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

David Fedor[*], **W. Rainey Johnson**, and **Sunil Singhal**[**]
Thoracic Surgery Research Laboratory, Department of Surgery, Perelman School of Medicine, 6 White Building 3400 Spruce Street, Philadelphia, PA, USA

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

[*]Corresponding author. Tel.: +1 570 851 8313; fax: +1 215 615 6562. [**]Corresponding author. Tel.: +1 215 662 4767; fax: +1 215 615 6562. dfedor@mail.med.upenn.edu, dmfedor03@gmail.com (D. Fedor), sunil.singhal@uphs.upenn.edu (S. Singhal).

Authorship statement

Guarantor of the integrity of the study: David Fedor.
Study concepts: David Fedor, Sunil Singhal.
Study design: David Fedor, Sunil Singhal.
Definition of intellectual content: David Fedor.
Literature research: David Fedor, Rainey Johnson.
Data acquisition: David Fedor.
Data analysis: David Fedor.
Statistical analysis: David Fedor.
Manuscript preparation: David Fedor, Rainey Johnson.
Manuscript editing: David Fedor, Rainey Johnson.
Manuscript review: Sunil Singhal.

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of additional large-scale studies to clearly define the parameters of local recurrence in order to provide useful guidance to clinicians.

Keywords

Cancer; Tumor; Recurrence; Local; Surgery; Resection; Lung

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 underreported 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), who found an initial local recurrence rate of 24% [11]. We compare this with Taylor and associates from the University of Virginia (n = 1143) [5]. Although both Taylor and Saynak found a high overall recurrence rate, Taylor found an initial local recurrence rate of only 8% [5]. The contrasting features of these two studies offer a strong example of how methodology influences outcomes. While Taylor's study

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concentrated on all recurrences, Saynak's focused on local recurrences [5,11]. As noted by Kelsey, those who specifically examine local recurrences tend to find more of them (observer bias) [9]. Additionally, the studies differ in method of counting local recurrence. Taylor writes, "Recurrences in patients who had simultaneous locoregional and distant recurrences were defined as distant recurrences for the purpose of the study." [5] This would decrease Taylor's local recurrence count to some extent. Saynak, however, did not disregard any local findings in this manner [11]. Even if the two studies' populations were identical, Saynak's methodology would produce a higher initial local recurrence rate.

Two of the studies in Table 1 (Nakagawa and Martini) examined only Stage I patients, so it is not surprising that their local recurrence rates are lowest among the seven studies. Additionally, as discussed above, Taylor's calculated local recurrence rate is likely under-representative given his methodology. Thus, the true local recurrence rate across all stages of initial cancer is closer to the values seen in the remaining four studies: between 13 and 24%.

Risk factors for local recurrence

Several aspects of a patient's primary disease and initial treatment influence the likelihood of recurrence. In a study involving over 1100 lung cancer resection patients, Taylor and colleagues described risk factors independently influencing recurrence rates. This study included only patients in whom an R0 surgical resection had been achieved. They showed that overall recurrence was more likely under each of the following conditions: PET-CT maximum standard up take value (SUV_{max}) greater than 5, increasing stage, and the use of preoperative radiation treatment [5]. SUV_{max} is a measure of cells' metabolic activity, and we would expect more aggressive cancers to display higher activity level as they divide more rapidly. The association with increasing stage also makes intuitive sense: a stage IA lung cancer mass is small (≤2 cm) and has not spread beyond its lobe of origin. It has also not spread to any lymph nodes. A stage IIIA cancer, on the other hand, is at or near the limit of what is generally considered curable by surgical resection. The primary tumor has grown large enough to infiltrate extra-pulmonary tissues, and regional lymph node involvement has been verified [14]. The association with radiation treatment, according to Taylor, is likely due to the aggressive nature of the tumor for which therapy was administered, and not due to the radiation itself [5].

Multiple studies have shown that local recurrence is more common in patients who undergo a wedge resection or segmentectomy as opposed to a full lobar resection [5,7]. This suggests that sub-lobar resection should be avoided when possible, as it increases the likelihood that the primary cancer will not be completely excised. Currently, sub-lobar resection is reserved for patients who, due to compromised cardiovascular status, cannot afford the loss of an entire lobe. Broadening of the indications for sub-lobar resection through improved efficacy is an area of very active investigation. Other identified risk factors specifically for local recurrence include tumor size and lymphovascular space invasion [11]. Increasing tumor size indicates that the cancer has likely been present for a longer time and thus has had more time to spread, whereas lymphovascular invasion gives cancer cells the ability to form satellite nodules and metastases.

Local recurrence risk vs. lung cancer stage

A limited number of studies have quantified the percentage of patients who suffer post-operative local recurrence by cancer stage. The results from three of these studies are listed in Table 2 [11,15,16]. We chose to tabulate these three specific studies because they include local recurrence risk values for all stages of localized cancer. The table shows a clear trend of increasing local recurrence with increasing stage of the initial lung cancer. This is expected, as locally advanced primary tumors (Stage IIA or greater) are more likely to result in recurrences due to their more invasive state and greater likelihood of access to lymphatic drainage and vasculature [10]. Once the cancer has access to the lymph system, its potential to metastasize increases dramatically, and the surgeon is much less likely to successfully remove the disease. What may be surprising is that Stage I primary tumors, although less likely than later stages to result in recurrence, still carry with them a substantial risk of developing local recurrences after surgery, ranging from 4 to 19% (Table 2) [11,15,16]. This carries significant implications. First, our ability to accurately stage a lung cancer is often poor. Many Stage I patients are actually under-staged because of the difficulty of detecting lymph node infiltration by the cancer. Multiple studies have shown that understaging occurs in roughly one third of clinically identified Stage I patients [17,18]. Beyond this common staging inaccuracy, surgeons' ability to completely identify and excise a lung cancer during surgery remains limited, even when the primary tumor is small.

The large discrepancies in the specific percentages among the three studies warrant explanation. Saynak and colleagues stated that their recurrence rates are based on five years of follow-up and that they chose patients who did not receive adjuvant or neoadjuvant therapy [11]. Choi et al. did not specify the length of follow-up used in determining recurrence, and they did include a small number of patients who received radiation and/or chemotherapy after surgery [16]. If Choi used a follow-up period shorter than five years, this, along with the adjuvant therapy, could have a downward influence on recurrence rates. Additionally, Saynak's study focused specifically on local recurrence, whereas Choi's study focused on recurrence in general. The investigators in Saynak's study may have been more focused on local recurrence as this defined their primary end point. Both Saynak and Choi excluded sub-lobar resection patients [11,16]. Pisters and colleagues specified a five-year follow up period [15], but did not elucidate other aspects of their methods.

Kelsey and associates did not list local recurrence rates by stage, but did offer hazard ratios: using stage IA as reference (HR = 1.0), stages, IB, IIA, and IIB had hazard ratios of 2.0, 2.6, and 1.9, respectively [9]. Kelsey's study did not include stage III patients. Kelsey did not offer an explanation for why the hazard ratio for stage IIB dropped below that of the earlier stages. It may be due to random error, as the stage IIA and IIB sample sizes made up just 4% and 11%, respectively, of the total cohort.

It is important to note that numerous studies in the PubMed database offer local recurrence rates, but they do not cover the full gamut from stage IA to stage IIIA. The vast majority considers only a single stage, tends to have small sample sizes, and focuses on a variable outside of our immediate interest, such as the use of a particular adjuvant therapy or surgical procedure. As such, published local recurrence rates vary widely.

Survival following local recurrence

Survival time following local recurrence, including those patients who receive salvage treatment, is less than one year on average. Local recurrence does offer a slight survival advantage over distant recurrence. Sugimura and colleagues analyzed over 1000 patients (271 of whom received salvage therapy) and found that those patients who developed only a local recurrence survived for a median of 9.8 months post-recurrence, with a 2 year survival rate of 17%. Those who recurred distantly, or both locally and distantly, had median survival times of 7.8 and 6.8 months, respectively [10]. Hotta and associates found a median post-local-recurrence survival time of 10.5 months, but did not calculate distant recurrence survival times [19]. Endo and colleagues did not break down median post-recurrence survival into local and distant categories, but rather into intrathoracic (25.5 months), extrathoracic (10.1 months), and both (4.8 months) ($p = 0.003$) [20]. The range in survival times varies among these three studies for several possible reasons. First, there is a large difference in the follow-up intervals across studies. Second, follow up care methods varied significantly. For example, Endo re-assessed patients every four months for the first two years, every six months from the third to fifth years, and annually every year after that. A CT scan was performed at every reassessment visit [20]. Sugimura's group reported collecting information from patients every six months for the first year, and then yearly thereafter, and Hotta's group did not specify follow-up intervals. Neither Sugimura nor Hotta discussed regular use of CT scans during re-assessment visits [10,19]. It may be that Endo's short re-assessment intervals and more frequent CT scans potentially led to earlier discovery of recurrence and longer post-recurrence survival time.

What factors affect post-recurrence survival time? Interestingly, Endo noted that a patient's survival time after recurrence is independent of the stage of the original cancer. Rather, length of survival depends on the location of the recurrence and the use of post-recurrence salvage therapy. Local recurrence is favorable to distant metastasis, and use of salvage therapy compares favorably to non-use [20]. Distant recurrence can develop from an earlier local recurrence which has metastasized, so it may not be surprising that distant recurrence carries more dismal survival; distant recurrence can indicate that a local recurrence has had substantial time to progress. As for the advantage of salvage therapy, it is difficult to determine whether the survival advantage comes from the therapy itself, or from the fact that this therapy is given only to those deemed strong enough to benefit from it. Salvage therapy selects for the patients expected to have longer survival times regardless of additional intervention, whereas the least functional patients are given only palliative care.

Salvage therapy options following local recurrence

Current salvage therapy options following local recurrence include surgical excision, radiotherapy, a combination of surgery and radiation, or a combination of radiation and chemotherapy. Although increased survival among those who receive salvage therapy is well documented, which local recurrence salvage therapy is most beneficial has not been definitively determined. Very little research has been published to elucidate this issue.

Curran and associates noted that surgical excision is appropriate when the recurrent cancer is limited to the lung parenchyma, bronchial stump, or chest wall. If, however, the malignancy is present in mediastinal lymph nodes, then surgery alone will not provide a cure. Potential salvage surgeries include complete pneumonectomy, tracheal sleeve pneumonectomy, and chest wall resection [21]. To our knowledge, no study has examined the effectiveness of each of these procedures in improving post-local-recurrence survival. Sugimura and colleagues found that while overall survival after local recurrence was 9.8 months, those who underwent salvage surgery (whether for local or distant recurrence) experienced a median survival of 22.9 months. Those who received both surgical and radiation therapy experienced a median survival of 13.1 months ($p < 0.01$). Those who received surgical salvage treatment specifically for recurrence in the lungs had a median survival time of 32.8 months [10]. Again, it is important to note that the increased survival time reflects not just the efficacy of the surgery, but also the fact that the patient's recurrence was limited enough to potentially allow for a surgical cure. That the combination of surgical and radiation therapy carries a lower survival benefit than surgery alone likely indicates not that the combination therapy is necessarily less effective, but that those identified as requiring radiation have cancer that has spread to the lymph nodes.

As with surgery, the use of radiotherapy for local recurrence has not been studied in a large controlled trial to our knowledge. The precise extent of its therapeutic benefit remains unknown. In a small 2006 study involving 29 local recurrence patients, all of whom received radiation salvage therapy, Kelsey and colleagues found a median survival time after radiation of 17 months [22]. Fifteen of the patients also received chemotherapy, and their median survival time was also 17 months. Kelsey's study lists eight prior studies, all with sample sizes less than 50, and median survival times ranging from 11 to 19 months [22]. The lack of a control group in these studies, along with the small sample sizes, makes it difficult to discern the benefit of radiotherapy. Kelsey mentions that one radiation patient was alive at 4 years following treatment, and another was alive at 13 years. Clearly, radiation carries potential for long-term remission. The typical increase in survival time, however, is not impressive. Sugimura and colleagues found that while the overall median survival time for local recurrence was 9.8 months, non-surgical treatment of recurrence in the lung increased survival time to 13.4 months [10]. Whether or not this marginal benefit is worth the side effects of radiotherapy must be decided by the individual patient.

The use of chemotherapy alone is not warranted to treat local recurrence. It is, however, regularly combined with radiotherapy to help eliminate distant metastases that may have occurred. Hotta and colleagues found that 68% of their patients who recurred locally went on to develop distant metastases, and thus they recommend the addition of chemotherapy to radiotherapy following any local recurrence [19]. The findings of Shawand Kelsey do not support this; both found no significant survival benefit from the addition of chemotherapy to radiation treatment [22,23]. As with the treatment options discussed above, the benefits of this combination require further study.

Discussion and recommendations

The initial objective of this review was to assist thoracic surgeons by consolidating and summarizing current data on the incidence, risk factors, and expected survival following post-surgical local recurrence in lung cancer. However, the dearth of data on this topic and inconsistencies in methodology among the larger studies make it difficult to draw conclusions with confidence. As such, there is a need for continued examination of this topic. Any new studies should meet the following criteria:

- Sufficient Sample Size: We recommend an initial sample size of at least 1000 subjects. The most useful studies available on this subject all included approximately 1000 initial patients and over 300 instances of recurrence [5,9,10]. This allowed the authors to sample numbers large enough to result in statistical significance in nearly every measured variable. All three of these studies occurred at single institutions, demonstrating that it is possible for individual academic centers to achieve these numbers. At this time, we do not recommend using the SEER database to perform a study on this topic because the methodologies used in defining and collecting recurrence data appear to vary substantially from one institution to another. Thus the data fed into the SEER database by these institutions will have originated from inconsistent collection methods.

- Use of a Consensus Definition of Local Recurrence: Classification of local versus distant recurrence remains inconsistent, resulting in confusion among providers and contributing to large variability in numerical results across studies. The thoracic oncology community must develop consensus definitions of these terms. We propose that ‘local’ be defined as the entire ipsilateral hemithorax (including the pleura and chest wall) and the ipsilateral mediastinal lymph nodes. We favor this definition because it aligns with what the surgeon is, in principle, able to visualize and dissect during resection of the primary tumor. In order to be of use, local recurrence rates should give surgeons an idea as to how they are performing in removing all cancer during curative resection. Thus, it should include only the areas that the surgeon can actually see during resection. Additionally, it is important to keep in mind that metachronous tumors can potentially masquerade as metastases of the originally resected primary tumor and therefore should be differentiated from local recurrences based on physical location and histology. This differentiation becomes difficult if the metachronous tumor is ipsilateral and histologically identical to the primary resected tumor. Under these circumstances, the treatment team must use its best judgment based on presence or absence of lymphatic infiltration of the resected primary tumor and the likelihood that the primary cancer may have spread via the lymph system, the vascular system, or direct contiguous transfer.

- Give Adequate Attention to Local Recurrence: To avoid undercounting of local recurrences, any patient in whom distant recurrence is detected should also be thoroughly screened for local lesions. This will aid in avoiding the common failure to detect local tumors present concomitantly with distant ones.

Additionally, consistent and accurate counting methods should be employed. For example, if both local and distant recurrences are detected, the patient should not be discounted from the local count, as we have seen in one of the large studies we examined.

- Quantify Recurrence Risk Across Multiple Variables: In addition to stage and location of the initial tumor, investigators should quantify risk according to PET/CT SUV_{max} values, tumor size, presence of lymphovascular invasion, and type of resection. The risk of local recurrence associated with each of these factors provides the surgeon with information he or she can use both to better inform the patient and to decide how aggressive to operate during tumor removal. Another reason to sort outcome data and risk by resection type is to help confirm or deny whether sublobar resection becomes more effective as this method of tumor removal continues to be refined.

- Consistent Follow-up Methods: Follow-up after surgical resection varies widely across studies in terms of time intervals, diagnostics, and total time. To avoid the variability that this produces in time to recurrence, recurrence rates, and post-recurrence survival, the thoracic oncology community should strive to develop a consensus on how post-resection patients will be followed. We recommend a total period of at least five years, as this will capture at least 90% of all recurrences. We also recommend follow-up visits with CT scans every six months during this period in order to measure recurrence times and initial recurrence locations in a reasonably precise manner.

Implementation of the above five recommendations will lead to production of future studies that provide more lucid and useful outcomes data and clinical guidance regarding local recurrence risk factors and incidence. With regard to salvage therapies following recurrence, we refrain from making any concrete recommendations and will only say that more studies are needed. The volume of data on this subject is very limited, and it is currently not possible to discern to what extent life expectancy following a given salvage therapy is due to the therapy itself as opposed to other factors. The patient's state of health at the time of recurrence discovery will influence which salvage therapy he or she receives.

Conclusion

Despite the shortcomings of the available data on the subject, it is reasonable to conclude that post-surgical local recurrence in non-small cell lung cancer patients remains a significant problem. High rates of local recurrence (between 13 and 24%) coupled with short post-recurrence survival times indicate room for improvement. A better understanding of what factors contribute to local recurrence and what factors influence post-recurrence survival time will help clinicians to make more beneficial treatment decisions. The purpose of this analysis was to inform the clinician on what is currently known regarding these topics. Unfortunately, much remains unknown or incompletely understood.

Perhaps the most effective way to decrease death from local recurrence is to prevent the recurrence itself through total excision. Given this, surgical oncologists continue to strive for greater effectiveness in achieving complete resection of lung tumors. Without reliable and consistent large-scale study data, however, surgeons are hampered in their ability to assess risk factors, accurately inform patients on the likelihood of success, and correctly determine how aggressively they should cut during resection. Additionally, reliable outcomes data allows surgeons to judge how well their current resection methods are working and how they may need to adjust to improve results. This is why the publication of quality local recurrence studies is so essential.

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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[5]	2012	1143	33 (378)	8 (94)	None listed	8 (94)
Saynak[11]	2010	335	33 (111)	12 (41)	12 (41)	24 (82)
Kelsey[9]	2009	975	26 (250)	7 (63)	8 (78)	15 (141)
Hung[13]	2009	933	31 (289)	8 (74)	5 (49)	13 (123)
Nakagawa[a],[12]	2008	397	22 (87)	7 (30)	None listed	7 (30)
Sugimura[10]	2007	1073	36 (390)	7 (79)	6 (62)	13 (141)
Martini[a],[7]	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.

[a]Stage I only.

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Table 2

Post-excision local recurrence rate (%) by lung cancer stage.

Study	Stage IA	IB	IIA	IIB	IIIA
Choi 2011[a],[16]	4	7	11	12	24
Saynak 2010[b],[11]	19	19	27	27	38–40
Pisters 2005[15]	10	10	N/A	12	15

This table lists local recurrence rate versus cancer stage for three select studies. Rates are listed as percentages.

[a]Values calculated using Choi's Table 5.

[b]Saynak lists local recurrent rate by TNM grade. TNM grade was translated to corresponding stage according to the 7th Edition of the AJCC standard.