Original Article

# The Rise in Metastasectomy Across Cancer Types Over the Past Decade

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**BACKGROUND:** Although studies of metastasectomy have been limited primarily to institutional experiences, reports of favorable long-term outcomes have generated increasing interest. In the current study, the authors attempted to define the national practice patterns in metastasectomy for 4 common malignancies with varying responsiveness to systemic therapy. **METHODS:** The National (Nationwide) Inpatient Sample was used to estimate the national incidence of metastasectomy for colorectal cancer, lung cancer, breast cancer, and melanoma from 2000 through 2011. Incidence-adjusted rates were determined for liver, lung, brain, small bowel, and adrenal metastasectomies. The average annual percentage change (AAPC) in metastasectomy by cancer type was calculated using joinpoint regression. **RESULTS:** Colorectal cancer was the most common indication for metastasectomy (87,407 cases; 95% confidence interval [95% CI], 86,307-88,507 cases) followed by lung cancer (58,245 cases; 95% CI, 57,453-59,036 cases), breast cancer (26,271 cases; 95% CI, 25,672-26,870 cases), and melanoma (20,298 cases; 95% CI, 19,897-20,699 cases). Metastasectomy increased significantly for all cancer types over the study period: colorectal cancer (AAPC, 6.83; 95% CI, 5.7-7.9), lung cancer (AAPC, 5.8; 95% CI, 5.1-6.4), breast cancer (AAPC, 5.5; 95% CI, 3.7-7.3), and melanoma (AAPC, 4.03; 95% CI, 2.1-6.0). Despite an increasing number of comorbidities in patients undergoing metastasectomy ($P<.05$ for each cancer type), inpatient mortality rates after metastasectomy fell for all cancer types, most significantly for colorectal (AAPC, −5.49; 95% CI, −8.2 to −2.7) and lung (AAPC, −6.2; 95% CI, −11.7 to −0.3) cancers. The increasing performance of metastasectomy was largely driven by high-volume institutions, in which patients had a lower mean number of comorbidities ($P<.01$ for all cancer types) and lower inpatient mortality ($P<.01$ for all cancers except melanoma). **CONCLUSIONS:** From 2000 through 2011, the performance of metastasectomy increased substantially across common cancer types, notwithstanding various advances in systemic therapies. Metastasectomy was performed more safely, despite increasing patient comorbidity. High-volume institutions appeared to drive practice patterns. ***Cancer* 2015;121:747-57.** *© 2014 American Cancer Society.*

**KEYWORDS:** metastasectomy, colorectal cancer metastasectomy, lung cancer metastasectomy, breast cancer metastasectomy, melanoma metastasectomy, surgical trends.

## INTRODUCTION

Historically, the role of surgery in patients with metastatic cancer was predominately limited to palliative or emergent operations. By the 1980s, however, a few centers were consistently performing surgical resections for select patients with metastatic cancer and reporting promising results.[1-3] In addition, theories of cancer biology began to suggest that in a subset of patients, oligometastatic disease might indeed represent the entire clinically relevant disease burden.[4] In these cases, complete resection was associated with prolonged disease-free survival and, in some patients, clinical cure. As a result, in selected patients surgical resection is now considered for the treatment of oligometastatic disease to most anatomic sites from many different primary cancer types.

Of the 5 most common cancer types, colorectal cancer has to our knowledge been the subject of the largest number of studies of metastasectomy. Multiple studies of patients undergoing isolated liver metastasectomy have now found 5-year survival rates of >50%,[5,6] and 10-year survival ranging from 17% to 36%.[7-10] In addition, long-term survival has been reported after resection of metastases to multiple other disease sites.[11-14] Indeed, what to our knowledge is the only randomized trial to investigate the efficacy of metastasectomy is currently underway for patients with colorectal metastases to the lung.[15]

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The role of metastasectomy in patients with other cancer types remains more controversial. Multiple metastasectomy series have now been published for breast cancer,[16-18] lung cancer,[14,19,20] and melanoma,[21-23] all of which have reported relatively favorable survival in carefully selected patients, but compared with those in colorectal cancer, the series are smaller and less frequently report long-term follow-up.

Paralleling the increased interest in and experience with metastasectomy, systemic therapies have continued to improve. The last decades have witnessed substantial improvements in systemic therapy for colorectal[24,25] and breast[26] cancers in particular. More recently, the prognosis of patients with metastatic melanoma has been substantially altered with the approval of both targeted and immune-based therapeutics.[27,28] Given the evolution in surgical thinking regarding metastasectomy and the changing efficacies of systemic therapy, we sought to describe the national trends in metastatic surgery across 4 of the most common cancer types. We hypothesized that metastasectomy was being performed with increasing frequency and sought to determine whether the varying responsiveness of diverse cancers to systemic therapy has influenced these trends.

## MATERIALS AND METHODS

Admissions from the National (Nationwide) Inpatient Sample (NIS) (2000-2011) involving a metastasectomy for colorectal cancer, lung cancer, breast cancer, or melanoma were included. Prostate cancer, although one of the 5 most common malignancies, was not included given the very limited role for metastasectomy in patients with this disease.[29] The NIS is maintained by the Healthcare Cost and Utilization Project (HCUP) and is the largest all-payer inpatient database in the United States. It captures a stratified sample of approximately 20% of the admissions in the United States and is weighted to allow for estimates of national rates.[30]

Cancer types were defined using HCUP clinical classification software.[31] The NIS captures up to 25 possible diagnoses and 15 procedures per admission record using *International Classification of Diseases, Ninth Revision* (ICD-9) codes. Because the indication for a procedure is not available in the NIS, specific metastasectomies were narrowly defined. To be included as a metastasectomy, an organ-specific resection (liver: codes 50.22 or 50.3; lung: codes 32.20, 32.29, and 32.3x-32.6x; brain: codes 01.3x or 01.5x; small bowel: codes 45.3, 45.31, 45.33, and 45.6x; or adrenal: codes 07.2x-07.3x) must have been performed during the same admission as a diagnosis of a metastasis to the corresponding site (liver: code 197.7; lung: code 197.0; brain: code 198.3; small bowel: code 197.4; or adrenal: code 198.7). In the case of lung cancer, lung resections were excluded from the definition of metastasectomy. Admissions associated with a diagnosis of multiple cancer types were excluded (3.83% of the total).

Additional variables of interest included inpatient mortality, which is provided by the NIS, and the number of Elixhauser comorbidities, as calculated by HCUP comorbidity software.[32] Elixhauser et al. classified comorbidities abstracted from administrative data into 30 groups, which are now widely used in studies of administrative data sets.[33] Hospital volume was calculated, and high-volume centers were defined separately for each cancer type. A high-volume center was defined as a hospital within the top 10% of metastasectomy volume for a given cancer, as has been previously described.[34] All other centers were classified as "low volume." Other analyzed variables included patient age and sex.

All data were transformed to national estimates using the weights provided by the NIS. The number of metastasectomies performed per year was incidence-adjusted to the 2000 US incidence for each cancer type. Annual national incidence rates were determined from the Surveillance, Epidemiology, and End Results registry.[35]

Joinpoint regression was used to determine the trends over time. Joinpoint regression is a technique used to identify changes in trend data, with the ability to fit multiple regression lines connected at a "joinpoint" if a statistically significant change in the trend occurs at a given time.[36] Log-linear models were used to allow for comparison of trends across cancer types with varied incidences. Given the relatively short study span, joinpoint regression was limited to a maximum of 1 joinpoint for each analysis. For each segment, the annual percent change (APC) can be calculated. When a joinpoint was defined, we report the average annual percent change (AAPC), which represents the weighted average change across the entire study period (2000-2011). For trends in which no joinpoint was defined (ie, a single line), the APC is equal to the AAPC. *P* values associated with the AAPC refer to the probability that a trend is significantly different from 0 (ie, no trend). For comparison of trends at high-volume and low-volume institutions, the probability that the trends were parallel was calculated according to a permutation procedure described by Kim et al.[37]

**TABLE 1.** National Estimates of Admissions for Metastasectomy by Cancer Type, 2000 Through 2011

| | Colorectal Cancer | | Lung Cancer | | Breast Cancer | | Melanoma | |
|---|---|---|---|---|---|---|---|---|
| | No. | 95% CI | No. | 95% CI | No. | 95% CI | No. | 95% CI |
| All admissions | 87,407 | (86,307-88,507) | 58,245 | (57,453-59,036) | 26,271 | (25,672-26,870) | 20,298 | (19,897-20,699) |
| Mean age (SE), y | 62.2 | 0.10 | 61.4 | 0.10 | 56.8 | 0.17 | 58.1 | 0.22 |
| Female sex | 46.0% | (45.3%-46.8%) | 45.8% | (44.9%-46.7%) | 99.4% | (99.2%-99.6%) | 33.6% | (32.2%-35.1%) |
| Liver metastasectomy | 41,312 | (40,500-42,125) | 503 | (405-601) | 1663 | (1486-1839) | 550 | (448-652) |
| Lung metastasectomy | 19,590 | (18,994-20,185) | NA[a] | NA[a] | 6609 | (6266-6951) | 5839 | (5534-6144) |
| Brain metastasectomy | 5588 | (5263-5912) | 52,944 | (52,167-53,720) | 16,091 | (15,591-16,590) | 11,094 | (10,718-11,471) |
| Small bowel metastasectomy | 20,916 | (20,303-21,529) | 2762 | (2535-2988) | 1724 | (1544-1905) | 2440 | (2233-2646) |
| Adrenal metastasectomy | 599 | (493-705) | 2067 | (1870-2264) | 230 | (165-295) | 471 | (377-566) |
| Mean no. of Elixhauser comorbidities | 1.98 | (1.96-2.00) | 2.72 | (2.69-2.75) | 1.87 | (1.83-1.91) | 1.84 | (1.80-1.88) |
| Inpatient mortality rate | 2.13% | (1.91%-2.34%) | 3.18% | (2.86%-3.51%) | 1.91% | (1.54%-2.28%) | 1.65% | (1.26%-2.04%) |

Abbreviations: 95% CI, 95% confidence interval; NA, not applicable; SE, standard error.
[a] Lung resections for lung cancer were not analyzed given the inability to differentiate between local recurrence, a second primary tumor, and a true metastasectomy.

A $P$ value <.05 was considered to be statistically significant. All data were transferred into STATA format using SAS statistical software (version 9.4; SAS Institute Inc, Cary NC) and the Stat/Transfer data conversion statistical program (version 11.0; Circle Systems Inc, Seattle, Wash). Analysis was performed using Stata 12.0/IC statistical software (StataCorp, College Station, Tex) and the Joinpoint Regression Program (Version 4.1.0-April 2014; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, Md). This study was reviewed and deemed exempt from approval by the University of Pennsylvania Institutional Review Board.

## RESULTS

### *Characteristics of Patients Undergoing Metastasectomy for Common Malignancies*

Colorectal cancer was the most frequent indication for metastasectomy (87,407 cases; 95% CI, 86,307-88,507 cases), followed by lung cancer (58,245 cases; 95% CI, 57,453-59,036 cases), breast cancer (26,271 cases; 95% CI, 25,672-26,870 cases), and melanoma (20,298 cases; 95% CI, 19,897-20,699 cases). The age and sex distributions varied by cancer type and are shown in Table 1. The sites of metastasectomy also varied by cancer type, with liver resection most commonly performed for colorectal cancer and brain resection most commonly performed for lung cancer, breast cancer, and melanoma. Patients undergoing metastasectomy for lung cancer had the highest number of Elixhauser comorbidities (mean, 2.72 comorbidities; 95% CI, 2.69-2.75 comorbidities), as well as the highest inpatient mortality rate (3.18%; 95% CI, 2.86%-3.51%) (Table 1).

### *Trends in Resection of Metastatic Disease by Cancer Type*

Incidence-adjusted metastasectomies for colorectal cancer in the United States increased from 6046 metastasectomies (95% CI, 5708-6384 metastasectomies) in 2000 to 11,587 metastasectomies (95% CI, 11,051-12,122 metastasectomies) in 2011, an AAPC of 6.83 (95% CI, 5.7-7.9) (Fig. 1A). This was predominately driven by an increase in liver metastasectomy, which increased from 2348 cases (95% CI, 2137-2558 cases) in 2000 to 6397 cases (95% CI, 5997-6796 cases) in 2011 (AAPC, 10.2; 95% CI, 8.6-11.9), and lung metastasectomy, which increased from 1184 cases (95% CI, 1030-1338 cases) to 2501 cases (95% CI, 2249-2752 cases) over the same period (AAPC, 9.4; 95% CI, 7.5-11.4) (Figs. 1B and 1C). Both brain and adrenal metastasectomies were performed with significantly increasing incidence, although the absolute numbers were small (Figs. 1D and 1F). Only small bowel metastasectomy demonstrated a decreasing incidence, with an AAPC of −1.69 (95% CI, −2.6 to −0.8) (Fig. 1E).

Overall incidence-adjusted metastasectomies for lung cancer also increased between 2000 and 2011 (AAPC, 5.8; 95% CI, 5.1-6.4). In 2006, the trend became increasingly steep, with an APC of 3.3 (95% CI, 2.4-4.3) before 2006 and an APC of 8.7 (95% CI, 7.5-9.9) since that time (Fig. 2A). Brain metastasectomies accounted for the vast majority of surgical resections, increasing from 3389 metastasectomies (95% CI, 3139-3640 metastasectomies) in 2000 to 6409 metastasectomies (95% CI, 6048-6771 metastasectomies) in 2011, and demonstrated a similar change in trend in 2006 (AAPC, 6.0; 95% CI, 5.3-6.6) (Fig. 2D). Adrenalectomy (AAPC, 5.98; 95% CI, 3.9-8.1) was also performed more frequently,

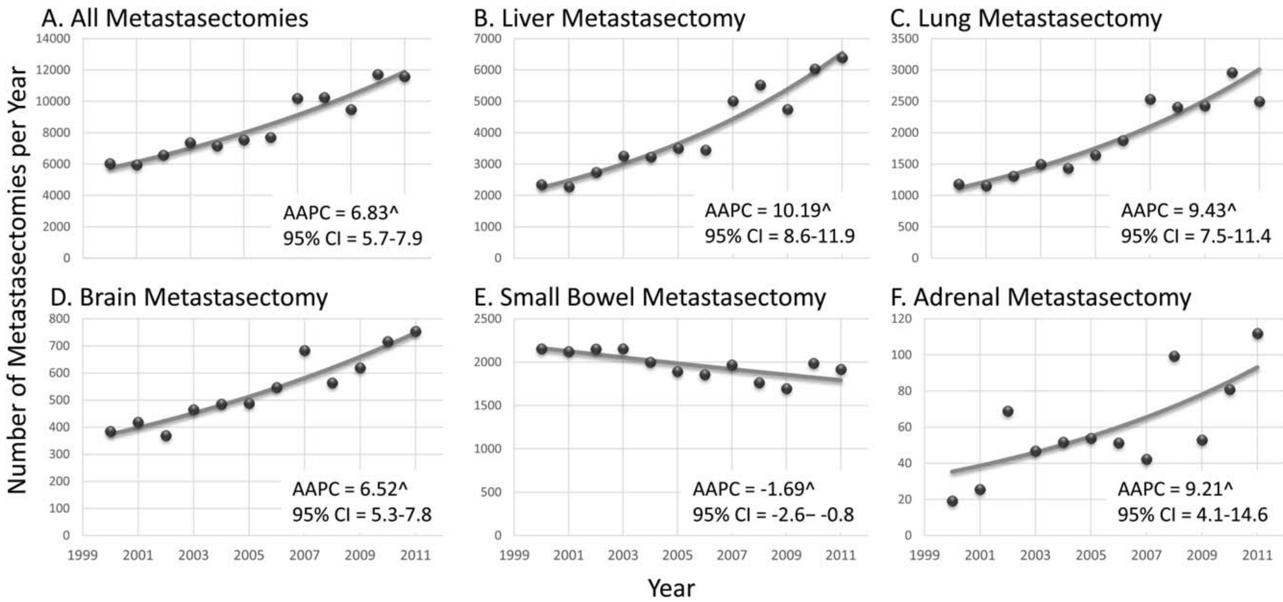


**Figure 1.** Metastasectomy rates for colorectal cancer are shown for (A) all metastasectomies, (B) liver metastasectomy, (C) lung metastasectomy, (D) brain metastasectomy, (E) small bowel metastasectomy, and (F) adrenal metastasectomy. AAPC indicates average annual percent change; ^, an AAPC that is significantly different from 0 ($P<.05$); 95% CI, 95% confidence interval. Note that the y-axis values vary for each panel.

although the absolute numbers were small (Fig. 2F). No significant changes in the performance of liver or small bowel metastasectomy for lung cancer were observed (Figs. 2B and 2E).

Incidence-adjusted metastasectomies for breast cancer increased from 1680 metastasectomies (95% CI, 1502-1857 metastasectomies) to 2991 metastasectomies (95% CI, 2753-3228 metastasectomies) from 2000 to

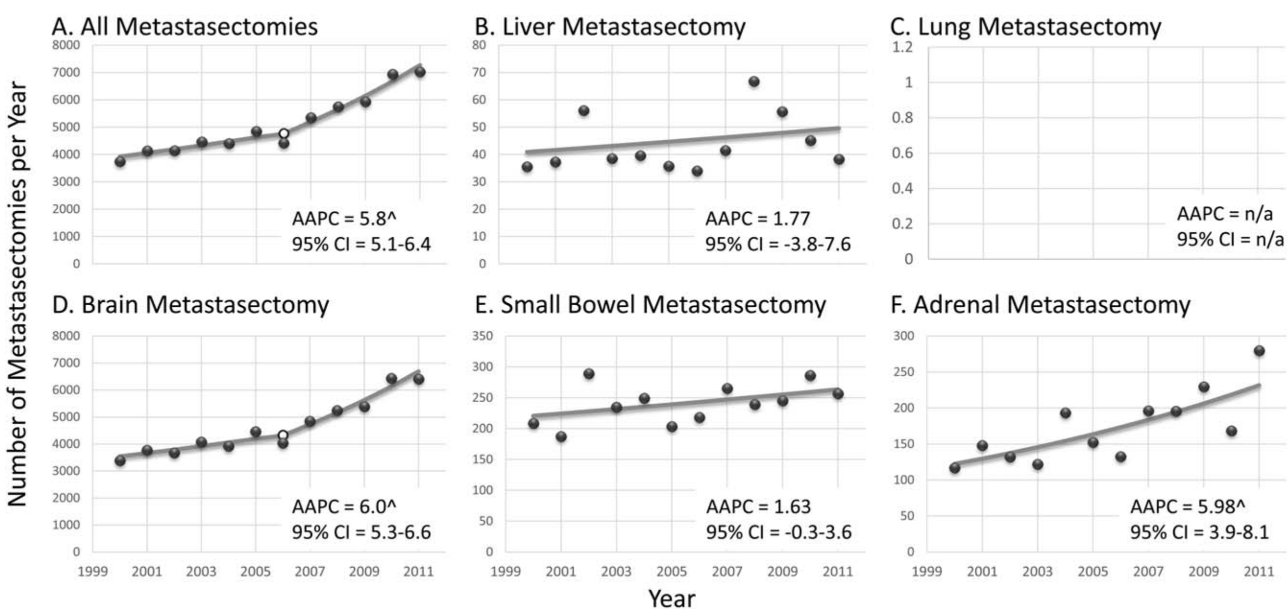


**Figure 2.** Metastasectomy rates for lung cancer are shown for (A) all metastasectomies and (B) liver metastasectomy. (C) Lung metastasectomy was omitted. Rates are also shown for (D) brain metastasectomy, (E) small bowel metastasectomy, and (F) adrenal metastasectomy. AAPC indicates average annual percent change; ^, an AAPC that is significantly different from 0 ($P<.05$); 95% CI, 95% confidence interval; n/a, not applicable. An open circle indicates a joinpoint (trend change). Note that the y-axis values vary for each panel.

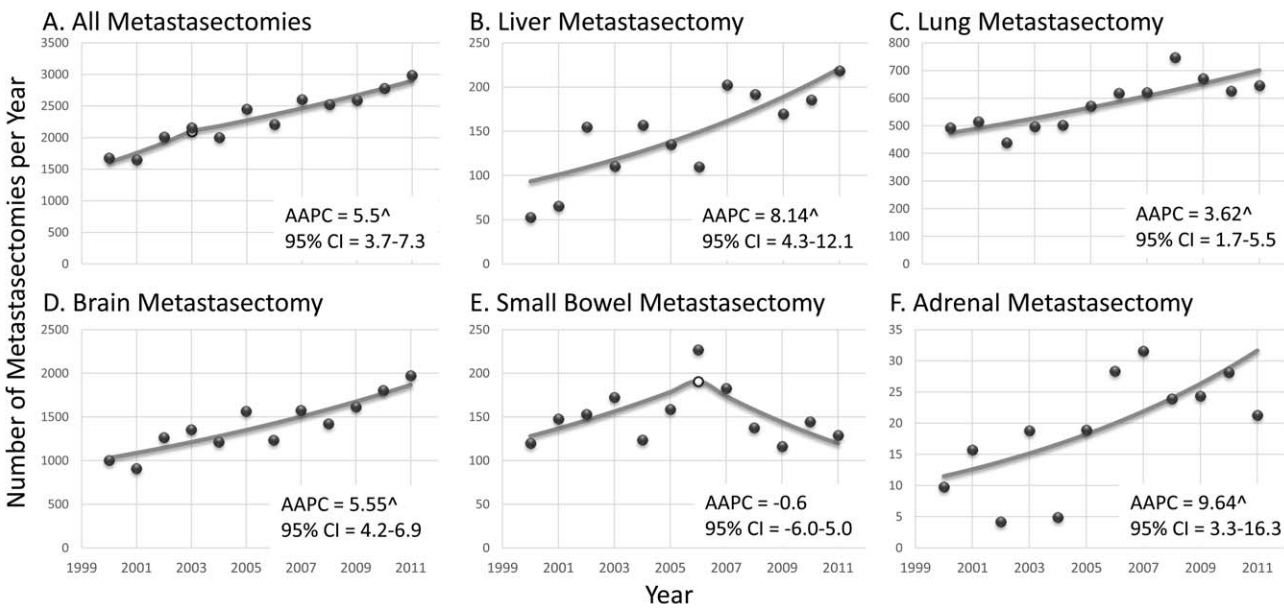


**Figure 3.** Metastasectomy rates for breast cancer are shown for (A) all metastasectomies, (B) liver metastasectomy, (C) lung metastasectomy, (D) brain metastasectomy, (E) small bowel metastasectomy, and (F) adrenal metastasectomy. AAPC indicates average annual percent change; ^, an AAPC that is significantly different from 0 ($P$<.05); 95% CI, 95% confidence interval. An open circle indicates a joinpoint (trend change). Note that the y-axis values vary for each panel.

2011 (AAPC, 5.5; 95% CI, 3.7-7.3), although the APC decreased from 9.2 (95% CI, 1.8-17.2) to 4.1 (95% CI, 3.1-5.2) in 2003 (Fig. 3A). Brain metastasectomy was the most commonly performed metastasectomy, increasing from 1004 cases (95% CI, 865-1142 cases) in 2000 to 1975 cases (95% CI, 1781-2169 cases) in 2011 (AAPC, 5.55; 95% CI, 4.2-6.9) (Fig. 3D). The performance of pulmonary (AAPC, 3.6; 95% CI, 1.7-5.5), liver (AAPC, 8.1; 95% CI, 4.3-12.1), and adrenal (AAPC, 9.6; 95% CI, 3.3-16.3) metastasectomies also increased significantly over the study period (Figs. 3B, 3C, and 3F). Small bowel metastasectomy demonstrated no significant change (Fig. 3E).

Melanoma was the least common indication for metastasectomy and also was associated with the slowest rate of increase in metastasectomies of the cancer types examined; overall incidence-adjusted metastasectomies increased from 1364 metastasectomies (95% CI, 1206-1522 metastasectomies) to 1676 metastasectomies (95% CI, 1521-1831 metastasectomies) from 2000 through 2011 (AAPC, 4.0; 95% CI, 2.1-6.0) (Fig. 4A). Brain metastasectomy was most common (AAPC, 3.7; 95% CI, 1.4-6.0), but lung, small bowel, and adrenal metastasectomies were all found to demonstrate significantly increasing trends (Figs. 4C-4F). Only liver metastasectomy for melanoma did not demonstrate a significant change in incidence (Fig. 4B).

### *Trends in Inpatient Mortality Rates by Cancer Type*

Inpatient mortality after metastasectomy was rare across all cancer types: 1.65% (95% CI, 1.26%-2.04%) for melanoma, 1.91% (95% CI, 1.54%-2.28%) for breast cancer, 2.13% (95% CI, 1.91%-2.34%) for colorectal cancer, and 3.18% (95% CI, 2.86%-3.51%) for lung cancer. Inpatient mortality rates declined for all cancer types from 2000 through 2011, although this change was only significant for colorectal and lung cancer metastasectomies (Fig. 5). Lung cancer metastasectomy, which had the highest initial mortality, demonstrated the most substantial decrease (AAPC, −6.2; 95% CI, −11.7 to −0.3), and the decline in mortality was particularly pronounced from 2008 through 2011 (APC, −18.1; 95% CI, −36.1 to 4.9) (Fig. 5B).

In addition, the inpatient mortality associated with individual resections across cancer types was analyzed. Small bowel metastasectomy was associated with the highest mortality (6.03%; 95% CI, 5.4%-6.7%), followed by brain (2.20%; 95% CI, 2.0%-2.5%), adrenal (1.79%; 95% CI, 0.8%-2.8%), liver (1.42%; 95% CI, 1.2%-1.7%), and lung (0.92%; 95% CI, 0.7%-1.2%) metastasectomy. From 2000 to 2011, a significant decrease in mortality by resection type was observed only for liver metastasectomy (AAPC, −6.42; 95% CI, −12.3 to −0.2). The mortality rates associated with other resection types did not vary significantly over the study period

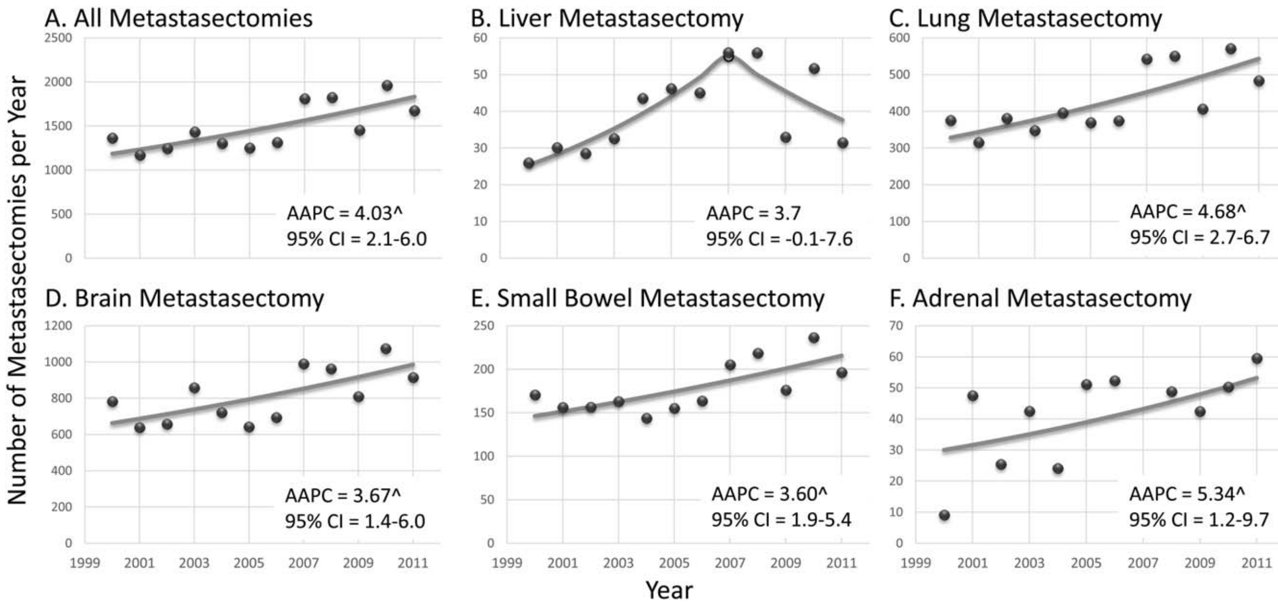


**Figure 4.** Metastasectomy rates for melanoma are shown for (A) all metastasectomies, (B) liver metastasectomy, (C) lung metastasectomy, (D) brain metastasectomy, (E) small bowel metastasectomy, and (F) adrenal metastasectomy. AAPC indicates average annual percent change; ^, an AAPC that is significantly different from 0 ($P<.05$); 95% CI, 95% confidence interval. An open circle indicates a joinpoint (trend change). Note that the y-axis values vary for each panel.

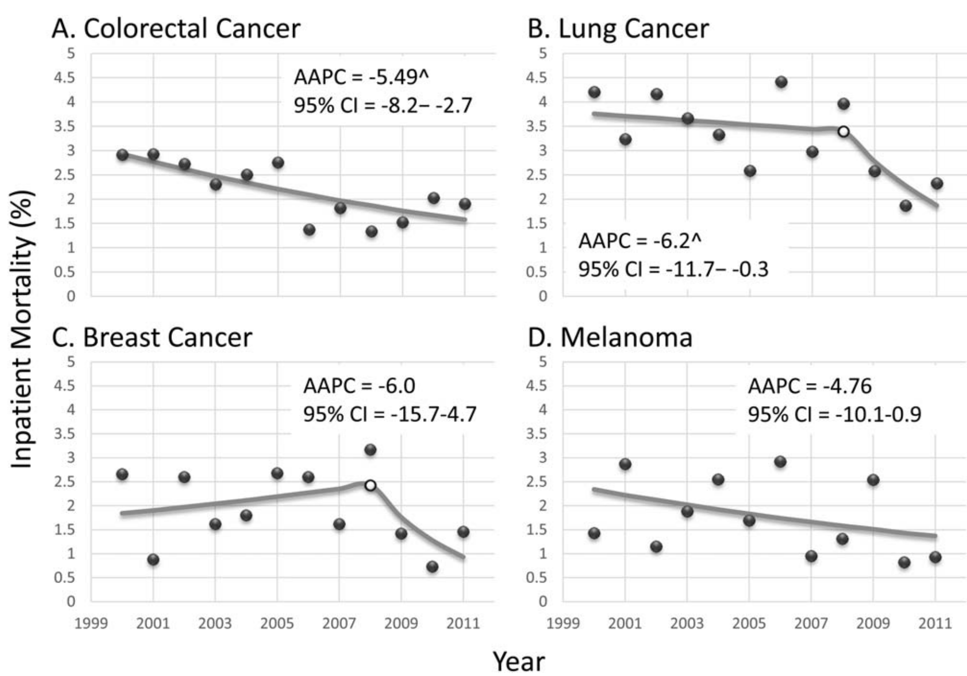


**Figure 5.** Inpatient mortality trends are shown by cancer type. (A) Metastasectomy rates for colorectal cancer are shown. (B) Metastasectomy rates for lung cancer are shown. (C) Metastasectomy rates for breast cancer are shown. (D) Metastasectomy rates for melanoma are shown. AAPC indicates average annual percent change; ^, an AAPC that is significantly different from 0 ($P<.05$); 95% CI, 95% confidence interval. An open circle indicates a joinpoint (trend change).

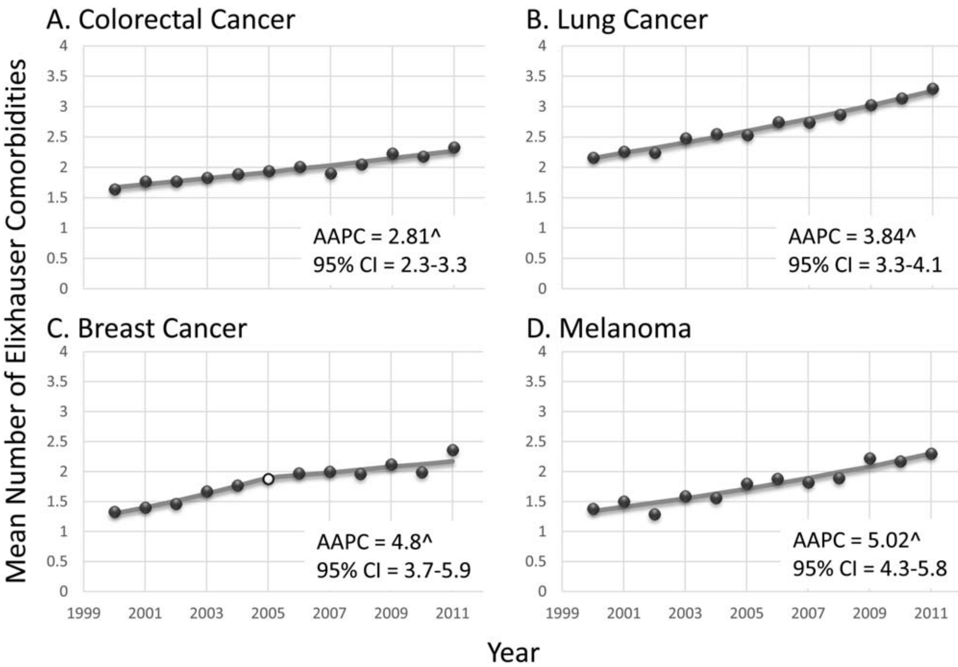


**Figure 6.** Elixhauser comorbidity trends are shown by cancer type. (A) Metastasectomy rates for colorectal cancer are shown. (B) Metastasectomy rates for lung cancer are shown. (C) Metastasectomy rates for breast cancer are shown. (D) Metastasectomy rates for melanoma are shown. AAPC indicates average annual percent change; ^, an AAPC that is significantly different from 0 ($P<.05$); 95% CI, 95% confidence interval. An open circle indicates a joinpoint (trend change).

(data not shown), although the decrease in mortality after brain metastasectomy approached statistical significance (AAPC, −5.6; 95% CI, −11.2 to 0.4 [$P=.10$]).

### *Trends in Elixhauser Comorbidities by Cancer Type*

Given the trend toward decreasing inpatient mortality, we sought to determine whether patient selection, as measured by the number of Elixhauser comorbidities, had changed as well. Overall, the mean number of Elixhauser comorbidities varied by cancer type, from melanoma (1.84; 95% CI, 1.80-1.88) and breast cancer (1.87; 95% CI, 1.83-1.91) to colorectal cancer (1.98; 95% CI, 1.96-2.00) and to lung cancer (2.72; 95% CI, 2.69-2.75). From 2000 through 2011, a significant increase in the mean number of comorbidities at the time of metastasectomy was observed for all cancer types (Fig. 6). Breast cancer and melanoma, which were associated with the lowest mean number of comorbidities in 2000 (1.33 and 1.38, respectively), demonstrated the most rapid increase in comorbidities (AAPC, 4.8 and 5.0, respectively) (Figs. 6C and 6D).

### *Comparison of High-Volume and Low-Volume Metastasectomy Centers*

We then sought to determine how institutional experience in metastasectomy affected practice patterns. High-volume status (defined as those centers with a metastasectomy volume within the top decile by cancer type) was determined to be ≥12 cases for colorectal cancer metastasectomy, ≥16 cases for lung cancer metastasectomy, ≥6 cases for breast cancer metastasectomy, and ≥8 cases for melanoma metastasectomy. High-volume centers performed 70.3% (95% CI, 69.8%-71.0%) of colorectal cancer, 59.6% (95% CI, 58.8%-60.5%) of lung cancer, 68.8% (95% CI, 67.6%-70.0%) of breast cancer, and 61.4% (95% CI, 60.1%-62.8%) of melanoma metastasectomies. The increasing trend in the performance of metastasectomies was nearly entirely limited to high-volume institutions (Fig. 7). In 2000, high-volume institutions performed 59.6% (95% CI, 56.9%-62.4%) of colorectal metastasectomies. By 2011, 76.2% of colorectal metastasectomies (95% CI, 74.1%-78.2%) were performed at high-volume centers (Fig. 7A). Similar, although less pronounced, differences were observed across all cancer types (Figs. 7B-7D).

It is interesting to note that although trends in the mean number of Elixhauser comorbidities were parallel at high-volume and low-volume centers (data not shown), patients treated at low-volume centers demonstrated a significantly higher number of Elixhauser comorbidities for all cancer types (Table 2). Similarly, trends in inpatient

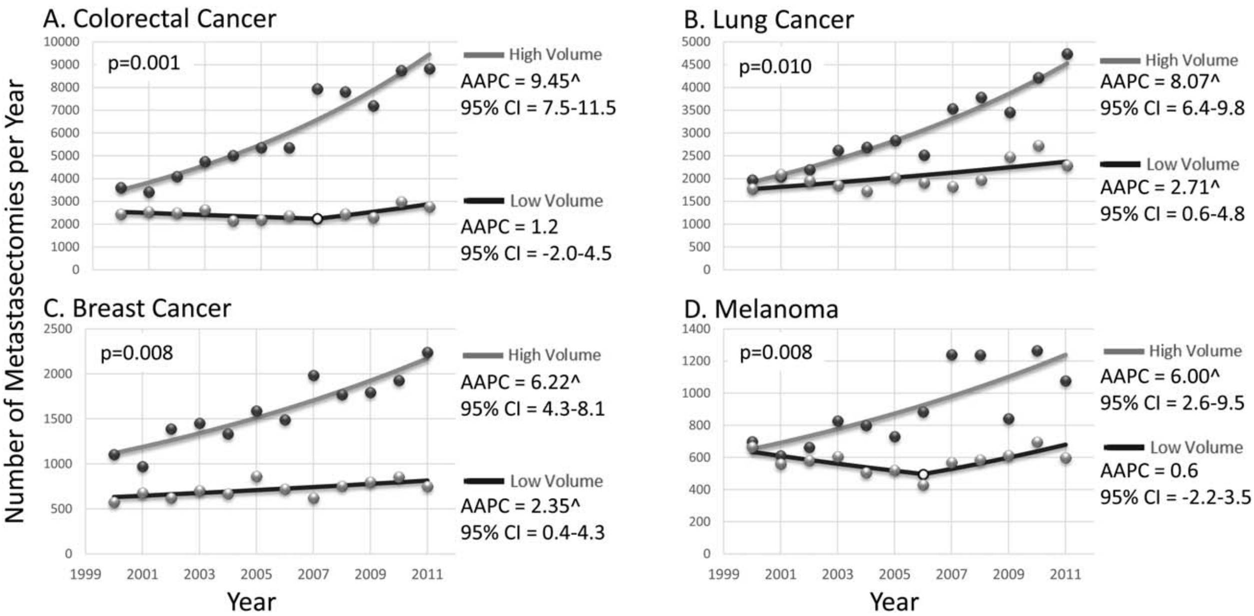


**Figure 7.** Metastasectomy rates at high-volume and low-volume centers are shown by cancer type. (A) Metastasectomy rates for colorectal cancer are shown. (B) Metastasectomy rates for lung cancer are shown. (C) Metastasectomy rates for breast cancer are shown. (D) Metastasectomy rates for melanoma are shown. AAPC indicates average annual percent change; ^, an AAPC that is significantly different from 0 (*P*<.05); 95% CI, 95% confidence interval. The *P* in the left upper quadrant of each panel represents the probability that the trends of high-volume and low-volume centers are parallel. An open circle indicates a joinpoint (trend change). Note that the y-axis values vary for each panel.

**TABLE 2.** Comparison of Patient Selection and Inpatient Mortality at High-Volume and Low-Volume Institutions

| | Colorectal Cancer | | | Lung Cancer | | | Breast Cancer | | | Melanoma | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* |
| Mean no of Elixhauser comorbidities | | | | | | | | | | | | |
| High-volume institutions | 1.84 | 1.81-1.86 | <.001 | 2.64 | 2.60-2.67 | <.001 | 1.79 | 1.74-1.83 | <.001 | 1.79 | 1.73-1.84 | .004 |
| Low-volume institutions | 2.32 | 2.28-2.36 | | 2.78 | 2.73-2.82 | | 2.04 | 1.97-2.12 | | 1.92 | 1.85-1.99 | |
| Inpatient mortality rate, % | | | | | | | | | | | | |
| High-volume institutions | 1.55% | 1.33%-1.77% | <.001 | 2.34% | 1.99%-2.70% | <.001 | 1.33% | 0.96%-1.70% | <.001 | 1.66% | 1.16%-2.16% | .957 |
| Low-volume institutions | 3.50% | 3.00%-4.00% | | 4.34% | 3.76%-4.93% | | 3.19% | 2.35%-4.03% | | 1.64% | 1.01%-2.27% | |

Abbreviation: 95% CI, 95% confidence interval.

mortality were parallel for all cancer types by volume status (data not shown). However, high-volume centers demonstrated significantly lower mortality rates compared with low-volume centers for all cancer types except melanoma, for which no difference was observed (Table 2).

### *Trends in Resection of Metastatic Disease by Anatomic Site*

In an effort to discern the role that advances in the surgical techniques of individual organ resections might play in the performance of metastasectomy, resections were analyzed separately by anatomic site across tumor types. Liver metastasectomies demonstrated the highest rate of increase of any metastatic site (AAPC, 10.0; 95% CI, 8.3-11.7). Lung and adrenal metastasectomies also increased significantly (AAPC, 7.4 [95% CI, 5.5-9.3] and AAPC, 6.3 [95% CI, 4.7-7.8], respectively). Brain metastasectomy demonstrated a slower rate of increase from 2000 through 2006 (AAPC, 4.0; 95% CI, 2.2-5.8), but increased significantly from 2006 to 2011 (AAPC, 7.8; 95% CI, 5.7-9.9). Only small bowel metastasectomies declined during the study period (AAPC, −0.9; 95% CI, −1.8 to −0.04).

## DISCUSSION

The current study used a nationally representative data set to estimate the incidence-adjusted number of metastasectomies performed for common solid organ malignancies in the United States from 2000 through 2011. We identified a significantly increasing trend in overall metastasectomies for all evaluated cancer types across the study period. Colorectal cancer was the most common indication for metastasectomy, followed by lung cancer, breast cancer, and melanoma. The inpatient mortality rate trended down in all cancer types, most significantly in colorectal and lung cancers. Nevertheless, the average number of comorbid diagnoses in patients undergoing metastasectomy increased during the study period. Furthermore, the increasing trends in the performance of metastasectomy were driven almost exclusively by an increasing number of cases performed at high-volume centers.

The precise etiology of these trends is likely multifactorial. The increase was observed across all anatomic sites (regardless of cancer type) except in small bowel metastases, suggesting that improvements in surgical technique specific to an anatomic site are not solely responsible. In colorectal cancer, the malignancy for which there were the most efficacious systemic therapies available during the study period, we observed the greatest increase in the use of metastasectomy. However, in breast cancer, improvements in systemic therapy occurred over the study period, but the increase in metastasectomy was not comparable to that observed in colorectal cancer. Furthermore, in melanoma, which demonstrated the lowest increase in the rate of metastasectomy, very limited systemic options were available until 2011 (the end of the study period).[27] This is perhaps suggestive that the improved prognosis associated with effective systemic therapies may allow additional opportunities for surgical intervention. One might speculate that with the recent advances in therapy for melanoma, the current decade will observe an increase in the rate of melanoma metastasectomy as the overall prognosis for patients with metastatic disease improves. However, the influence of systemic therapy alone is clearly limited, because substantial and significant increases were noted in metastasectomy regardless of cancer type.

Certainly, as interest has grown in metastasectomy, an increasing number of studies have reported favorable associated outcomes.[14,16-23] The experience in colorectal cancer is particularly robust,[7-9] and the promising outcomes in that disease may have led to an increased willingness to attempt metastasectomy in patients with other types of cancer as well.

Perioperative morbidity and mortality must be a consideration when determining the appropriateness of surgical resection, particularly in patients with advanced malignancies. The decreasing trends in inpatient mortality (statistically significant for colorectal cancer and lung cancer) suggest that these procedures are now being performed more safely than ever before. Notably, liver and brain metastasectomies were associated with the most substantial decreases in mortality. A decrease in the surgical mortality may lower the threshold for the performance of metastasectomy. Indeed, we detected these inpatient mortality trends despite an increase in the incidence of patient comorbidities. The ability to safely perform metastasectomy in increasingly ill patients certainly expands the potential pool of patients able to undergo the procedure and may help to explain the increase in its use.

The role of high-volume institutions in metastasectomy is interesting. We found that high-volume centers (defined as the top 10% by volume) perform $\geq$60% of all the metastasectomies across cancer types. As has been observed in many other major surgeries,[34,38] high-volume centers have a lower incidence of inpatient mortality after metastasectomy for all cancer types except melanoma. However, it is surprising to note that patients at high-volume institutions appear to have fewer comorbidities than those at low-volume centers. This may be consistent with experienced practitioners taking a more cautious approach to patient selection, which indeed has been considered paramount to successful surgery in patients with advanced malignancies.[39]

There are several limitations associated with the current study. Foremost, this work relies on administrative data and as such is limited by the accuracy and completeness of the coding process. It is possible that trends in the coding process itself have changed, which may introduce bias into the reported trends. In particular, this may be the case for the number of Elixhauser comorbidities, which may have been more thoroughly coded over time, as risk-adjusted outcomes are increasingly scrutinized. In addition, the data set is limited to inpatient admissions. This is particularly limiting in the interpretation of mortality rates because postoperative deaths occurring after discharge or transfer to hospice would not be captured. Furthermore, the definition of "high volume" in the current study was limited to patients undergoing metastasectomy. It is possible that centers with a high volume of a certain type of procedure (ie, liver resection) do not coincide exactly with high-volume metastasectomy centers. Finally, the surgical indication for metastasectomy was not available in the data set. As such, it is unclear whether these metastasectomies were performed for curative intent or palliation. It is interesting to note that small bowel metastasectomy was the lone resection type noted to decrease during the study period. This may be because small bowel resections are frequently performed in the palliative setting for a symptomatic obstruction and much less commonly are the lone site of metastasis. Therefore, it appears unlikely that the increase observed across the other sites is due to substantial changes in the practice of surgical palliation.

Given that our definition of metastasectomy was based on the matching of a primary cancer diagnosis, a metastatic site diagnosis, and a procedure code, if one of these codes was omitted a metastasectomy would not be captured. We would thus anticipate that these data, if anything, underestimate the true incidence of these procedures. Similarly, the current study did not attempt to capture metastasectomies of anatomic sites beyond the ones stated. As such, the overall rate of metastasectomy does not include resections of intraperitoneal disease, lymph node disease, or other more rare sites.

The performance of metastasectomy is increasing across cancer types. The inpatient mortality rates are stable or decreasing for all cancer types, despite metastasectomies being performed among patients with an increasing number of comorbidities. High-volume centers are driving the trends in the performance of metastasectomy. Changes in systemic therapy did not appear to substantially impact trends during the period of the current study, suggesting that the role of surgical intervention in patients with metastatic disease is generally not diminished by medical advances. Furthermore, these findings highlight the importance of continued study of the long-term outcomes among these patients. Although the ability to perform more and safer surgical procedures does potentially increase the number of patients who can tolerate a metastasectomy, it does nothing to broaden the influence of the procedure on the natural history of the disease. Thus, careful patient selection and continued study to determine which patients may derive oncologic benefit from metastasectomy remain critical.

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