Management of Primary Rectal Lymphoma: A Single Institution Experience

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Abstract

BACKGROUND: There is a paucity of literature regarding primary rectal lymphoma. Due to its rarity, and frequent changes in histological subtyping and classification, treatment has not been standardized. The objective of this study was to retrospectively review our experience with the management of primary rectal lymphoma over a 30-year period.

METHODS: All adult patients (?18 years) diagnosed with primary rectal lymphoma between 1982 and 2012 were identified. Demographics, symptoms, mode of diagnosis, type of lymphoma, grade, stage, risk factors, tumor size, treatment(s), response, and status following treatment were reviewed.

RESULTS: Seventeen patients were identified (10 male) with an average age of 53.6 years (range, 30-79). The most common subtypes were mucosa associated lymphoid tissue type lymphoma (n=7, 41%) and diffuse large B cell lymphoma (n=6, 35%). Four treated with a combination of surgical / endoscopic resection and chemotherapy achieved a complete response. Two treated with chemotherapy alone recurred. Four endoscopic resections resulted in 2 recurrences. Out of 5 treated with surgery alone, 2 recurred. One treated with H. pylori eradication resulted in a complete response, and 1 refused treatment and died. Median follow-up was 52 months (range, 18-138) months. At last follow-up, 15 patients (88%) were alive with no evidence of disease.

CONCLUSIONS: Our findings suggest that multimodal therapy including both surgical / endoscopic removal and chemotherapy was associated with better outcomes, although the numbers of different types of lymphoma are too small to draw any definitive conclusions. A multi-institutional collaboration will be necessary to determine the best treatment approach.

KEYWORDS: Primary rectal lymphoma, management, outcomes
INTRODUCTION

The gastrointestinal (GI) tract is the predominant site for extranodal lymphomas (stomach 48%, small bowel 26%, colorectal 12%, pancreas 2%, esophagus 1%).

Well described in the literature, GI lymphomas can occur as a primary (localized) or secondary (systemic) process. Despite their rarity, primary GI lymphomas are important since their diagnosis, management, and prognosis is distinct from other GI malignancies and lymphomas of other sites. While comprising less than 1% of all GI lymphomas, primary rectal lymphoma (PRL) remains the third most common cause of rectal cancer after adenocarcinoma (90-95%) and carcinoid (5%). [1]

There is a paucity of literature regarding PRL. Due to its rarity, and the frequent changes in histological subtyping and classification, treatment has not been standardized. As a result, interpretation of outcomes in the current literature is difficult. Using the most current staging criteria, histology, and classification systems, we reviewed our institution’s experience over a 30-year period with the management of PRL.

MATERIALS / METHODS

Institutional review board approval was obtained. Surgical and pathological databases were used to retrospectively identify all patients treated for PRL.
between 1982 and 2012 at the Mayo Clinic in Rochester, MN. We included all adult patients (≥18 years) with a diagnosis of PRL based on the Dawson criteria: no palpable superficial lymphadenopathy on initial physical examination, no mediastinal lymphadenopathy, normal total and differential white blood cell counts, normal bone marrow biopsy, no liver or splenic involvement, and only regional nodes affected by disease. [2]

Patient records were reviewed for demographic features, presenting symptoms, method of diagnosis, type of lymphoma including pathological features, history of inflammatory bowel disease, immunocompromised status, treatments received, tumor size, and status following treatment. Descriptive statistics are reported as a percentage of the total and continuous variables as the mean, or median, and range.

RESULTS
Seventeen patients were identified (10 male, 58%) with a median age of 58 years (range, 30-79). Sixteen patients (94%) had Non-Hodgkin lymphoma. The most common histopathological subtypes were mucosa associated lymphoid tissue (MALT) type lymphoma (n=7, 41%) and diffuse large B cell lymphoma (DLBCL) (n=6, 35%). A single case of Hodgkin’s lymphoma (HL), anaplastic large cell lymphoma (ALCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) were also identified (Table 1).
A total of 7 patients (41%) were either taking immunosuppressants, diagnosed with HIV, and/or had inflammatory bowel disease (IBD). A single case of ALCL was noted in a patient taking azathioprine for chronic ulcerative colitis (CUC), and DLBCL was found in 3 patients with CUC and 1 with indeterminate colitis (IC). Of those with DLBCL and IBD, 2 with CUC were on immunosuppression. HIV was noted in 1 patient with HL, and a solitary case of MALT lymphoma was seen in a patient treated with tacrolimus and prednisone following liver transplantation (Table 1).

Five patients were noted to be asymptomatic at presentation while the remainder presented with a combination of rectal bleeding, weight loss, fatigue, constipation, anorectal pain, and a change in stool caliber. In 3 patients, the presenting symptoms were not documented (Table 1).

The method of diagnosis was not documented in 10 (58%) patients. One lesion was found on digital rectal examination, another was diagnosed following a proctocolectomy for CUC, and the 5 were found endoscopically (Table 1).

Stage at diagnosis was I-EA in 14 (82%), II-EA in 2 (12%), and unknown in 1 who refused further workup and treatment. Both patients with stage II-EA were diagnosed with DLBCL. Histologic grade was only recorded in 8 (47%), with a single case of low grade FL and high grade DLBCL. The remaining 6 cases were all low grade MALT lymphoma (Table 2).
Tumor size was documented in 13 (76%) patients and ranged from multiple small rectal nodules to 15cm. Macroscopic tumor characteristics and distance from the anal verge was not recorded (Table 2).

Treatment details and response patterns for individual patients are outlined in Table 2, with all treatments administered electively. A single case of ALCL associated with immunosuppression and CUC persisted following treatment with chemotherapy (R-CHOP). A total proctocolectomy with creation of an end ileostomy resulted in a complete response. Patients with DLBCL treated with a combination of resection and chemotherapy resulted in a complete response in all (n=5). One case of DLBCL in an immunocompetent patient treated with R-CHOP alone resulted in recurrence. Autologous stem cell transplantation was administered, though unsuccessful. A solitary case of FL resected endoscopically recurred, though a complete response was obtained after treatment with chemotherapy (Rituximab). One patient with HL associated with HIV refused all workup and treatment. Out of 7 cases of MALT PRL all were initially treated with resection alone, and 3 experienced recurrence. One was treated with chemotherapy (chlorambucil), 1 with H. pylori eradication consisting of twice daily dosing of lansoprazole 30mg, amoxicillin 500mg, and clarithromycin 500mg for 2 weeks, and 1 with re-resection, all of which had subsequent complete pathological responses. One documented case of MCL demonstrated complete response after undergoing a low anterior resection (Table 2).
Median follow-up and disease free survival was 51 months (range, 8-138). At last follow-up 15 patients (88%) were alive with no evidence of disease. Two patients (12%) died from their disease at 8 and 21 months after diagnosis. In these 2 patients, 1 with a greater than 10cm stage II-EA DLBCL experienced a recurrence within 5 months of R-CHOP and underwent autologous stem cell transplantation without success, and the other with HL and HIV refused all treatment (Table 2).

**DISCUSSION**

This review of 17 patients treated for PRL at our institution over a 30-year period demonstrated significant variations in treatment modalities. The most common types were MALT and DLBCL. The best overall response rates were observed with a multimodal approach that included resection and chemotherapy. Although different proposals exist for diagnosing primary versus systemic rectal lymphoma, the Dawson Criteria is the most widely used and accepted, and the one we adhered to in our study. [2-8] The criteria include no palpable superficial lymphadenopathy on initial physical examination, no mediastinal lymphadenopathy, normal total and differential white blood cell counts, normal bone marrow biopsy, no liver or splenic involvement, and only regional nodes affected by disease. When the criteria were proposed in 1961, operative findings dictated primary versus systemic involvement. Currently, we have the benefit of high-resolution imaging, colonoscopic examination, and pathological confirmation.
of biopsies to assist in accurate preoperative diagnosis, classification, and staging.

Systems for classifying lymphomas have changed dramatically through the years making it difficult to compare results from clinical studies. Early studies employed a completely different nomenclature than what is utilized today. In 1982, the International Working Formula Classification system was devised in an attempt to consolidate the different classification systems (Rappaport, Lennert, Lukes and Collins, Kiel, British National Lymphoma Investigation, Dorfman) being utilized around the world at that time. The Working Formula Classification was a clinical system based on histology (low, intermediate, high grade, and others), and attempted to classify lymphomas into prognostic categories. [9] The introduction of the Revised European American Classification (REAL) system in 1994, arranged lymphomas by cell type of origin, added immunophenotyping, genetic, and morphologic features, and identified the thirteen most common types of non-Hodgkin’s lymphoma. [10] In 2008 the World Health Organization (WHO) instituted an updated classification system by adding information on cell surface markers and genetics, distinguished between B, T, and natural killer (NK) cells, and included seventy different types of known lymphomas. [11] Our study reviews our institution’s experience in the management of PRL using the most current histological, classification, and staging criteria.
Staging of lymphoma is based on the Ann Arbor system and the Cotswolds modification. Stage I localizes to a single region, Stage II involves two separate areas confined to one side of the diaphragm, Stage III demonstrates spread to both sides of the diaphragm, and Stage IV encompasses diffuse or disseminated involvement. Letter designations in reference to lymphoma include: A - absence of constitutional symptoms, B - presence of constitutional (systemic) symptoms, and E - involvement of a single contiguous extranodal site. Constitutional symptoms include unexplained fevers of at least 101.5°F, drenching night sweats, and loss of more than 10% of body weight over the previous 6 months (without dieting). PRL is restricted to stage I, and II when only regional nodes are affected by disease. [12-13] In our series, 14 (82%) patients had Stage I-EA disease, 2 (12%) Stage II-EA disease, and 1 (6%) who refused all workup and treatment an unknown stage.

The 5 largest series in the literature detailing a combined total of 70 cases of PRL revealed a female to male ratio of 1.3:1, and an average age of 56.3 years. Appropriately documented mean disease free survival in 4 of the studies was 58.8 months. [2-6] Other than a slight male predominance (58% / 1.4:1) this compares well to our data.

Mucosa associated lymphoid tissue lymphoma has been the most commonly diagnosed type of PRL since the adoption of the Internal Working Formula Classification in 1982, and the publication by Isaacson and Wright in 1983.
describing MALT lymphoma as a distinct type of B-cell lymphoma. [14] The second most commonly documented type is DLBCL. [15-16] Primary Hodgkin’s rectal lymphoma is extremely rare with few reported cases in the literature. [17-20] In our series we found 7 (41%) cases of MALT, 6 (35%) cases of DLBCL, and 1 case each of HL, mantle cell lymphoma, FL, and anaplastic large cell primary rectal lymphoma.

Patients typically present with non-specific symptoms including vague abdominal pain and a change in bowel habits. Other presenting symptoms can include weight loss, tenesmus, peritonitis, obstruction, and bleeding. In our series we found similar symptoms. Mucosal ulceration does not typically occur and a high index of suspicion is required to make the correct diagnosis. [4-6]

Although no direct causal link has been established, multiple risk factors are associated with PRL. These include immunocompromised states, inflammatory bowel disease, perineal radiation, acquired immunodeficiency (HIV/AIDS), and male homosexuality. [7, 21-24] Our series identified 7 patients with risk factors associated with PRL. Length of time from the initial diagnosis of IBD and the duration and dosage of immunosuppressant medication was not recorded in our study. For those taking immunosuppressants we identified 4 (23%) patients taking immunosuppressants, 1 HIV positive patient, and 5 (29%) patients with inflammatory bowel disease. Of those with IBD, 4 had CUC and 1 was diagnosed with IC. Among patients taking immunosuppressants in our study, 3
were being treated for CUC. The length of time from the initial diagnosis and the duration or dosage of immunosuppressant therapy was not specifically evaluated in this study.

A variety of treatment options for PRL have been described in the literature including observation, local or endoscopic excision, surgical resection, chemotherapy, radiotherapy, *H. pylori* eradication, antibiotic therapy, intraluminal hyperthermia, and a combination of these modalities administered in a neoadjuvant or adjuvant setting. Most treatments are described in the context of a single case, and few large series have been published. Prior to the Working Formula Classification, Dawson et al. reported on 12 cases of PRL and concluded that surgery appeared to provide a survival advantage. [2] In 1962 Culp et al., from Mayo Clinic, reviewed 20 cases over a 10 year period and concluded the best means of treatment was a combined approach of surgery and radiation. [3] Perry et al., from St. Marks Hospital, published their results on 22 patients and recommended surgical resection as the treatment of choice. [4] Devine and colleagues reported an additional twelve cases in 1986 and concluded that primary lymphoma of the rectum should be treated with surgical excision followed by radiation therapy. If the tumor cannot be excised completely, debulking likely does not provide palliation, and chemoradiotherapy should be the treatment of choice. [5] The last large series to describe PRL prior to the adoption of the Working Formula Classification was published by Shepherd et al. in 1988, in which they concluded surgery should be the primary
treatment with radiation and/or chemotherapy reserved for advanced cases. [6] Following the Working Formula Classification only a few small case series have been published. In 1998 Matsumoto et al. described 6 cases of mucosal associated lymphoid tissue of the colon and rectum, of which 3 cases were primary rectal involvement. These 3 cases were treated with a combination of local excision, partial resection, and \textit{H. pylori} eradication, and no definitive conclusions could be drawn. [25] Niino and Yamamoto outlined 8 cases of MALT PRL in 2010, in which all patients were treated with antibiotic therapy. Five experienced a complete response, and 3 did not respond, which prompted further treatment with chemotherapy. Response to chemotherapy was not noted. [26] Chihara et al., in 2010, reported on 2 stage IIA MALT PRL patients who received R-CHOP chemotherapy resulting in a complete response. [27] In 2012 Okamura et al. documented 3 cases of MALT PRL treated with radiotherapy only, and concluded that radiation at a total dose of 30 Gy is both effective and safe for the treatment of rectal MALT lymphoma. [28] In our series, a multimodal approach including surgical / endoscopic resection and chemotherapy appeared to provide a slight advantage.

There is a paucity of published literature regarding PRL. It is often included in the category of lymphomas of the gastrointestinal tract, and not considered separately. Many reported cases of PRL do not adhere to the Dawson Criteria, describe secondary rectal involvement, illustrate previously published cases, represent non-rectal synchronous lesions, or are poorly documented with short
follow-up. [15, 24, 29-36]

As noted by Dawson et al. in 1961, “no one centre can hope to see enough primary intestinal (lymphoma) cases to be able to lay down any generally useful prognostic criteria or to arrive at any definite conclusions about the best methods of treatment”. [2] Unfortunately, this statement still holds true today. Even in large tertiary referral centers, and secondary to the rarity of the disease, the number of cases is too small to publish generalized prognostic criteria, or to arrive at definitive conclusions regarding the best methods of treatment. This represents the main limitation of our study. Review of the literature would suggest that multimodal therapy provides an advantage in regards to decreased recurrence, although analysis of the data regarding treatment is difficult due to a lack of uniformity, which is also a limitation in our study.

CONCLUSIONS

In our cohort, the most common type of primary rectal lymphoma was mucosa associated lymphoid tissue and diffuse large B-cell lymphoma. Forty-one percent of our patients had inflammatory bowel disease and/or were immunocompromised. This study suggests that multimodal therapy that includes both surgical / endoscopic removal and chemotherapy was associated with better outcomes, although the numbers of different types of lymphoma are too small to draw any definitive conclusions. A multi-institutional collaboration to collect data
on this population will be necessary to determine the best treatment approach in patients with primary rectal lymphoma.

REFERENCES:


### Table 1 - Demographic, Presentation, and Diagnostic Information

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Date Diagnosed</th>
<th>Age at Diagnosis</th>
<th>Sex</th>
<th>Risk Factors</th>
<th>Symptoms</th>
<th>Method of Diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>ALCL</td>
<td>1/05</td>
<td>30</td>
<td>M</td>
<td>CUC and Immunosuppression (Azathioprine)</td>
<td>Rectal Pain, Weight Loss</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>DLBCL</td>
<td>9/99</td>
<td>34</td>
<td>M</td>
<td>CUC and Immunosuppression (6-MP, Prednisone)</td>
<td>Medical Refractory CUC (BRBPR, diarrhea, ABD discomfort)</td>
<td>Post Surgery</td>
</tr>
<tr>
<td>3</td>
<td>DLBCL</td>
<td>10/99</td>
<td>77</td>
<td>M</td>
<td>None</td>
<td>BRBPR and Anal Pain</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>DLBCL</td>
<td>4/00</td>
<td>34</td>
<td>M</td>
<td>CUC</td>
<td>BRBPR</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>DLBCL</td>
<td>3/01</td>
<td>58</td>
<td>M</td>
<td>IC</td>
<td>Asymptomatic</td>
<td>Palpable lesion on DRE</td>
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<tr>
<td>6</td>
<td>DLBCL</td>
<td>4/09</td>
<td>38</td>
<td>M</td>
<td>CUC and Immunosuppression (Infliximab, Prednisone)</td>
<td>Medical Refractory CUC (BRBPR, diarrhea, ABD discomfort)</td>
<td>NR</td>
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<td>5/10</td>
<td>41</td>
<td>M</td>
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<td>Rectal Pain, Weight Loss, Stool Caliber Change</td>
<td>NR</td>
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<td>8</td>
<td>FL</td>
<td>8/02</td>
<td>79</td>
<td>F</td>
<td>None</td>
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<td>Colonoscopy</td>
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<td>HL</td>
<td>11/88</td>
<td>48</td>
<td>M</td>
<td>HIV</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
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<td>5/94</td>
<td>68</td>
<td>F</td>
<td>None</td>
<td>Asymptomatic</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>11</td>
<td>MALT</td>
<td>10/97</td>
<td>58</td>
<td>F</td>
<td>None</td>
<td>Asymptomatic</td>
<td>Colonoscopy</td>
</tr>
<tr>
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<td>10/97</td>
<td>64</td>
<td>F</td>
<td>None</td>
<td>BRBPR</td>
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</tr>
<tr>
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<td>3/98</td>
<td>69</td>
<td>F</td>
<td>None</td>
<td>Asymptomatic</td>
<td>NR</td>
</tr>
<tr>
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<td>MALT</td>
<td>1/03</td>
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<td>MALT</td>
<td>4/06</td>
<td>68</td>
<td>M</td>
<td>Immunosuppression (Tacrolimus, Prednisone)</td>
<td>Fatigue</td>
<td>Colonoscopy</td>
</tr>
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<td>16</td>
<td>MALT</td>
<td>4/10</td>
<td>31</td>
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<td>None</td>
<td>Constipation, Bloating, Intermittent Nausea</td>
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<td>17</td>
<td>MCL</td>
<td>2/94</td>
<td>71</td>
<td>M</td>
<td>None</td>
<td>None</td>
<td>NR</td>
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</table>

**Abbreviations:**
- ABD – Abdominal
- ALCL – Anaplastic Large Cell Lymphoma
- BRBPR – Bright Red Bleeding Per Rectum
- CUC – Chronic Ulcerative Colitis
- DLBCL – Diffuse Large B-Cell Lymphoma
- DRE – Digital Rectal Examination
- FL – Follicular Lymphoma
- HIV – Human Immunodeficiency Virus
- HL – Hodgkin’s Lymphoma
- IC – Indeterminate Colitis
- MCL – Mantle Cell Lymphoma
- MALT – Mucosa Associated Lymphoid Tissue
- NR – Not Recorded
- 6MP – 6 mercaptopurine

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## Table 2 - Tumor Information

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Stage</th>
<th>Grade</th>
<th>Tumor Size</th>
<th>Treatment</th>
<th>Response</th>
<th>Follow-up (months)</th>
<th>Status at Last Follow-up</th>
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<tr>
<td>1</td>
<td>ALCL</td>
<td>I-EA</td>
<td>NR</td>
<td>NR</td>
<td>R-CHOP</td>
<td>Persistence after chemo</td>
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<td>NED</td>
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<td>2</td>
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<td>I-EA</td>
<td>NR</td>
<td>10cm</td>
<td>TPC/EI+CHOP</td>
<td>CR</td>
<td>71</td>
<td>NED</td>
</tr>
<tr>
<td>3</td>
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<td>I-EA</td>
<td>NR</td>
<td>4.5cm</td>
<td>APR+CHOP</td>
<td>CR</td>
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<td>NED</td>
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<td>4</td>
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<td>NR</td>
<td>Multiple small rectal nodules</td>
<td>ER + CHOP</td>
<td>CR</td>
<td>138</td>
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<td>I-EA</td>
<td>High</td>
<td>8mm</td>
<td>ER + R-CHOP</td>
<td>CR</td>
<td>133</td>
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<td>DLBCL</td>
<td>I-EA</td>
<td>NR</td>
<td>NR</td>
<td>TPC/IPAA</td>
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<td>NR</td>
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<td>FL</td>
<td>I-EA</td>
<td>Low</td>
<td>5mm</td>
<td>ER</td>
<td>Recurred - Year NR</td>
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<td>HPE</td>
<td>CR</td>
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<td>I-EA</td>
<td>Low</td>
<td>1cm</td>
<td>TAE</td>
<td>Recurred - 2010</td>
<td>18</td>
<td>NED</td>
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<tr>
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<td>NR</td>
<td>NR</td>
<td>LAR</td>
<td>CR</td>
<td>50</td>
<td>NED</td>
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</table>

ALCL – Anaplastic Large Cell Lymphoma  
APR – Abdominoperineal Resection  
CHOP – Cyclophosphamide / Hydroxydaunorubicin / Oncovin / Prednisone  
CR – Complete Response  
DLBCL – Diffuse Large B-Cell Lymphoma  
EI – End Ileostomy  
ER – Endoscopic Removal  
FL – Follicular Lymphoma  
HPE – *H. pylori* Eradication  
HL – Hodgkin’s Lymphoma  
IPAA – Ileal Pouch Anal Anastomosis  
LAR – Low Anterior Resection  
MCL – Mantle Cell Lymphoma  
MALT – Mucosa Associated Lymphoid Tissue  
NED – No Evidence of Disease  
NR – Not Recorded  
RCHOP – Rituxumab + CHOP  
TAE – Transanal Excision  
TPC – Total Proctocolectomy