RISK OF RECURRENCE IN CERTAIN EARLIER-STAGE CANCERS:

Non–Small Cell Lung Cancer (NSCLC), Melanoma, Head and Neck Squamous Cell Carcinoma (HNSCC), and Renal Cell Carcinoma (RCC)

As a surgeon, you play a critical role beyond the resection of the primary tumor.[1] The risk of recurrence after resection is a concern, even in earlier-stage cancers.[2-6] Below is some helpful information to keep in mind as you assess your patients' risk of recurrence in collaboration with your medical oncologist colleagues.[1,7]

- Recurrence due to metastatic spread is a multistep process that can take months or years before it becomes detectable.[2]
- Dissemination of cancer cells from primary to distant sites can occur even before diagnosis of the primary tumor.[2,8]
- The risk of recurrence may vary based on tumor type.[2,8]

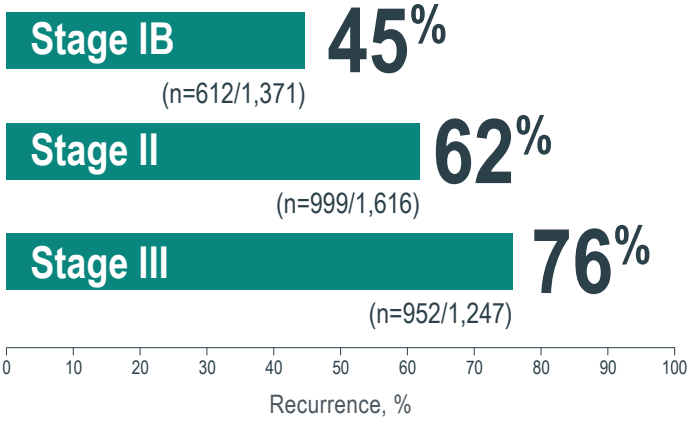
Rate of recurrence or death, after resection, with or without adjuvant chemotherapy, within 5 years by stage of NSCLC.[3]

Lung Adjuvant Cisplatin Evaluation (LACE): A pooled analysis by the LACE Collaborative Group.[3]

Study Details: The LACE study was a retrospective, pooled analysis by the LACE Collaborative Group that included 4,584 patients with completely resected NSCLC across 5 randomized trials from 1994 to 2001. Of these patients, 2,281 received adjuvant cisplatin-based chemotherapy. The primary end point was overall survival (OS) and a secondary end point was disease-free survival (DFS). The interactions between patient subgroups or treatment types and chemotherapy effect on OS were analyzed using hazard ratios and log-rank tests stratified by trial.[3]

Inclusion and Exclusion Criteria: Trials eligible for inclusion were those that randomly assigned more than 300 patients with completely resected NSCLC to receive postoperative cisplatin-based chemotherapy vs no chemotherapy or cisplatin-based chemotherapy plus postoperative radiotherapy (administered sequentially) vs postoperative radiotherapy alone.[3]

Rate of Recurrence or Death Within 5 Years by Stage[3]



Additional recurrence data in NSCLC from a separate study are included on the next page.

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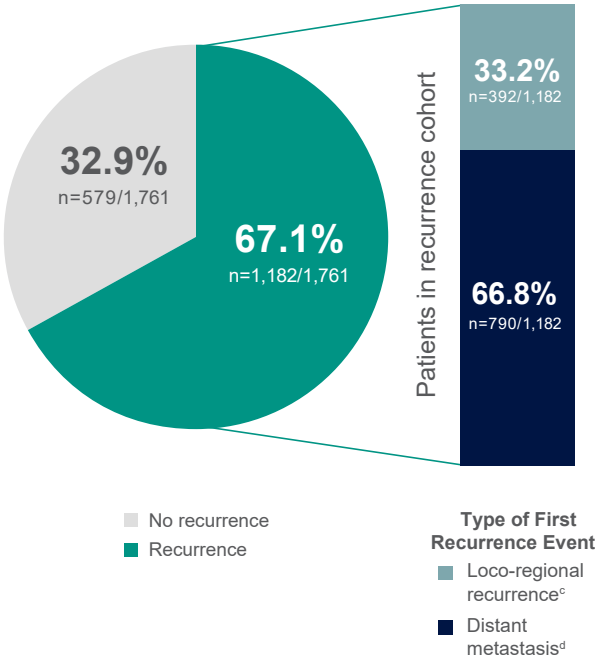
NSCLC after resection: Rate and type of first recurrence.[9]

Data from a retrospective observational study of patients with stage IB (tumor size ≥4 cm)–IIIA NSCLC, after resection, with or without adjuvant chemotherapy.[9,a]

Study Details: Data collected from the SEER-Medicare database for the years 2007–2019 were used to identify patients with newly diagnosed stage IB (tumor size ≥4 cm)–IIIA NSCLC (per AJCC 7th edition) who received primary surgery (lobectomy, bilobectomy, or pneumonectomy) within 6 months of initial NSCLC diagnosis, with or without adjuvant chemotherapy, and did not receive neoadjuvant chemotherapy or neoadjuvant/adjuvant radiation therapy. A total of 1,761 patients with earlier-stage NSCLC who received primary surgery met the eligibility criteria and were included in the study, including 1,182 (67.1%) patients identified with disease recurrence anytime during follow-up (median follow-up time from initial surgery to death: 55.0 months).[9]

Limitations: The SEER-Medicare database only includes Medicare patients aged ≥65, therefore, the results from this study may not reflect outcomes among a younger patient population with NSCLC. Patients who did not receive treatment in the event of recurrence or did not have codes associated with metastasis in their claims were also missed. The data used in this study were obtained from 2007 to 2019, which was before the approval of any targeted or immunotherapies for NSCLC in the United States. Coding inaccuracies may have led to misclassification bias and misidentification of patients with NSCLC recurrence. Some clinical information, such as complete resection status, is not available in the data. Therefore, a 90-day treatment-free interval was used to indicate the end of primary treatment and served as a proxy for the disease-free state.[9]

Rate and Type of Recurrence After Resection[9,b]



The risk of recurrence after complete resection in stage IIB and IIC melanoma: A retrospective analysis.[4]

Study Design for Real-World Retrospective Chart Review: This study was a retrospective chart review of 567 adult patients who were followed for a median of 38.8 months after complete resection of stage IIB or IIC cutaneous melanoma between 2008 and 2017. Patients in this study had at least 2 visits after diagnosis recorded within the US Oncology Network, a community-based network of over 480 cancer centers in 25 states. Eighty (14.1%) patients in the study received adjuvant treatment for stage IIB or IIC melanoma; of those who received adjuvant treatment, 77 (96.3%) received IFN-alpha. Recurrence in this study was defined as physician-documented recurrence or progression.[4]

37% (n=140/375)

RECURRENCE RATE
in patients with completely resected
Stage IIB melanoma

43% (n=83/192)

RECURRENCE RATE
in patients with completely resected
Stage IIC melanoma

50% (n=70/140) of those patients with completely resected stage IIB melanoma whose disease recurred after resection experienced **distant metastasis as their first recurrence.**

58% (n=48/83) of those patients with completely resected stage IIC melanoma whose disease recurred after resection experienced **distant metastasis as their first recurrence.**

Additional recurrence data in melanoma from a separate study are included on the next page.

AJCC = American Joint Committee on Cancer; IFN-alpha = interferon-alpha; NSCLC = non–small cell lung cancer; SEER = Surveillance, Epidemiology and End Results.

[a]Per AJCC 7th edition. [b]Outcome of primary surgery (complete vs partial resection) is not available in the data. [c]Loco-regional recurrence was defined as a new diagnosis of loco-regional disease, and/or additional surgery, curative radiation therapy, and chemoradiation following a 90-day treatment-free interval after the initial surgery.[9] [d]Distant metastasis was defined as a diagnosis of metastatic disease, and/or additional palliative radiation therapy, and systemic therapy for advanced NSCLC following a 90-day treatment-free interval after the initial surgery.[9]

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The risk of recurrence after complete resection in stage III melanoma: A retrospective analysis.[10,11]

Study Design for Multi-Country Retrospective Chart Review: This study was a retrospective chart review of 251 adult patients who had undergone complete resection from 2011–2016 for stage III cutaneous melanoma followed by a minimum of 2 years of watch-and-wait. Patients included in this study were from North America, South America, and Europe.[10]

44% (n=40/91)
RECURRENCE RATE in patients with completely resected Stage IIIA melanoma[11]

44.5% (n=49/110)
RECURRENCE RATE in patients with completely resected Stage IIIB melanoma[11]

74% (n=37/50)
RECURRENCE RATE in patients with completely resected Stage IIIC melanoma[11]

53% (n=125/251) Of the 50% of patients with completely resected **stage IIIA, IIIB, or IIIC melanoma** whose disease recurred after resection, 53% experienced unresectable or **distant metastasic disease as their first recurrence.**[11]

Rates of recurrence from a retrospective study among patients with locally advanced head and neck squamous cell carcinoma (LA HNSCC).[12]

A retrospective review of data from the SEER-Medicare database

Study Details: A retrospective study to assess real-world clinical outcomes for newly diagnosed patients with stage III–IVB LA HNSCC as staged according to the AJCC 6th and 7th editions. The study included 526 patients with cancers of the oral cavity, oropharynx, larynx, and hypopharynx and was conducted utilizing the Surveillance, Epidemiology, and End Results (SEER) Medicare database for cases diagnosed between 2007–2017. Eligible participants were adults aged 66 years or older who underwent surgical resection as primary treatment within 4 months of their initial diagnosis.[12]

55.7%
Cumulative incidence rate of recurrence at 5 years[12]

Most recurrences (73%) occurred within the first year after primary treatment initiation[12]

- 58.2% of patients underwent surgery followed by radiation and/or systemic therapy, while 27.4% of the patients underwent primary surgery only.

Limitations of the SEER-Medicare study were[12]:

- Findings may have limited generalizability due to the inclusion of Medicare beneficiaries aged ≥66 years only.
- HNSCC recurrence was identified based on various procedure codes, diagnosis codes, and drug codes; coding inaccuracies may have led to misclassification bias and misidentification of patients with HNSCC recurrence.

AJCC = American Joint Committee on Cancer.

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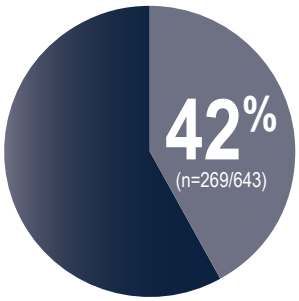
For certain patients with renal cell carcinoma (RCC) after nephrectomy, an observational analysis of 643 patients using SEER-MEDICARE DATA from 2007 to 2016 revealed[6]:

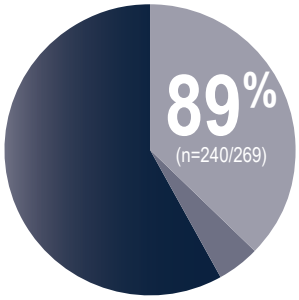


of certain patients with RCC post nephrectomy EXPERIENCED RECURRENCE[6]

ANALYSIS POPULATION[6,13]

- T2, Grade 4, N0, M0
- T3, N0, M0
- T4, N0, M0
- T any stage, N+, M0
- **Median follow-up duration of analysis was 23 months.**
- 95% of patients analyzed had T3 tumors.

Of those patients who experienced recurrence,



HAD METASTATIC DISEASE[6]

ANALYSIS LIMITATIONS[6]

- Recurrence was inferred from the database codes rather than directly determined based on clinical data.
- The analyzed SEER-Medicare data represent patients ≥65 years. Hence, the results from this analysis may not reflect outcomes among the younger patient population.
- Impacts of recurrence may be confounded by unmeasured characteristics. Caution must be used when considering causal inference from this analysis.

In an analysis of the same SEER-Medicare data from 2007 to 2016 for a subset of patients with RCC post nephrectomy, all patients with T3N0 tumors were at risk of recurrence[6]

5-Year Post Nephrectomy Recurrence Rates[6,13]

45%

of T3N0 patients in this observational analysis **EXPERIENCED RECURRENCE**

37%	**T3 Grades 1–2** (N=297)
50%	**T3 Grade 3** (N=250)
72%	**T3 Grade 4** (N=64)

Note: Patients were followed from the date of initial nephrectomy until the earliest of recurrence or censoring at 1) death, 2) end of Medicare Part A, B, or D eligibility, and 3) end of data availability on December 31, 2016.[13]

ANALYSIS POPULATION[6]

- T2, Grade 4, N0, M0
- T3, any grade, N0, M0

Analysis Limitations (above) continued to apply throughout the analysis.

M0 = no distant metastasis; N+ = regional lymph node metastasis; N0 = no regional lymph node metastasis; SEER = Surveillance, Epidemiology, and End Results; T = primary tumor; T2 = tumor >7 cm in greatest dimension, limited to the kidney; T3 = tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia; T4 = tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland).[14]

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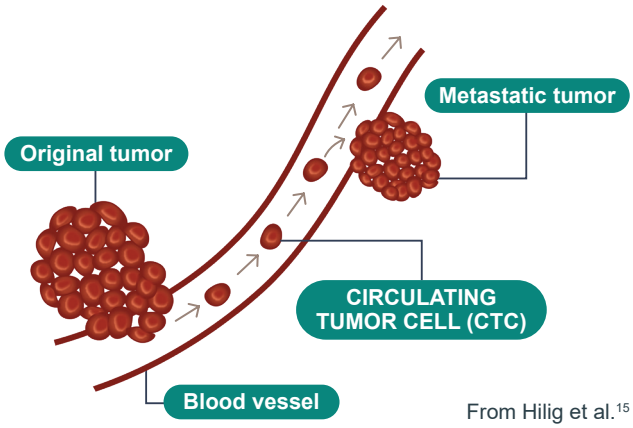
Micrometastases May Contribute to Metastatic Recurrence

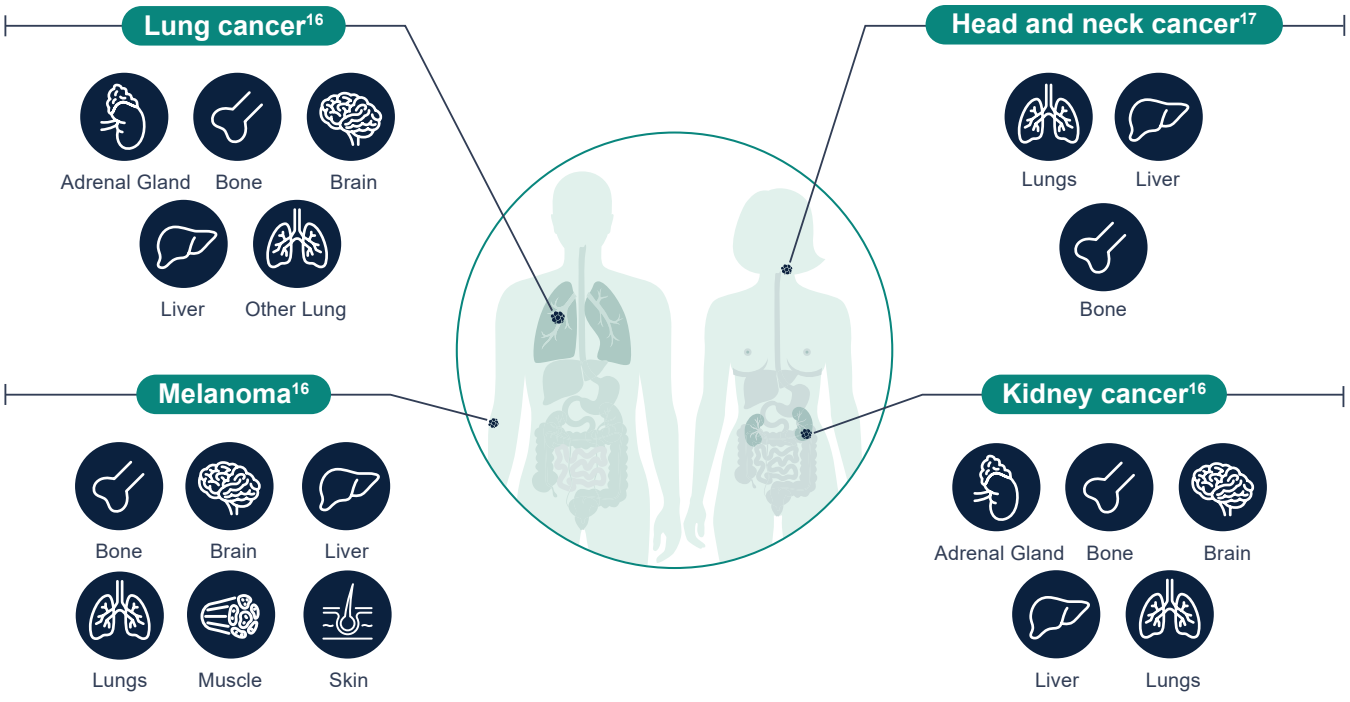
Micrometastases are small numbers of cancer cells that spread from the primary tumor to distant sites in the body. They may be undetectable on a screening or diagnostic test.[15]



From Hilig et al.[15]

Main Sites of Metastasis for Certain Tumor Types[a]

Cancer can spread to almost any part of the body, although different types of cancer are more likely to spread to certain organs than others.[16]



Collaborate with your multidisciplinary treatment team, including medical oncologist colleagues, to assess your patient's risk of recurrence.[1,7]

[a]Not including the lymph nodes.[16]

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