European Journal of Surgical Oncology 45 (2019) 279–283

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Surgery in perforated pediatric intestinal lymphoma

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ARTICLE INFO

Article history:
Received 20 May 2018
Received in revised form
14 July 2018
Accepted 17 August 2018
Available online 6 September 2018

Keywords:
Perforation
Intestinal lymphoma
Pediatrics

ABSTRACT

Background: Perforation is the most common surgical complication in pediatric intestinal lymphoma. During operation, many surgical decisions are debatable.
Aim: To assess the outcome of surgical management of perforated pediatric intestinal lymphoma.
Patients and methods: This is a retrospective analysis of all pediatric patients (<18 years old) with intestinal lymphoma treated in our hospital between July 2007 and June 2017. Risk factors for perforation, type of management and outcome in cases of intestinal perforation were analyzed.
Results: The study included 240 patients with intestinal lymphoma. Perforation developed in 16 patients (6.7%) with a median age of 5.3 (range: 2.8–15.7) years. Most of the patients (92.5%) had Burkitt lymphoma. The ileum was the most common site of perforation (n = 10). Perforation occurred at presentation (n = 2), during induction (n = 10), during maintenance chemotherapy (n = 2), or at relapse (n = 2). Primary resection anastomosis was done in 12 patients. The resected specimen showed a viable tumor in ten patients. Wound infection (25%) and dehiscence (12.5%) were the most common postoperative complications. The 5-year overall and event-free survivals of patients with perforation were 78.6% and 71.4%, respectively, compared with 85.5% and 81.2% in non-perforated patients; the difference was not significant (p = 0.374 and p = 0.270, respectively).
Conclusion: Perforation is not an adverse prognostic factor for survival in pediatric intestinal lymphoma patients. Primary resection anastomosis seems to be a safe option if complete tumor resection is feasible.

Introduction

Non-Hodgkin lymphoma (NHL) is the most common gastrointestinal malignancy in children, and the predominant histology is Burkitt lymphoma [1]; in 85% of NHL cases in pediatric patients the intestine is involved, and in 93% the ileocolic region is involved [2]. The majority of patients with intestinal lymphoma generally respond well to medical treatment. However, several complications – such as obstruction, perforation, fistula or bleeding – may require surgical treatment [3].

The transmural nature of the tumor can precipitate complications such as bleeding and bowel perforation [4]. Perforation and peritonitis are life-threatening due to spillage of enteric contents in an already immunocompromised patient. Intestinal perforation leads to considerable morbidity and mortality from sepsis, multiple organ failure, prolonged hospitalization, complications of wound healing, and delay in the initiation of chemotherapy [5–7].

Imaging modalities are essential tools for diagnosis and evaluation of gastrointestinal lymphoma and its complications such as obstruction, perforation, and fistulization. The most commonly used modalities are barium studies and contrast-enhanced computed tomography (CECT); the latter provides a better overall assessment of the disease stage [8].

In adults, intestinal perforation in gastrointestinal lymphoma

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https://doi.org/10.1016/j.ejso.2018.08.022
0748-7983/

has been found to be an indicator of poor prognosis [9,10]. However, in children this complication has less certain prognostic implications. This may be attributed to the better response to chemotherapy and greater physiological reserve in children.

This retrospective review of our institutional experience was done to address the location, timing, surgical management and outcome of perforation in the course of the disease of pediatric patients with intestinal lymphoma. The ultimate goal is to improve the multidisciplinary management of these cases.

Patients and methods

Children's medical records from the cancer hospital database were retrospectively reviewed to identify all patients with biopsy-proven intestinal lymphoma between July 2007 and June 2017. The study was approved by the Institutional Review Board.

The records were further reviewed to identify patients who presented with or developed intestinal perforation, defined as the presence of free air under the diaphragm on abdominal imaging and/or demonstration of a perforated bowel at laparotomy. All patients had had abdominal computed tomography at initial assessment and post-chemotherapy according to the institutional management protocol. Data collected included patient demographics, anatomical site and histopathology of the primary tumor, timing and location of the perforation, intraoperative findings, type of surgery, postoperative complications, state at the last follow-up visit, duration of follow-up, and cause of death.

All the statistical analyses were performed using SPSS software, version 20 (SPSS Inc, Chicago, IL, USA). Descriptive statistics are reported as number and percentage or median and range as appropriate. Survival analysis was made using the Kaplan–Meier method. The overall survival (OS) was calculated from the date of the diagnostic biopsy until death from any cause or date of last follow-up visit. The event-free survival (EFS) was calculated from the date of complete remission to the date of relapse, death or last follow-up visit. The log-rank test was used to compare survival curves. The significance level was set at 0.05.

Results

Between July 2007 and the end of June 2017, 240 patients were identified with biopsy-proven primary intestinal lymphoma. Burkitt's lymphoma was the most common pathological subtype (n = 222, 92.5%), followed by anaplastic large-cell lymphoma (n = 12, 5%) and lymphoblastic lymphoma (n = 6, 2.5%). All patients diagnosed with intestinal lymphoma presented initially with concentric, transmural bowel involvement by tumor tissue and aneurysmal dilatation of the lumen. Wall thickness initially ranged from 1.9 to 5.8 cm (median 3.9 cm). Intestinal perforation was diagnosed in 16 patients (6.6%): seven males and nine females. The median age was 5.3 years (range: 2.8–15.7 years). All perforation cases were Burkitt's lymphoma. None of the patients had more than one episode of perforation. There was no significant difference in tumor and patient characteristics between perforated and non-perforated groups (Table 1).

Two perforation events (12.5%) occurred at initial presentation, and 14 (87.5%) occurred during treatment with chemotherapy. In these 14 perforations, the median time of perforation was 26 days (range: 4–36 days) after chemotherapy initiation. Thirteen patients (81.3%) had free air and fluid in the peritoneal cavity, and two cases had localized air loculi at the site with perforation. One case had air in the bowel wall with necrosis denoting gangrene. Nine patients (56.3%) had mesenteric lymph nodes in association with bowel infiltration forming a mass nodal complex. Seven patients (43.8%) had small bowel feces sign (SBFS), i.e., particulate-type material in the dilated small bowel. The most common site of perforation was the ileum (n = 10, 62.5%), followed by the ileocecal area (n = 4, 25%) and the jejunum (n = 2, 12.5%). The clinical characteristics of the 16 patients with intestinal perforation are summarized in Table 2.

At exploration, six patients (37.5%) had diffuse spillage of intestinal contents and peritonitis, while the perforation was contained in the remaining nine patients. In one patient there was impending perforation due to a gangrenous loop of intestine. Primary anastomosis was done in 12 patients (75%) where complete gross resection was done, and the edges of the intestine were viable with no gross residual tumor. Three patients (18.8%) had a resection of the perforated segment with diverting stoma because the resection was not complete and the edges were inflamed and edematous. One case had a stoma with no resection as the tumor was irresectable involving a large amalgamated segment of the intestine.

Pathological examination of the resected specimen during surgery for perforation revealed ten patients (57%) with viable tumor at the perforation site, while in the remaining six patients there was no evidence of viable lymphoma.

Wound infection was the most common complication (n = 4, 25%), followed by postoperative lung atelectasis and pneumonia (n = 2, 12.5%). Out of the four patients with wound infection, two developed wound dehiscence in which a negative-pressure wound therapy was used, and primary fascial closure was done. None of the patients had postoperative intestinal leakage, fistula or collection that needed surgical or radiological intervention.

Two patients – one having had primary resection anastomosis and the other resection with stoma – died within 1 month due to

Table 1
Characteristic of the 240 patients with intestinal lymphoma.(perforated vs non perforated group).

	Non perforated	Perforated	P value
Number	224	16	
Mean Age	6.4	6.2	0.75
Median	5.1	5.3	
Range	(2–15.8)	(2.8–15.7) years	
Sex			
Male	122	7	0.157
Female	102	9	
Pathology			
Burkitt's	206	16	0.275
ANAPLASTIC LARGE CELL LYMPHOMA	12	0	
LYMPHOBLASTIC LYMPHOMA	6	0	
Wall thickness			
Burkitt's lymphoma			
Mean	3.6	4	0.097
Median, rang	3.9(1.9–5.8)	4.3(2.5–6.5)	

Table 2
Characteristics of the 16 patients who developed intestinal perforation.

Clinical characteristics	Number 16
Site of perforation	
Ileum	10
Jejunum	2
Ileocecal	4
Timing of perforation	
Initial	2
Induction	7
Maintenance	5
Relapse	2
Surgery	
Primary resection anastomosis	12
Resection with stoma	3
Stoma with no resection	1

generalized sepsis and respiratory failure. One patient died 3 months after surgery from chemotherapy-related complications (Table 3). The 5-year cumulative OS of the perforated group was 78.6% compared to 85.5% in the non-perforated group ($p = 0.374$). The 5-year cumulative EFS of the perforated group was 71.4% compared to 81.2% in the non-perforated group ($p = 0.270$). (Figs. 1and 2)

Discussion

Intestinal lymphoma is one of the most common pediatric non-Hodgkin lymphomas. The tumor often involves the bowel wall and the root of the mesentery [5]. In some patients these tumors are not resectable at presentation [3]. Intestinal perforation is a common complication of intestinal lymphoma [4] and is associated with high mortality rates because of spillage of enteric contents in an immunocompromised patient [5–7].

Perforations in patients who receive chemotherapy are caused by rapid tumor necrosis, lysis, and tissue impairment due to excessive granulation as a result of chemotherapy [11]. Despite occasional series in the literature reporting chemotherapy-induced bowel perforation in adults, there is a paucity of reports in the pediatric literature [2].

In the literature, the incidence and prognostic implications of perforation in pediatric intestinal lymphoma vary considerably. In this single-institution study, the rate of perforation in patients with biopsy-proven intestinal lymphomas was 6.7%. These results are comparable to those of LaQualgia et al. who reported a perforation rate of 6% in a series of 68 children with intestinal lymphoma [12]. In another set of 28 pediatric Burkitt's intestinal lymphoma, none of the patients had a perforation [13]. Other investigators reported a perforation rate of 7.4% related to chemotherapy [14]. In agreement with others, all of the perforated cases in the present study had Burkitt's lymphoma, and 75% of the perforations involved the small bowel [10,12].

Perforated intestinal lymphoma has been recognized as an indicator of poor prognosis in adults; however, this complication has a less specific prognostic significance in children. Fallon et al. [15] reported a 60% overall 5-year mortality in adults with an intestinal perforation, which was higher than that in pediatric lymphoma with abdominal involvement (15–39%) [16]. In the present study, the 5-year OS and EFS of the perforated patients were 78.6% and 71.4% respectively, compared to 85.5% and 81.2% in the non-perforated patients. The differences were not statistically significant ($p = 0.374$ and $p = 0.270$, respectively). Better prognosis in pediatric patients may be explained by better response to chemotherapy and the healthier physiological reserve in pediatric patients.

Perforation creates complex treatment challenges for the surgeon and oncologist, prompting a series of difficult decisions about primary resection anastomosis versus ostomy, the extent of resection, the management of peritonitis and postoperative complications, and the restarting of chemotherapy. In the present study, primary resection anastomosis was possible in 75% of the 16 patients with no postoperative intestinal leakage or fistula. We proceeded to primary anastomosis if we could resect the entire tumor and the edges of the intestine were healthy. Otherwise, a diverting stoma was done. Other studies recommend staged operative resection to minimize the risk of anastomotic leakage and early enteral nutrition to maximize immune defenses [15]. The next cycle of chemotherapy was delayed by a median of 17 days. This delay did not affect OS or EFS.

In the literature, perforation follows chemotherapy initiation by 4 days–5 weeks. In the present study, perforation occurred during chemotherapy in 14 patients after a median of 26 days of chemotherapy initiation.

The degree of wall thickening in peripheral T-cell lymphoma is usually mild to moderate, as opposed to the marked thickening that is often seen in B-cell lymphomas [17]. In the present study, although there was no statistically significant difference in wall thickness between different types of lymphoma, there was a trend towards greater thickness in Burkitt's lymphoma.

In patients with Burkitt's lymphoma affecting a long segment of the bowel loops with concentric and transmural involvement, the clinical suspicion of perforation must be confirmed by CECT to detect early perforation. In the current study, there were no particular CT criteria to predict perforated cases.

Ara et al. [18] reported a higher percentage of perforation in the small bowel than in the large bowel. Vaidya et al. [19] also reported that the most widespread perforation area is in the small intestine, and the most frequent perforation is observed in the diffused major B-cell subtype. In agreement with others, most of the perforated cases in the present study were Burkitt's lymphoma; 75% of the perforations were in the small bowel and 25% in the ileocecal region.

Conclusion

Perforation is not an adverse prognostic factor for survival in pediatric intestinal lymphoma patients. A primary resection

Table 3
Post operative mortality in relation to the timing of perforation and type of surgery.

timing of perforation	number	median time to the perforation in days	procedure		death within one month of surgery
			1ry anastomosis	Stoma	
At presentation	2	–	0	2	–
After chemotherapy					
Induction	7	7	6	1	2
consolidation	5	22	5	0	
Relapse	2	28	1	1	

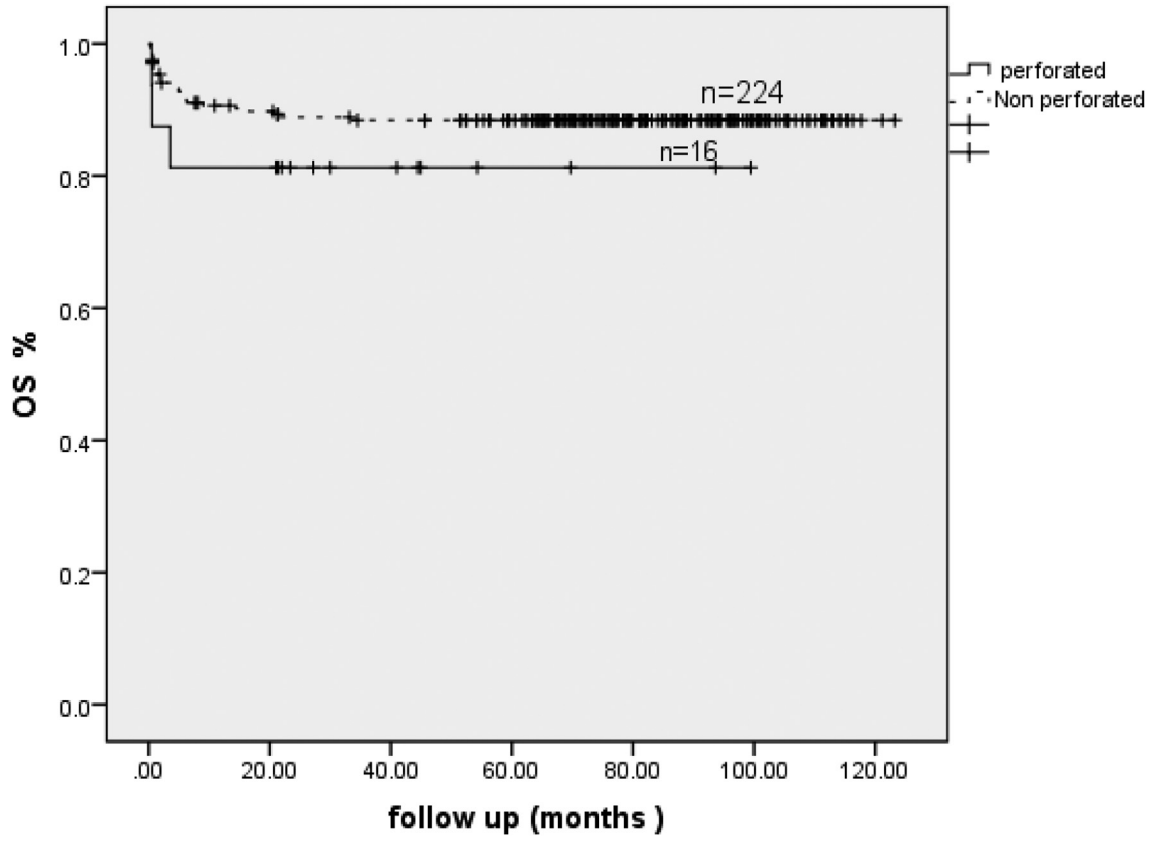

Fig. 1. Overall survival (OS) in the perforated versus non-perforated groups.

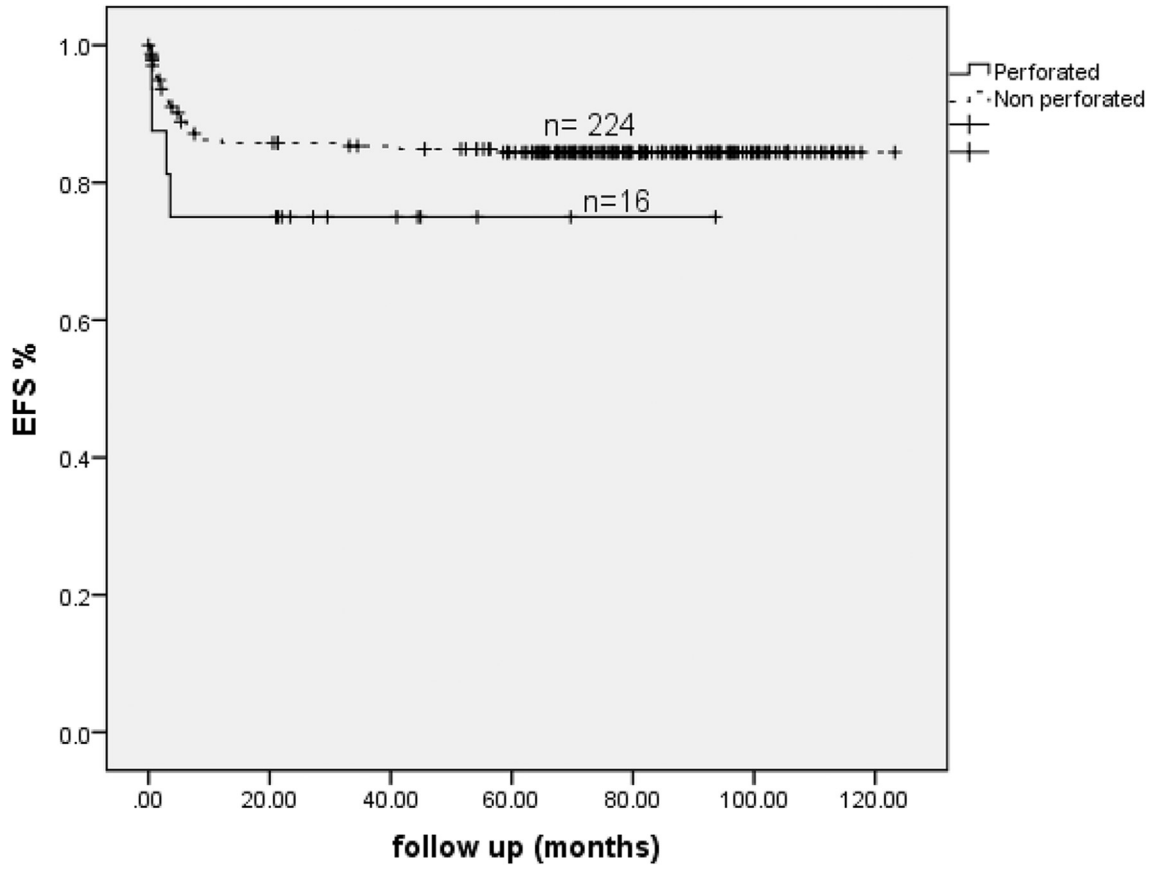

Fig. 2. Event-free survival (EFS) in the perforated versus non-perforated groups.

anastomosis seems to be a safe option if complete tumor resection is feasible.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.08.022.

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