RISK OF RECURRENCE IN CERTAIN EARLIER-STAGE CANCERS:

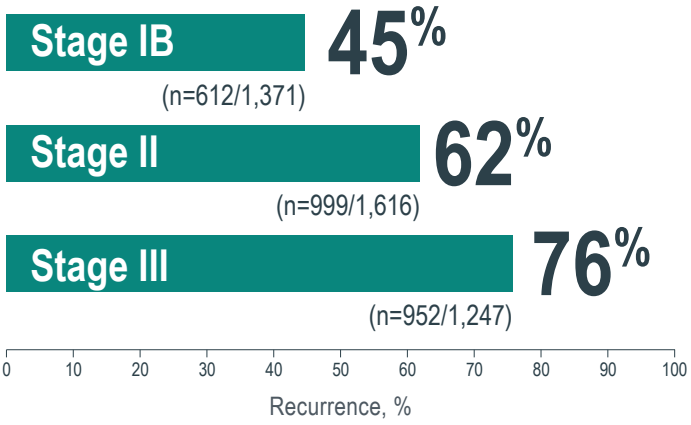
Non–Small Cell Lung Cancer (NSCLC), Melanoma, and Renal Cell Carcinoma (RCC)

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.[2-5] Below is some helpful information to keep in mind as you assess your patients' risk of recurrence in collaboration with your medical oncologist colleagues.[1,6]

- 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.[2,7]
- The risk of recurrence may vary based on tumor type.[2,7]

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

Study Details: The rate of recurrence or death is based on a 2008 pooled analysis by the LACE Collaborative Group. The study 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,a]



Additional NSCLC data are included on the next page.

[a]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]

LACE = Lung Adjuvant Cisplatin Evaluation.

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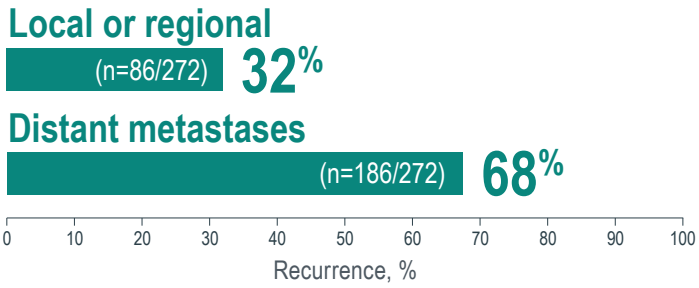
In a separate retrospective study of patients with stage IB–IIIA NSCLC, after resection, with or without adjuvant chemotherapy, 33% of patients had recurrence[8]

(n=272/831)

Out of the 33% with recurrence, the first recurrence was metastatic for some[8]



Study Details: A retrospective observational study consisting of data collected via medical record abstraction among 831 patients with complete resection of stage IB–IIIA NSCLC per AJCC 7th edition in France, Germany, and the United Kingdom. Eligible patients were diagnosed between January 1, 2009, and December 31, 2011, with a median follow-up time of 26 months. Nearly half of the patients (48.4%; n=402/831) received adjuvant systemic therapy. The primary objective of the study was to identify and quantify the treatment patterns of these patients. As a second objective, the study also aimed at evaluating disease recurrence and progression for the same patients.[8]

Recurrence risk following resection of stage IIB or IIC melanoma based on a retrospective study[4]

32% (n=73/226) **RECURRENCE** in patients with resected stage IIB melanoma

46% (n=52/112) **RECURRENCE** in patients with resected stage IIC melanoma

30% of those patients with **stage IIB melanoma** whose disease recurred after resection (n=22/73) had **systemic disease as their first recurrence**.

- The sites of first recurrence for remaining patients were local/ in-transit (47%; n=34/73) and regional nodal (23%; n=17/73).

52% of those patients with **stage IIC melanoma** whose disease recurred after resection (n=27/52) had **systemic disease as their first recurrence**.

- The sites of first recurrence for remaining patients were local/ in-transit (29%; n=15/52) and regional nodal (19%; n=10/52).

Study Design: A retrospective review of 738 adult patients from a prospectively maintained, single-institution database, with resected pathologic stage II primary cutaneous melanoma (AJCC 7th edition). All patients were treated at Memorial Sloan Kettering Cancer Center between January 1993 and December 2013. Patients underwent pathological nodal staging by sentinel lymph node biopsy or elective lymph node dissection. Median follow-up of patients with stage IIB and stage IIC melanoma was 50.2 and 46.2 months, respectively.[4]

AJCC = American Joint Committee on Cancer; NSCLC = non–small cell lung cancer.

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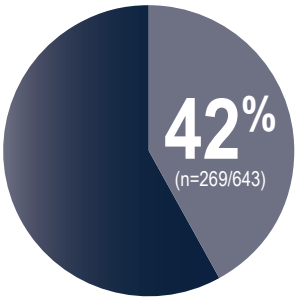
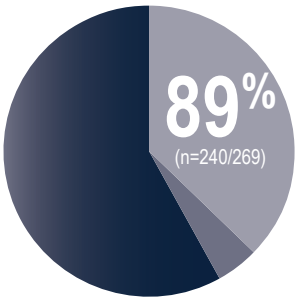
For certain patients with renal cell carcinoma (RCC) after nephrectomy, an observational analysis of 643 patients using SEER-MEDICARE DATA from 2007 to 2016 revealed[5]:



of certain patients with RCC post nephrectomy EXPERIENCED RECURRENCE[5]

Of those patients who experienced recurrence,



HAD METASTATIC DISEASE[5]

ANALYSIS POPULATION[5,9]

- 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.

ANALYSIS LIMITATIONS[5]

- 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[5]

5-Year Post Nephrectomy Recurrence Rates[5,9]

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.[9]

ANALYSIS POPULATION[5]

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

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

M0 = no distant metastasis; N0 = no regional lymph node metastasis; N+ = 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).[10]

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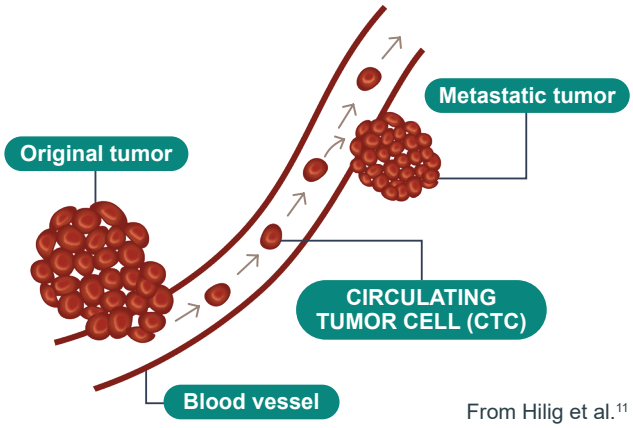
Micrometastases May Contribute to Metastatic Recurrence

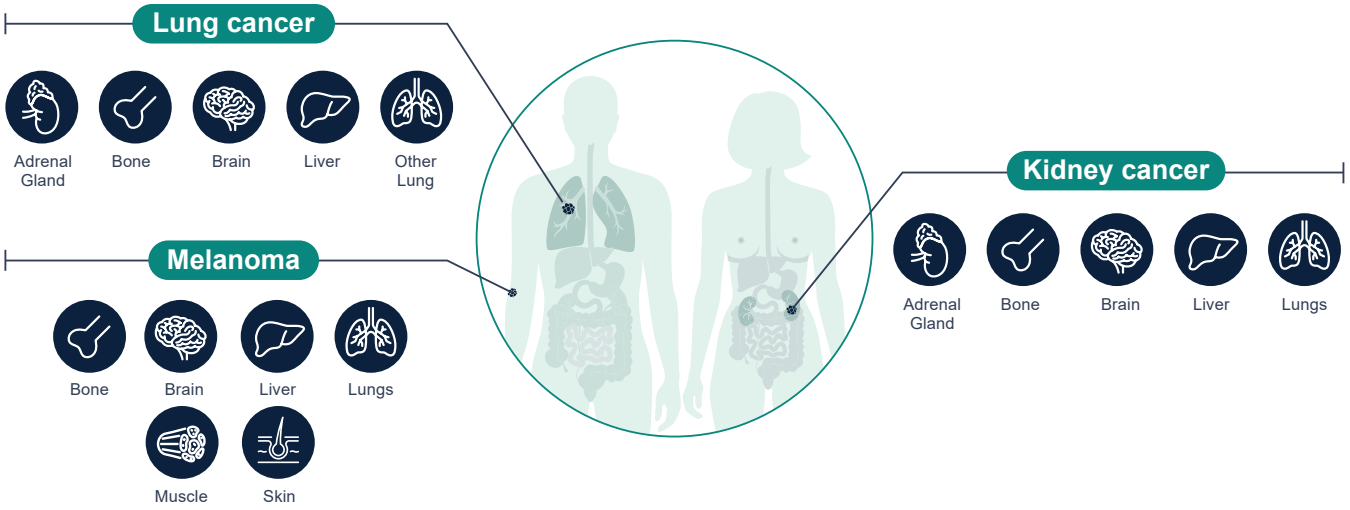
Micrometastases are small numbers of cancer cells that spread from the primary tumor to distant sites in the body. They may be undetectable on a screening or diagnostic test.[11]



From Hilig et al.[11]

Main Sites of Metastasis for Certain Tumor Types[12,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.



Collaborate with your medical oncologist colleagues and multidisciplinary treatment team to assess your patient's risk of recurrence.[1,6]

[a]Not including the lymph nodes.[12]

1. Berardi R, Morgese F, Rinaldi S, et al. Benefits and limitations of a multidisciplinary approach in cancer patient management. *Cancer Manag Res*. 2020;12:9363–9374. **2.** Sauer S, Reed DR, Ihnat M, Hurst RE, Warshawsky D, Barkan D. Innovative approaches in the battle against cancer recurrence: novel strategies to combat dormant disseminated tumor cells. *Front Oncol*. 2021;11:659963. **3.** Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552–3559. **4.** Lee AY, Droppelmann N, Panageas KS, et al. Patterns and timing of initial relapse in pathologic stage II melanoma patients. *Ann Surg Oncol*. 2017;24(4): 939–946. **5.** Sundaram M, Song Y, Rogerio JW, et al. Clinical and economic burdens of recurrence following nephrectomy for intermediate high- or high-risk renal cell carcinoma: a retrospective analysis of Surveillance, Epidemiology, and End Results-Medicare data. *J Manag Care Spec Pharm*. 2022;28(10):1149–1160. **6.** Selby P, Popescu R, Lawler M, Butcher H, Costa A. The value and future developments of multidisciplinary team cancer care. *Am Soc Clin Oncol Educ Book*. 2019;39:332–340. **7.** Klein CA. Cancer progression and the invisible phase of metastatic colonization. *Nat Rev Cancer*. 2020;20(11):681–694. **8.** Chouaid C, Danson S, Andreas S, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. *Lung Cancer*. 2018;124:310–316. **9.** Sundaram M, Song Y, Rogerio JW, et al. Clinical and economic burdens of recurrence following nephrectomy for intermediate high- or high-risk renal cell carcinoma: a retrospective analysis of Surveillance, Epidemiology, and End Results-Medicare data [supplementary appendix]. *J Manag Care Spec Pharm*. 2022;1–12. **10.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer v2.2024. National Comprehensive Cancer Network. Accessed January 10, 2024. http://www.nccn.org **11.** Hillig T, Nygaard A-B, Nekiunaite L, Klingelhöfer J, Sölétormos G. In vitro validation of an ultra-sensitive scanning fluorescence microscope for analysis of circulating tumor cells. *APMIS*. 2014;122(6):545–551. **12.** Metastatic cancer: when cancer spreads. National Cancer Institute. Updated November 10, 2020. Accessed June 12, 2023. www.cancer.gov/types/metastatic-cancer

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