



## Review

## Local recurrence following lung cancer surgery: Incidence, risk factors, and outcomes



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## ABSTRACT

**Purpose:** To date, few large-scale original studies have focused specifically on local recurrence following curative lung cancer surgery. This review seeks to consolidate and analyze data from these studies regarding local recurrence incidence, risk factors, salvage treatments, and outcomes to increase awareness in the Oncology community and to spark new research in this area.

**Methods:** PubMed literature was searched for large-scale cohort studies involving recurrence following lung cancer surgery. Studies with a primary focus on local recurrence and studies that examined overall recurrence but provided relevant numerical data on local recurrence were included. Each chosen study's methods were critically analyzed to reconcile as best as possible large differences in reported results across the studies.

**Results:** Up to 24% of patients recur locally following lung cancer surgery. Risk of local recurrence increases with the stage of the primary cancer, but even stage I patients experience local recurrence up to 19% of the time. Overall survival time following local recurrence varies widely across studies, from 7 to 26 months, and may be related to frequency of follow-up visits. Salvage therapy appears to increase survival time. However, estimates of this increase vary widely, and measurements of benefits of the various salvage options are confounded by lack of control of subjects' condition at the time of salvage therapy administration.

**Conclusions:** Local recurrence following lung cancer surgery is a significant problem warranting additional research. At present, data on this topic is scarce. We recommend initiation of additional large-scale studies to clearly define the parameters of local recurrence in order to provide useful guidance to clinicians.

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## Introduction

Lung cancer is the most common malignancy in the United States and kills 160,000 Americans each year, placing it well ahead of any other cancer in terms of sheer mortality [1]. Lung cancer causes more deaths per year in the United States than the next four most common cancers combined (colon, breast, pancreas, and prostate) [2]. Furthermore, at \$39 billion, it accounts for more than a quarter of total cancer costs [3]. Surgery is the preferred therapy for patients with lung cancer who qualify for resection [4]. This review attempts to consolidate and clarify the published data available on incidence, risk factors, treatment, and outcomes in lung cancer patients who develop local recurrences after surgery. In doing so, it also reveals the current shortage of reliable data available to aid clinicians in better understanding the phenomenon of local recurrence. Further large scale studies using consistent methods are warranted in order to provide clarity on this topic.

## Journal article search terms and selection criteria

The following search term combinations were used in PubMed to locate potential sources: “carcinoma, non-small-cell lung/surgery[MAJR] AND recurrence” and “lung neoplasms/pathology[MAJR] AND recurrence”. Both prospective and retrospective English language cohort studies with at least 300 subjects receiving initial resection were reviewed, and selection from the search results was based on relevance to the topic of local lung cancer recurrence following curative surgery. Additionally, the bibliographies of articles found using the above criteria were used to identify other cohort studies for potential inclusion. In two instances, we used multiple relevant studies from the same institution that appeared to cover the same time period and possibly the same patients. In these cases, the studies in question, although from the same institution, focused on different topics and were used to support different aspects of this review.

## The definition of local recurrence

The definition of local recurrence varies across the literature. Some studies limit the definition of local recurrences to those found in the bronchial stump, staple line, ipsilateral hilum, and ipsilateral mediastinum [5]. Others have expanded this definition to include the entire ipsilateral lung and contralateral hilar and mediastinal lymph nodes [6]. Still many others provide no clear description of how local recurrence was defined in determining results. A precise definition is important here, as a local recurrence following cancer surgery suggests that the primary malignancy was not completely removed at the time of the operation. Typically, a local recurrence occurs for at least one of three reasons. First, the surgeon may not achieve negative margins on the primary tumor, and thus microscopic deposits would re-grow. Second, the cancer may have spread

to regional lymph nodes which are undetected or not removed. Third, if the cancer had developed satellite nodules or metastases in other portions of the ipsilateral lung, then the malignancy will maintain a local foothold after surgery.

This review focuses on local recurrence and does not include analysis of metachronous tumors. It is important to differentiate between these two entities because they carry significant differences in prognosis and treatment. A metachronous tumor is a primary tumor that appears some time after discovery of the resected primary tumor. It is completely unrelated to the initial primary tumor that was excised. If a newly discovered cancer is physically distinct and separate from the original tumor and has a different histology, then it is likely a metachronous tumor. Also, even if the histologies are identical, but the new tumor is present in a different anatomical portion of the lung, and there is no cancer infiltration in the lymph system connecting the two portions of lung, then this would be considered a metachronous tumor [7]. Although we will not discuss treatment of multiple primary tumors in this review, we note that these tumors occur either synchronously or asynchronously in up to 10% of lung cancer patients [8].

## Local recurrence after lung cancer surgery is rapid and common

Postoperative recurrences following lung cancer surgery typically occur rapidly: 50–90% present within two years following the initial operation, and 90–95% occur within 5 years [2]. Although distant recurrence is more commonly reported, local recurrence is a significant aspect of lung cancer, accounting for as many as a quarter of recurrences after pulmonary resection. Kelsey and colleagues point out that local recurrences are probably under-reported because distant metastases are easier to detect with imaging and often occur first after surgery. Local recurrences developing concomitantly with distant ones are frequently missed [9].

Seven large studies (range: 335–1143 subjects) in cohorts with resectable lung cancer showed widely varying local recurrence rates (See Table 1) [5,7,9–13]. Across the existing literature, the range of reported recurrence rates is quite large due to small sample sizes and variability in primary disease stages, follow-up times and counting methods. We focus on these seven studies because they all included a relatively large number of patients, and most (5 of 7) examined a wide range of stages. Four of the studies tracked only first recurrences [5,10,12,13], while the other three present both initial and follow-on recurrences [7,9,11]. For the sake of consistency, we list only the first recurrences from each study, meaning that these numbers reflect cases in which the first recurrence was either local or a combination of local and distant, but not distant alone. Local recurrences that were discovered subsequent to initial distant recurrences are not included.

The high-end outlier within these seven studies comes from Saynak and colleagues at the University of North Carolina ( $n = 335$ ),

**Table 1**  
Likelihood of local recurrence following lung cancer surgery.

| Author                   | Year | Number of patients | Percent of patients recurring (n) | Percent of patients with initial recurrence purely local (n) | Percent of patients with initial recurrence mixed (n) | Percent of patients with any initial local recurrence (n) |
|--------------------------|------|--------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------|
| Taylor <sup>5</sup>      | 2012 | 1143               | 33 (378)                          | 8 (94)                                                       | None listed                                           | 8 (94)                                                    |
| Saynak <sup>11</sup>     | 2010 | 335                | 33 (111)                          | 12 (41)                                                      | 12 (41)                                               | 24 (82)                                                   |
| Kelsey <sup>9</sup>      | 2009 | 975                | 26 (250)                          | 7 (63)                                                       | 8 (78)                                                | 15 (141)                                                  |
| Hung <sup>13</sup>       | 2009 | 933                | 31 (289)                          | 8 (74)                                                       | 5 (49)                                                | 13 (123)                                                  |
| Nakagawa <sup>a,12</sup> | 2008 | 397                | 22 (87)                           | 7 (30)                                                       | None listed                                           | 7 (30)                                                    |
| Sugimura <sup>10</sup>   | 2007 | 1073               | 36 (390)                          | 7 (79)                                                       | 6 (62)                                                | 13 (141)                                                  |
| Martini <sup>a,7</sup>   | 2005 | 598                | 27 (159)                          | 5 (32)                                                       | None listed                                           | 5 (32)                                                    |

This table lists local recurrence information from seven select studies. Percentages have been rounded to the nearest whole number.

<sup>a</sup> Stage I only.

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