

# Surgery plus chemotherapy versus chemotherapy alone in primary intestinal lymphoma: a meta-analysis

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## Abstract

**Objective:** Primary intestinal lymphomas (PILs) are uncommon tumors, but their incidence is increasing. Currently, their management is centered around systemic treatments, such as chemotherapy and radiotherapy, whereas surgery is restricted to selected indications. This meta-analysis aimed to evaluate the role of surgery in PIL treatment.

**Methods:** We collected publications comparing surgery plus chemotherapy versus chemotherapy alone in patients with PIL from 2000 to 2021. All trials analyzed the summary odds ratios (ORs) of endpoints, including the 5-year overall survival (OS), 3-year OS, and 3-year progression-free survival rates. Combined pooled ORs were analyzed using fixed- or random-effects models according to heterogeneity.

**Results:** Six studies were included. Compared with chemotherapy alone, surgery plus chemotherapy was associated with significantly higher 5-year OS [OR = 4.88, 95%confidence interval (CI) = 1.91–12.44, Z = 3.32], 3-year OS (OR = 3.83, 95%CI = 2.33–6.30, Z = 5.30), and 3-year progression-free survival (OR = 3.51, 95%CI = 2.20–5.58, Z = 5.29).

**Conclusions:** Surgery plus chemotherapy was associated with better outcomes than chemotherapy alone, especially in the early stages. Therefore, surgery plus chemotherapy may be the preferred strategy for appropriately selected patients with PIL.

The protocol for this systematic review was registered at INPLASY (INPLASY202180102) and is available in full (<https://doi.org/10.37766/inplasy2021.8.0102>).

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## Keywords

Surgery, chemotherapy, primary intestinal lymphoma, overall survival, progression-free survival, meta-analysis

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## Introduction

Primary intestinal lymphomas (PILs) are a group of heterogeneous, rare malignancies. The intestines are the second most common site of lymphoma involvement after the stomach, accounting for 30% to 40% of primary gastrointestinal lymphomas.<sup>1,2</sup> PIL most commonly presents with abdominal pain (approximately 70%), whereas colonic lymphoma may present with weight loss (43%) or an abdominal mass (29%), and small bowel lymphoma may be associated with ileus (38%), weight loss (29%), bleeding (21%), perforation (16%), or a palpable mass (12%).<sup>3</sup> Diffuse large B-cell lymphomas (DLBCLs) account for most PILs.<sup>4</sup>

Most small bowel lymphomas are B-large cell lymphomas.<sup>5</sup> In locally advanced lymphomas of the small bowel, surgical resection is indicated for tumors with undefined histology or complicated by intestinal occlusion, bleeding, and perforation.<sup>6</sup> Surgery may be advocated before chemotherapy for bulky lesions to prevent bowel perforation.

In the colon-rectum location, mucosa-associated lymphoid tissue lymphomas are more common.<sup>7</sup> The National Comprehensive Cancer Network guidelines proposed the same protocols for the colon and small intestine. The surgical approach includes segmental resection of the colon or local excision for rectal tumors.

Surgery lost its leading role and is currently the treatment of choice only in acute complicated cases or in the prevention of chemotherapy- and/or radiotherapy-related

complications secondary to rapid tumor necrosis. The aim of preventive surgery is to reduce the high incidence of severe morbidity and mortality due to an emergency laparotomy in highly compromised patients.

The management of PIL is controversial. Various treatment approaches have been applied, including systemic chemotherapy, primary surgical resection of intestinal lesions, and postoperative chemotherapy. However, optimal treatment practices remain undefined. Among current studies, the role of surgery in intestinal lymphoma remains ambiguous<sup>5,8</sup>

Based on the assumption that PIL is a localized disease, surgical treatment was traditionally considered the cornerstone of therapy, showing impressive results in terms of prolonged disease-free survival and overall survival (OS). Recently, this approach has been extensively revised, and the management of PIL is centered around systemic treatments, such as chemotherapy and radiotherapy.

We conducted a meta-analysis to compare surgery plus chemotherapy with chemotherapy alone in PIL by analyzing OS and progression-free survival (PFS) as the primary outcomes.

## Materials and methods

### Study identification

We conducted this meta-analysis according to the recommendations of The Cochrane Collaboration. Because this was a

meta-analysis using public databases, ethics review and informed consent were not applicable. We conducted a comprehensive literature search of PubMed, EMBASE, Google Scholar, Cochrane Library, and Clinical trial databases from January 2000 to January 2021. Because PIL is a relatively rare disease, a 21-year period [2000–current] was selected. If this period produced insufficient papers, then it was extended to include historical papers. The search was performed using the terms “primary intestinal lymphoma” OR “primary small intestinal lymphoma” OR “primary small bowel lymphoma” OR “primary colonic lymphoma” OR “primary large intestine lymphoma”, “surgery” OR “operation”, AND “chemotherapy” in English-language publications (including abstracts). In addition, we manually searched bibliographies of reviews, original studies, and relevant conference articles and contacted some investigators directly.

### *Inclusion criteria*

Different types of malignant lymphoma are heterogeneous, and different histology classifications and staging systems have various prognoses. The inclusion criteria were the following: (1) study design: compared surgery with chemotherapy (surgical group) versus chemotherapy alone (medical group) in the treatment of intestinal lymphoma tumors or retrospective studies reporting full results on the treatment of PIL; (2) study population: patients with PIL and >20 participants; (3) therapy: surgery plus chemotherapy versus chemotherapy; (4) treatment outcome reported: endpoints were 3-year OS, 5-year OS, and 3-year PFS rates; (5) most lymphomas included were high-grade (aggressive) subtype lymphomas and very few were

low-grade (indolent) subtype lymphomas; and (6) included different Lugano stages.

### *Exclusion criteria*

Studies were excluded from this meta-analysis if the outcomes of interest were not reported for both groups; (2) they included patients who had other diseases that substantially affect survival; or (3) were reviews or case reports.

### *Data extraction and quality assessment*

Data extraction was conducted independently by Yefei Shu and Wei Yang, and discrepancies were resolved by Xiaofeng Xu and Ling Xu before the final analysis. We recorded the first author, publication year, study location, study year, design, study population characteristics, and follow-up time. Authors of included studies were contacted for additional information not described in published reports. All included studies were graded using the Newcastle–Ottawa Scale. The scale consists of three items regarding the reporting of participant selection, comparability of surgical and medical groups, and outcome assessment. The total quality scale was 9 points. Articles with  $\geq 6$  points were considered high quality.

### *Statistical analysis*

All statistical analyses were conducted with Review Manager 5.3 (RevMan) software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The association between surgery plus chemotherapy versus chemotherapy alone was based on data from retrospective trials. The endpoints of interest in the pooled analysis were the 5-year OS, 3-year OS, and 3-year PFS rates, and the endpoint was considered as a weighted average of individual estimates of the odds ratio

(OR) in each included study using the inverse variance method.

### Assessment of heterogeneity

A sensitivity analysis was also performed to examine the impact on the overall results, depending on heterogeneity across the included studies. Heterogeneity was first tested using the Chi-squared test, with a P value  $<0.01$  representing statistical significance. However, because tests of heterogeneity have a relatively low power when a small number of studies is included, we further explored heterogeneity using the  $I^2$  test, which is independent of the number of combined studies. If  $I^2$  is equal to 0%, there is no heterogeneity (fixed-effects model used). If  $I^2 > 50\%$ , heterogeneity is indicated (random-effects model used).

### Results

Using the search strategy outlined above, 421 publications were identified. However, 324 studies were excluded following title and abstract review. Eighteen studies were excluded because they did not meet the inclusion criteria for this review, and six studies were investigated in detail (Figure 1). All included studies were considered to be of at least moderate quality. The primary characteristics of the eligible studies are shown in Table 1.

Regarding the pooled analysis of the 5-year OS rate for comparing surgery plus chemotherapy versus chemotherapy alone, four studies reported data on the 5-year OS rate<sup>1,9-11</sup> (Figure 2). The results suggested that patients who received surgery plus chemotherapy had a significantly higher 5-year

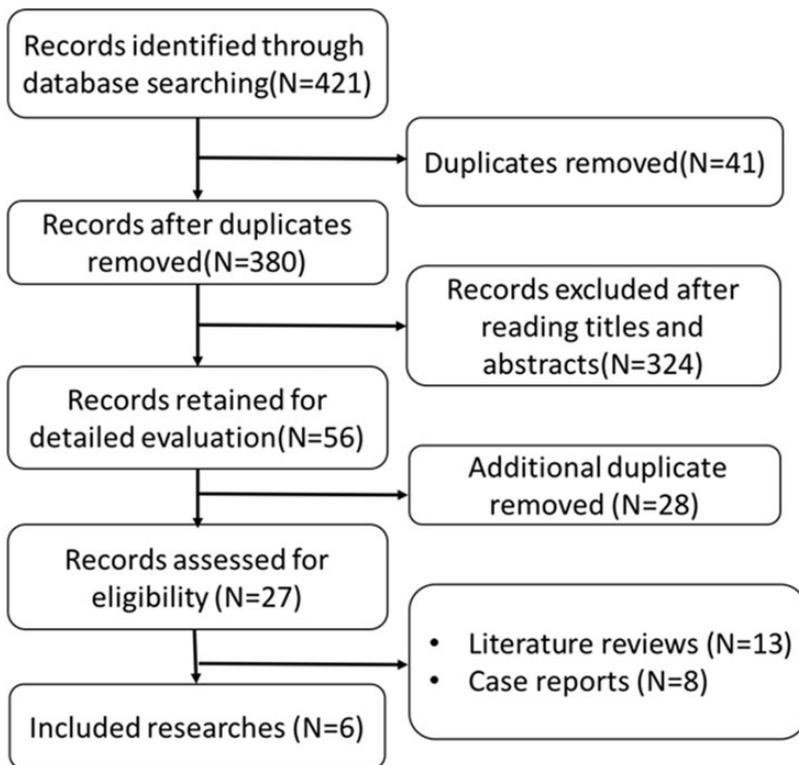
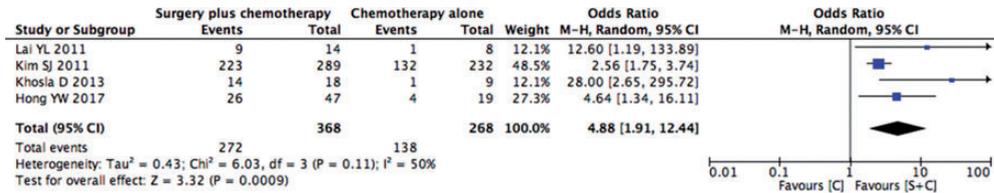


Figure 1. Flow diagram of the study selection.

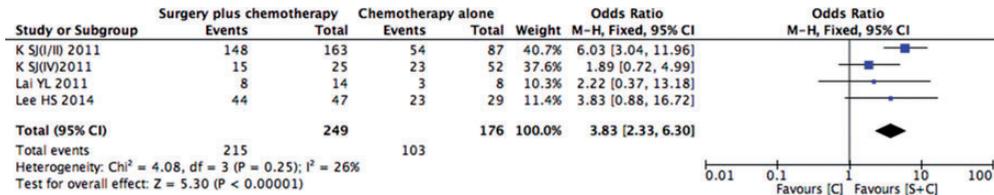
**Table 1.** Characteristics of the studies included in this meta-analysis.

Author; year	Country	Histology	S+C:C	Number (men:women)	Study	Age (median)	Follow-up time (years)	Outcome
Kim SJ 2011 <sup>1</sup>	Korea	Multiple	289:232	521 (1.7:1)	Retrospective	56	5	5-year OS rate: 77% versus 57%. However, this beneficial effect of surgery was only statistically significant in patients with BCLs (P < 0.001), not TCLs (P = 0.460)
Lai YL 2011 <sup>9</sup>	Taiwan	DLBCL (most primary colonic lymphoma)	14:8	29 (19:10)	Retrospective	71 (range, 23–86)	5	3-year OS: 75.5% vs. 28.6% 5-year OS: 62.1% vs. 14.3%
Khosla D, 2013 <sup>10</sup>	India	DLBCL (55.6%)	18:9	27	Retrospective	51 (range, 7–76)	4	5-year OS: 79.5% vs. 13.9%
Hong YW 2017 <sup>11</sup>	Taiwan	BCL TCL	60:22	82 (60:22)	Retrospective	62.5:69	3.9	OS (median): 4.89 years vs. 0.71 years PFS (median): 1.76 years vs. 0.58 years
Lee HS 2014 <sup>12</sup>	Korea	DLBCL	47:29	76 (1.00:1.45)	Retrospective	56.5 (range, 15–85)	3	3-year PFS: 92.2% vs. 74.8% 3-year OS: 94.2% vs. 80.7%
Xu J 2016 <sup>13</sup>	China	Most BCLs with very few TCLs (24 %)	22:6	59 (39:20)	Follow-up	Most were middle aged and older adults	2	OS: 2.66 years vs. 1.44 years

DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PFS, progression-free survival; S+C, surgery + chemotherapy; C, chemotherapy alone; BCL, B-cell lymphoma; TCL, T-cell lymphoma.



**Figure 2.** Pooled analysis of 5-year overall survival rates. CI, confidence interval; C, chemotherapy alone; S+C, surgery + chemotherapy.



**Figure 3.** Pooled analysis of 3-year overall survival rates. CI, confidence interval; C, chemotherapy alone; S+C, surgery + chemotherapy.

OS rate versus those who underwent chemotherapy alone [OR = 4.88, 95% confidence interval (CI) = 1.91–12.44, Z = 3.32, P = 0.0009].

Regarding the pooled analysis of the 3-year OS rate for comparing surgery plus chemotherapy versus chemotherapy alone, four studies reported data on the 3-year OS rate<sup>4,9,12</sup> (Figure 3). The results suggested that patients who received surgery plus chemotherapy had a significantly higher 3-year OS rate versus those who underwent chemotherapy alone (OR = 3.83, 95% CI = 2.33–6.30, Z = 5.30, P < 0.00001).

For the pooled analysis of the 3-year PFS rate to compare surgery plus chemotherapy versus chemotherapy alone, three studies reported data on the 3-year PFS rate<sup>4,12</sup> (Figure 4). The results suggested that patients who received surgery plus chemotherapy had a significantly higher 3-year PFS rate versus those who had undergone chemotherapy alone (OR = 3.51, 95% CI = 2.20–5.58, Z = 5.29, P < 0.00001).

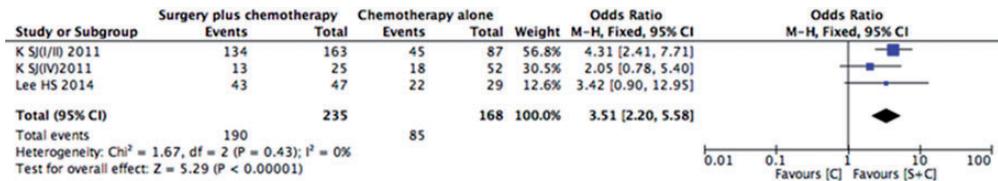
Regarding heterogeneity, I<sup>2</sup> > 50% indicated obvious heterogeneity, and the

random-effects model was used. If I<sup>2</sup> ≤ 50%, the fixed-effects model was used. The included studies were heterogeneous.

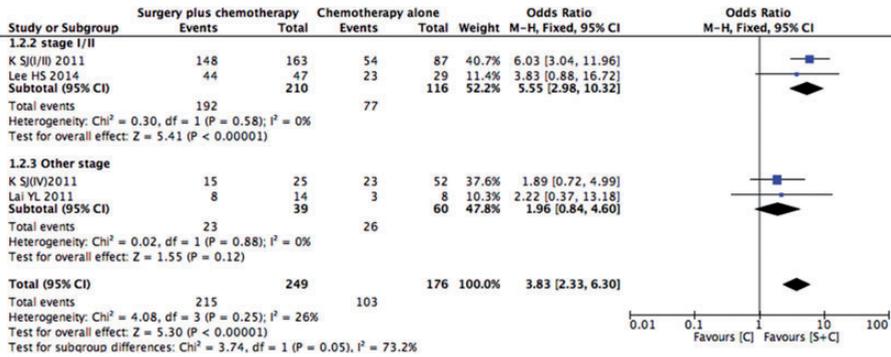
A subgroup analysis according to stages for the 3-year OS rate demonstrated that Stage I/II patients with PIL who received surgery plus chemotherapy had a significantly higher 3-year OS rate and 3-year PFS rate versus those who had undergone chemotherapy alone (OR = 5.55, 95% CI = 2.98–10.32, Z = 5.41, P < 0.00001, Figure 5; OR = 4.15, 95% CI = 2.44–7.07, Z = 5.24, P < 0.00001, Figure 6). The included articles did not provide relevant data regarding the survival of different pathological types of lymphoma. Therefore, we did not perform a subgroup analysis according to pathology types.

### Discussion

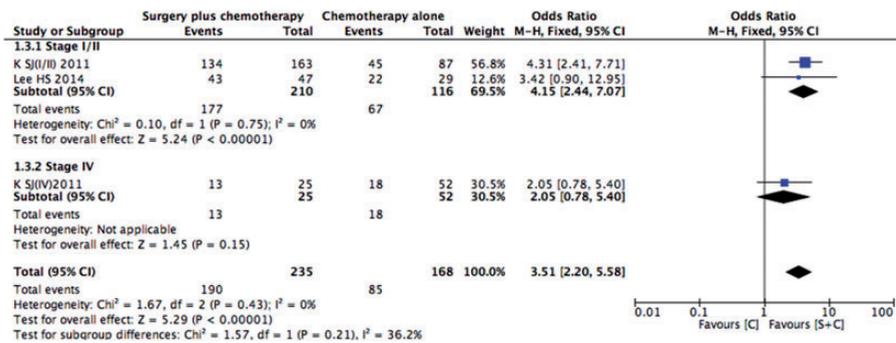
The aim of this meta-analysis was to compare surgery plus chemotherapy versus chemotherapy alone in patients with PIL, but only six studies investigated these two approaches.<sup>1,9–13</sup> We conducted this



**Figure 4.** Pooled analysis of 3-year progression-free survival rates. CI, confidence interval; C, chemotherapy alone; S+C, surgery + chemotherapy.



**Figure 5.** Subgroup analysis according to stages for the 3-year overall survival rate. CI, confidence interval; C, chemotherapy alone; S+C, surgery + chemotherapy.



**Figure 6.** Subgroup analysis according to stages for the 3-year progression-free survival rate. CI, confidence interval; C, chemotherapy alone; S+C, surgery + chemotherapy.

meta-analysis to compare 5-year OS rates between surgery plus chemotherapy and chemotherapy alone in primary small bowel and colon lymphoma. Overall, surgery plus chemotherapy was more effective than chemotherapy. In addition to efficacy data from trials, our findings provide useful

information for clinicians for well-balanced discussions with their patients on the risks and benefits of treatment options for advanced cancer.

In this meta-analysis, we did not perform a subgroup analysis based on pathology type because of the limited number of

subjects. DLBCL accounts for most PILs. In a previous study, the 3-year OS was higher in patients treated with R-CHOP (59%) compared with CHOP (29%).<sup>4</sup> In patients with localized disease (Lugano Stage I/II), surgery plus chemotherapy yielded a lower relapse rate (15.3%) than chemotherapy. In one article, comparisons of OS and PFS according to the treatment strategy showed no significant differences between the two groups.<sup>4</sup> For patients with Lugano Stage IV, the response and relapse rates did not differ between the two groups.<sup>4</sup>

Age >60 years, Eastern Cooperative Oncology Group-Performance Status  $\geq$  grade 2, increased serum lactate dehydrogenase levels,  $\geq$ 2 extranodal involvements, Lugano Stage IV, high-to-intermediate/high IPI risk, and surgery/chemotherapy were previously identified as prognostic indicators for OS. However, only the treatment strategy based on primary surgical resection followed by chemotherapy was an independent prognostic factor for OS.<sup>4</sup> Among the functional scales, physical, role, cognitive, and social functioning did not differ, and only emotional functioning was decreased in the surgery/chemotherapy group. Among the symptom scales, nausea, vomiting, appetite loss, and financial difficulties did not differ significantly between treatment groups. However, patients in the surgery/chemotherapy group were significantly inferior to those who received chemotherapy alone in terms of constipation, diarrhea, insomnia, and dyspnea.<sup>4</sup>

One of the main limitations of our study is the retrospective nature of most studies included in the meta-analysis. These studies were heterogeneous and combined different types of malignant lymphomas, histology classifications, and staging systems.

Surgery remains the treatment of choice in acute complicated cases of PIL, although there is no evidence in the literature regarding the use of preventive surgery.

Despite the absence of high-quality randomized control trials demonstrating the effectiveness of chemotherapy without local surgical resection in patients with PIL, the evidence present in the literature and analyzed in our review supports a systemic approach for patients with PIL.<sup>9,13</sup>

## Conclusion

Overall, surgery plus chemotherapy was more effective than chemotherapy in patients with PIL, especially in the early stages. Our results provide further evidence supporting the benefits of surgery plus chemotherapy. However, the studies that included different types of malignant lymphomas were heterogeneous and used different histology classifications and staging systems. Prospective clinical studies are needed for further verification, and additional subgroup analyses are warranted in the future.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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