3) mastectomy without radiation but with reconstruction (Mast+Recon).

Methods: Using the MarketScan database, we identified 35,406 breast cancer patients treated from 2000 to 2011 with these local therapies. We quantified the total time burden as the sum of inpatient days (inpatient-days), outpatient days excluding radiation fractions (outpatient-days), and radiation fractions (radiation-days) in the first two years postdiagnosis. Multivariable regression evaluated the effect of local therapy on inpatient-days and outpatient-days adjusted for patient and treatment covariates.

Results: Adjusted mean number of inpatient-days was 1.0 for Lump+WBI, 2.0 for Mast alone, and 3.1 for Mast+Recon (P < 0.001). Adjusted mean number of outpatient-days was 42.9 for Lump+WBI, 42.2 for Mast alone, and 45.8 for Mast+Recon (P < 0.001). The mean number of radiation-days for Lump+WBI was 32.4. Compared with Mast+Recon (48.9 days), total adjusted time burden was 4.7 days shorter for Mast alone (44.2 days) and 27.4 days longer for Lump+WBI (76.3 days). However, use of a 15 fraction WBI regimen would reduce the time burden differential between Lump+WBI and Mast+Recon to just 10.0 days.

Conclusions: Although Mast+Recon confers the highest inpatient and outpatient time burden, Lump+WBI carries the highest total time burden. Increased use of hypofractionation will reduce the total time burden for Lump+WBI. (Plast Reconstr Surg Glob Open 2021;9:e3904; doi: 10.1097/GOX.0000000000003904; Published online 4 November 2021.)

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INTRODUCTION

Women with early stage breast cancer often have multiple local therapy options from which to choose, including breast conservation therapy (eg, lumpectomy followed by radiation) and mastectomy with or without reconstruction. Because survival rates are comparable across these treatment strategies,1–3 patients must take into consideration other factors when deciding how to proceed.4–6 One such important factor (captured by the concept of “treatment burden”) is defined as a combination of “workload” (the time and energy required on behalf of the patient for the treatment of a condition) and the effect of this workload on physical and psychosocial well-being.7–9 Treatment burden consists of four distinct dimensions: side effects, financial burden, personal burden, and time burden.10 Previous studies have compared the side effects,10–13 financial burden, and personal burden14–16 across local therapy options for breast cancer. However, to the best of our knowledge, no prior studies have compared the time burden associated with these options. Given the established differences in postoperative length of stay17,18 and complication rates10,11 associated with these options, understanding other factors when deciding how to proceed is warranted.4–6

One such important factor (captured by the concept of “treatment burden”) is defined as a combination of “workload” (the time and energy required on behalf of the patient for the treatment of a condition) and the effect of this workload on physical and psychosocial well-being.7–9 Treatment burden consists of four distinct dimensions: side effects, financial burden, personal burden, and time burden.10

Previous studies have compared the side effects,10–13 financial burden, and personal burden14–16 across local therapy options for breast cancer. However, to the best of our knowledge, no prior studies have compared the time burden associated with these options. Given the established differences in postoperative length of stay17,18 and complication rates10,11 between breast-conserving and mastectomy-based surgical approaches, we cannot simply assume that the time burden associated with breast-conserving therapy exceeds the time burden associated with a mastectomy-based approach by an amount equivalent to the number of radiation fractions. Thus, systematic measurement of the total time burden entailed by each local therapy option is warranted.

Understanding the differences in time burden across local therapy options would assist clinicians and their patients when weighing the pros and cons of various local therapies, and would also elucidate the extent to which changes in radiation fractionation schedules may affect the time burden associated with breast-conserving therapy. Accordingly, we sought to quantify and compare the time burden for the three most common local therapy options for early breast cancer: (1) lumpectomy plus whole breast irradiation (Lump + WBI), (2) mastectomy without radiation or reconstruction (Mast alone), and (3) mastectomy without radiation but with reconstruction (Mast+Recon).

METHODS

Data Source

Patients were selected from the MarketScan Commercial Claims and Encounters database (Truven Health Analytics, Ann Arbor, Mich.).19 The MarketScan database is a convenience sample of individual-level insurance claims derived from large employers and health insurers that provide private insurance for patients under the age of 65. Our institutional review board granted this study exempt status because all observations were de-identified.

Cohort Selection

Using a validated, claims-based algorithm,19 we identified incident breast cancer cases in the MarketScan database from 2000 to 2011 (n = 162,873). To fully capture pre-treatment comorbid conditions and posttreatment outcomes of interest, we included only patients with complete insurance coverage from 12 months before diagnosis through 24 months after diagnosis. Patients were excluded if they had distant metastases (as determined by diagnosis codes). (See table 1, Supplemental Digital Content 1, which displays the claim codes used to determine treatment and clinical covariates. http://links.lww.com/PRSGO/B823.)

We also excluded patients who received neoadjuvant chemotherapy or who underwent mastectomy followed by postmastectomy radiation, as these treatment patterns are indicators of more advanced disease. Finally, we included only those patients who were treated with one of the three local therapy options selected for the current study (Lump+WBI, Mast alone, Mast+Recon), yielding 35,406 patients for our study cohort. (See table 2, Supplemental Digital Content 2, which displays the selection criteria for the study cohort. http://links.lww.com/PRSGO/B823.)

Study Variables

We used Common Procedural Terminology and International Classification of Diseases (version 9) procedure codes to classify surgery and radiation within 1 year of diagnosis (SDC 1, http://links.lww.com/PRSGO/B823). We limited the Lump+WBI group to patients who received 15 or more unique external beam radiation treatments and no brachytherapy within 1 year of diagnosis. In accordance with previously developed methods,19 we defined the Mast+Recon group as patients who had a code for mastectomy within 1 year of diagnosis and a code for breast reconstruction within 2 years of diagnosis. Within this group, we also used codes to classify patients by reconstruction type, including autologous, implant-based, combination of autologous and implant-based, tissue expander only (indicating that no definitive reconstruction was performed within 2 years of mastectomy), or other.

Other claims-derived patient and treatment variables included age, Charlson comorbidity score,20–25 year of diagnosis, axillary surgery, axillary node status, chemotherapy receipt (none, non-trastuzumab-based, and trastuzumab-based), endocrine therapy receipt, and type of insurance coverage. We used Common Procedural Terminology codes and National Drug Codes to determine receipt of adjuvant trastuzumab and endocrine therapy within 1 year.
of diagnosis. (See table 3, Supplemental Digital Content 3, which displays the National Drug Codes used to determine receipt of adjuvant trastuzumab and endocrine therapy. http://links.lww.com/PRSGO/B823.)

Outcomes
The primary outcome of interest was total time burden, which we defined as the number of days that patients spent interacting with the healthcare system over the course of their primary breast cancer treatment. We considered total time burden to be the sum of three distinct outcomes that were calculated on the basis of claims: “inpatient-days,” “outpatient-days,” and “radiation-days.”

The outcome “inpatient-days” was calculated for all patients and was defined as the number of unique days spent as an inpatient in a hospital from the date of diagnosis until 2 years after diagnosis. Patients who underwent an outpatient surgical procedure and required no hospital admissions in the 2 years after diagnosis were considered to have an inpatient-days count of 0.

The outcome “outpatient-days” was calculated for all patients and was defined as the number of unique days spent interacting with the healthcare system as an outpatient from the date of diagnosis until 2 years after diagnosis. These interactions included surgical procedures, clinic visits, imaging studies, administration of intravenous medications (including chemotherapy), and physical therapy, among others. (See table 4, Supplemental Digital Content 4, which displays the twenty most common outpatient-day codes by local therapy type. http://links.lww.com/PRSGO/B823.)

We specifically did not count days on which the only claims were for laboratory studies or pathology services. In addition, we did not count days on which the only claims were for radiation treatment, as these were captured in a separate category.

The outcome “radiation-days” was calculated for Lump+WBI patients only and was defined as the number of radiation fractions received from the date of diagnosis until 1 year after diagnosis. Any radiation-related services that required the patient to be present (eg, simulation) and occurred before the start of RT were counted toward the outpatient-days total and not the radiation-days total, as we wanted to isolate the effect of number of fractions on the total time burden. We specifically did not count days on which the only claims were for dosimetry or physics services. In addition, we did not count any claims for re-simulation, re-planning, or on-treatment visits with the radiation oncologist that occurred during the course of RT. If a patient had an inpatient admission or non-radiation outpatient healthcare interaction on the same day as a radiation treatment, these days were counted toward the inpatient-days and outpatient-days totals, respectively.

Statistical Analysis
We calculated the mean number of inpatient-days, outpatient-days, and radiation-days for all patients. We also calculated the mean number of outpatient-days per 30-day interval from diagnosis through 2 years in an effort to ascertain the distribution of outpatient visits over the course of treatment.

We used multivariable negative binomial regression to evaluate the independent effect of treatment group on the number of inpatient-days and outpatient-days after controlling for covariates. This model was used instead of Poisson regression to account for overdispersion in the data. Covariates were selected a priori on the basis of clinical relevance and/or univariate significance (P < 0.25). The final multivariable models were used to provide estimates of adjusted mean inpatient-days and outpatient-days for each treatment group.

We conducted an exploratory analysis to assess the effects of reconstruction type on the number of inpatient-days and outpatient-days. To do this, we divided the Mast+Recon treatment group into five subgroups according to reconstruction type. This exploratory analysis was conducted using the same statistical approach and covariates as the primary models.

Analyses were conducted using SAS, v. 9.3 (SAS Institute, Cary, N.C.). All statistical tests were two-sided and a P value of 0.05 or less was considered significant.

Table 1. Baseline Characteristics by Local Treatment Strategy (n = 39,518)

| Variable                        | Lump + WBI (n = 16,700), No. (%) | Mast Alone (n = 11,432), No. (%) | Mast + Recon (n = 11,386), No. (%) | P     |
|---------------------------------|----------------------------------|---------------------------------|----------------------------------|-------|
| Age (y)                         |                                  |                                 |                                  |       |
| <40                             | 610 (3.5)                        | 178 (2.8)                       | 1214 (10.5)                      | <0.001|
| 40–49                           | 4676 (26.9)                      | 1255 (19.4)                     | 4772 (37.8)                      |       |
| 50–59                           | 9000 (51.8)                      | 3426 (53.0)                     | 4848 (41.9)                      |       |
| 60–64                           | 3084 (17.8)                      | 1607 (24.9)                     | 1131 (9.8)                       |       |
| Type of coverage                |                                  |                                 |                                  |       |
| non-HMO                         | 14,282 (82.2)                    | 5187 (80.2)                     | 9573 (81.0)                      | <0.001|
| HMO                             | 3088 (17.8)                      | 1279 (19.8)                     | 2197 (19.0)                      |       |
| Covered individual              |                                  |                                 |                                  |       |
| Employee                        | 10,742 (61.8)                    | 3783 (58.5)                     | 6756 (58.4)                      | <0.001|
| Dependent                       | 6628 (38.2)                      | 2683 (41.5)                     | 4814 (41.6)                      |       |
| Charlson comorbidity index 0    |                                  |                                 |                                  |       |
| 1                               | 15,712 (90.5)                    | 5987 (86.4)                     | 10,699 (92.5)                    | <0.001|
| ≥2                              | 1452 (8.5)                       | 717 (11.1)                      | 756 (6.5)                        |       |
| Chemotherapy                    |                                  |                                 |                                  |       |
| No                              | 10,636 (61.2)                    | 3636 (56.2)                     | 7392 (63.1)                      | <0.001|
| Yes                             | 6734 (38.8)                      | 2830 (43.8)                     | 4268 (36.9)                      |       |
| Axillary surgery                |                                  |                                 |                                  |       |
| No                              | 3595 (20.7)                      | 721 (11.2)                      | 1860 (16.1)                      | <0.001|
| Yes                             | 13,775 (79.3)                    | 5745 (88.8)                     | 9710 (83.9)                      |       |
| Axillary node positive          |                                  |                                 |                                  |       |
| No                              | 15,103 (86.9)                    | 5284 (81.7)                     | 10,126 (87.5)                    | <0.001|
| Yes                             | 2267 (13.1)                      | 1182 (18.3)                     | 1444 (12.5)                      |       |
| Endocrine therapy               |                                  |                                 |                                  |       |
| No                              | 7052 (40.6)                      | 3077 (47.6)                     | 6283 (54.3)                      | <0.001|
| Yes                             | 10,318 (59.4)                    | 3389 (52.4)                     | 5287 (45.7)                      |       |
| Year                            |                                  |                                 |                                  |       |
| 2000                            | 271 (1.6)                        | 244 (3.8)                       | 226 (2.0)                        | <0.001|
| 2001                            | 303 (1.7)                        | 255 (3.9)                       | 241 (2.1)                        |       |
| 2002                            | 337 (1.9)                        | 397 (6.1)                       | 328 (2.8)                        |       |
| 2003                            | 644 (3.7)                        | 527 (8.2)                       | 533 (4.6)                        |       |
| 2004                            | 845 (4.9)                        | 461 (7.1)                       | 601 (5.2)                        |       |
| 2005                            | 1160 (6.7)                       | 534 (8.3)                       | 754 (6.5)                        |       |
| 2006                            | 1244 (7.2)                       | 548 (8.5)                       | 820 (7.1)                        |       |
| 2007                            | 1990 (11.5)                      | 706 (10.9)                      | 1272 (11.0)                      |       |
| 2008                            | 1955 (11.3)                      | 647 (10.0)                      | 1323 (11.4)                      |       |
| 2009                            | 2971 (16.5)                      | 745 (11.5)                      | 1928 (15.8)                      |       |
| 2010                            | 3059 (17.6)                      | 764 (11.8)                      | 1894 (16.4)                      |       |
| 2011                            | 2691 (15.5)                      | 638 (9.9)                       | 1750 (15.1)                      |       |

HMO, health maintenance organization.
The Lump+WBI group served as the referent in all multivariable models.

RESULTS

Patient Characteristics

We identified 35,406 women diagnosed with early-stage breast cancer between 2000 and 2011 and treated with Lump+WBI (n = 17,370), Mast alone (n = 6466), or Mast+Recon (n = 11,570). The median age was 53 years (interquartile range, 47–58 years). Additional patient and treatment characteristics are listed in Table 1.

Outcomes

The unadjusted mean number of inpatient-days by treatment group was 1.0 for Lump+WBI [95% confidence interval (CI), 1.0–1.1], 2.4 for Mast alone (95% CI, 2.2–2.6), and 3.2 for Mast+Recon (95% CI, 3.1–3.3). After adjusting for covariates, the model-derived mean number of inpatient-days was significantly higher for Mast alone (2.0 days) and Mast+Recon (3.1 days) compared with Lump+WBI (1.0 days, \( P < 0.001 \), Table 2).

The unadjusted mean number of outpatient-days was 44.4 for Lump+WBI (95% CI, 44.0–44.8), 45.3 for Mast alone (95% CI, 44.6–46.0), and 46.3 for Mast+Recon (95% CI, 45.8–46.8). After adjusting for covariates, the model-derived mean number of outpatient-days was significantly higher for Mast+Recon (45.8 days) compared with Mast alone (42.2 days) and Lump+WBI (42.9 days, \( P < 0.001 \), Table 3). Qualitatively, the greatest variability in the number of unadjusted outpatient-days per month across treatment groups was observed in the first 8 months; patients treated with Lump+WBI seemed to have...
more outpatient-days in the early months compared with Mast alone and Mast+Recon, but fewer outpatient-days in later months (Fig. 1).

For patients treated with Lump+WBI, the mean number of radiation-days was 32.4 (95% CI, 32.3–32.5), which is consistent with a course of conventionally fractionated WBI (typically 25–30 fractions to the whole breast plus 5–8 fractions for a tumor bed boost).

In our exploratory analysis of time burden by reconstruction type, we found that after adjusting for covariates, breast reconstruction with an autologous approach was associated with the largest difference in inpatient-days compared with Lump+WBI (5.2 versus 1.0 days, \( P < 0.001 \)), whereas breast reconstruction with a combined autologous/implant approach was associated with the largest difference in outpatient-days compared with Lump+WBI (47.7 days versus 42.9 days, \( P < 0.001 \)). (See table 5, Supplemental Digital Content 5, which displays the multivariable negative binomial regression model of inpatient-days and outpatient-days, including reconstruction type. http://links.lww.com/PRSGO/B823.)

In all, the total adjusted time burden (inpatient-days + outpatient-days + radiation-days) was 76.3 days for Lump+WBI, 44.2 days for Mast alone, and 48.9 days for Mast+Recon. This translates to a time burden “excess” imposed by the addition of adjuvant radiation therapy of 32.1 days compared with Mast alone and 27.4 days compared to Mast+Recon. If all patients in the Lump+WBI group had been treated with a 15-fraction regimen, the time burden excess imposed by adjuvant radiation therapy would be reduced to 14.7 days compared with Mast alone and 10.0 days compared with Mast+Recon (Fig. 2).
DISCUSSION

In this claims-based study of over 35,000 breast cancer patients treated with three common local therapy strategies, we found that patients who were treated with Lump+WBI had the highest associated time burden, with patients spending an average of about 76 days engaged in treatment-related activities in the first 2 years following diagnosis. However, when considering the components of time burden separately, patients who were treated with Lump+WBI had significantly fewer outpatient-days than patients treated with Mast alone and significantly fewer inpatient and outpatient days than patients treated with Mast+Recon.

Our findings validate the well-established notion that, when considering inpatient-days, outpatient-days, and radiation-days together, surgery followed by radiation therapy is a more time-intensive approach to local therapy than surgery alone. However, to the best of our knowledge, this is the first study to systematically quantify and compare these differences. Moreover, by parsing the total time burden into three separate components, we were able to ascertain how local therapy strategies compare with regard to different types of interactions with the healthcare system. This approach is particularly informative because an overnight stay in the hospital has different treatment burden implications than a standard postoperative outpatient visit or a 30-minute radiation treatment.

In addition, because radiation-days were tabulated in a separate category, our findings may serve as an evidence-based benchmark by which to judge fractionation schema, specifically with regard to how a given schedule contributes to narrowing the time burden gap between local therapy strategies. For instance, the average number of radiation fractions received in the Lump+WBI group was about 32. However, around the time that the study period ended in 2011, the long-term results of three randomized trials demonstrating the equivalency of conventionally fractionated WBI and hypofractionated WBI were published and prompted the release of an American Society for Radiation Oncology evidence-based guideline for the use of hypofractionation. As a result of these publications, the use of hypofractionated WBI among appropriately selected patients in the United States increased from 11% in 2008 to 35% in 2013. This proportion should continue to increase as more data become available regarding the safety and efficacy of hypofractionation in American patients and we can assume that many patients included in the current analysis would now be eligible for WBI treatment in as few as 15 fractions, given that 15 fraction schedules were used for over half the patients in the START B trial and all patients in the recently presented IMPORT Low trial. Such a treatment course would add an average of only 10 additional days of treatment compared with Mast+Recon. Similarly, a five fraction radiation regimen would be predicted to have an equivalent time burden in comparison with Mast+Recon and a single fraction or intraoperative approach would be expected to yield a net time benefit compared with Mast+Recon.

The results of our study are an important addition to the literature because time away from normal activities is a foremost consideration for many women with breast cancer. In a claims-based analysis of insured breast cancer patients treated with breast conservation surgery, Pan et al found that women with at least one child less than 7 years of age were less likely to receive adjuvant RT than women with older children or with no children. The authors also found that women in the youngest age group (20–50 years) were less likely to receive adjuvant RT than women in the older age groups, despite the clear evidence that young patients experience the greatest absolute benefit from adjuvant RT. The results from Pan et al. suggest that estimates of the total time commitment associated with a specific local therapy, such as those presented in our study, may help patients select a treatment option that they will be able to complete.

Our findings also add to the existing but limited literature on treatment burden in cancer care. In a cross-sectional survey study of 814 cancer patients, Henry et al examined several components of treatment burden: chemotherapy- and radiation-associated side effects (including fatigue) and missed work days due to treatment-related activities. The authors found that among the 34% of respondents who were actively working during treatment, the average number of days missed due to the delivery of chemotherapy or radiation was 26 days per year; and the average number of days missed due to the side effects of treatment was 18 days per year. In a similar survey study, Bradley et al found that among 239 employed breast cancer patients, the median number of missed work days was 22 days. Interestingly, the authors found that in the first 6 months after diagnosis, patients treated with surgery plus radiation (without chemotherapy) missed significantly fewer work days (10 days) than women treated with surgery alone (15 days). As the authors suggest, this difference likely reflects variation in the extent of surgery, as the proportion of patients receiving mastectomy was higher in the surgery alone group. Furthermore, patients are frequently able to schedule their radiation treatments around work obligations, and therefore the number of missed work days is not necessarily a reliable surrogate for the time burden of treatment.

Comparing treatments on the basis of missed work days is valuable; however, because many cancer patients are unemployed or not actively working, such studies represent only a fraction of cancer patients. In addition, survey studies are susceptible to response bias and recall bias that may lead patients to underestimate the time they spent receiving treatment. A major strength of our study is that we used insurance claims to provide a quantitative measure of the time burden associated with a course of definitive therapy in a large sample of patients treated in diverse settings. Furthermore, the inclusion of other claims-derived variables, such as axillary lymph node positivity, use of axillary surgery, and chemotherapy receipt, in our analyses allowed us to at least partially account for tumor and treatment characteristics that may substantially confound less robust analyses of time burden.

Our study had several limitations. First, because we used the MarketScan dataset, we were only able to include patients aged younger than 65 years, and therefore our results apply only to this age group. Second, we were not
able to specifically differentiate between cancer- and non-cancer related inpatient-days and outpatient-days. That is to say, any hospital stay or clinic visit that occurred in the 2 years following cancer diagnosis counted toward the inpatient-days or outpatient-days total, regardless of the purpose of the visit. However, our cohort was comprised of a relatively young group of women (median age of 53), and we attempted to account for this limitation by adjusting for comorbidity in the multivariable models.

In summary, we used claims-based data to quantify the time burden associated with three common local therapies for early-stage breast cancer. These findings highlight the potential for shorter radiation schedules to close the time burden gap between breast-conservation and mastectomy-based approaches to local therapy. Of course, time burden is only one component of the cumulative effect of local therapy, and should be considered in combination with treatment side effects, economic burden, and quality of life outcomes. Once patients understand how these components compare across local therapy strategies, they can work together with their physicians to select the treatment that best aligns with their priorities and values.

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