ORIGINAL ARTICLE

The Role of Surgical Resection, Radiation Dose, and Radiation Field Size in the Management of Gastric Lymphoma: Retrospective Study

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ABSTRACT

Objective: This retrospective review sought to determine outcomes in gastric lymphoma and analyse the effect of field size and radiation dose on patterns of recurrence and toxicity.

Patients and Methods: The study group comprised 31 patients (25 men and 6 women) whose mean age was 62 years. Fifteen patients had low-grade lymphoma, including 6 with mucosa-associated lymphoid tissue lymphoma, and 16 had intermediate- to high-grade lymphoma. Surgical resection was a component of therapy in 15 cases, whereas radiation therapy was the sole local therapy in 16 cases. Involved-field radiation therapy was delivered to 17 patients — typically with chemotherapy for intermediate- to high-grade lymphoma and alone for mucosa-associated lymphoid tissue lymphoma. Whole-abdomen radiation therapy was used in 14 patients. The median radiation dose was 30 Gy (range, 20-40 Gy). The median follow-up duration was 41 months.

Results: Five-year cause-specific survival, overall survival, and recurrence-free survival were 79%, 49%, and 84%, respectively. There was no significant difference between patients according to whether or not they underwent surgical resection. No patient experienced an in-field or marginal failure after radiation. There was no significant difference between involved-field radiation therapy and whole-abdomen radiation therapy with respect to the Radiation Therapy Oncology Group acute gastrointestinal toxicity scores or disease control. Five (16%) of 31 patients developed a second malignancy a mean of 6.3 years after radiation.

Conclusions: Radiotherapy without surgical resection resulted in excellent local control in gastric lymphoma, with no observed in-field failures at a median dose of 30 Gy. Similar acute toxicities were observed with involved-field and whole-abdomen radiation therapy.

Key Words: Lymphoma; Radiotherapy; Stomach neoplasms; Treatment outcomes

INTRODUCTION

Approximately half of all early-stage non-Hodgkin’s lymphomas are extranodal, with the gastrointestinal tract representing the most common site of involvement.1 Diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma occur in nearly equal proportions at this site and represent the vast majority of gastric lymphoma histologies.2,3 Historically, surgical resection with or without adjuvant radiation therapy (RT) or chemotherapy was considered necessary treatment for primary gastric lymphoma. Recently, the role of surgery has been called into question by a number of retrospective studies4-8 and a large multicentre prospective clinical trial.9 The German Multicenter Study, conducted by Koch et al.,9 compared surgery and adjuvant RT with RT alone. Patients with high-grade lymphoma were also treated with 4 to 6 cycles of cyclophosphamide, doxorubicin, vincristine (Oncovin; Eli Lilly and Co, Indianapolis, IN, United States), and prednisone (CHOP) chemotherapy independent of local therapy. To enhance acceptance and accrual, the trial was designed as a non-randomised study, which allowed surgeons to determine the treatment arm to which patients were assigned. Patients...
Management of Gastric Lymphoma
treated with stomach-conserving therapy had a 5-year survival rate of 84%, compared with 82% among patients treated with surgical resection plus RT.

Early-stage MALT lymphomas are commonly treated with antibiotics, in light of documented complete responses after eradication of Helicobacter pylori.10-12 Despite initial optimism, the durability of remission remains questionable, given short follow-up durations and high rates of polymerase chain reaction (PCR) B-cell monoclonality after H pylori eradication.13-15 In contrast, RT has been shown to be effective definitive therapy for gastric MALT lymphoma. Schechter et al16 reported a 2-year disease-free survival rate of 100% among 17 patients treated with local RT alone.

Although a role for RT in the management of gastric lymphoma is clearly established, the details of treatment, such as optimal dose and field size, are not well defined. Treatment portals have ranged from ‘involved field’ to the whole abdomen. For patients receiving RT without resection, doses have ranged from 30 to 50 Gy.17 This retrospective study aimed at examining the association that field size and radiation dose had with patterns of recurrence and toxicity in patients with primary gastric lymphoma.

PATIENTS AND METHODS
We analysed records from 31 patients with primary gastric lymphoma who were treated with RT between 1967 and 2001 at the University of Florida. Patients treated with palliative intent were excluded from analysis. A total of 29 patients had primary gastric lymphoma, and 2 had synchronous gastric and intestinal lymphomas. The mean age of the 6 women and 25 men was 62 years (range, 25 to 80 years).

Tumour histology was reported using the accepted system at the time of diagnosis (the Working Formulation,18 the Revised European-American Lymphoma classification,19 or the World Health Organization classification20). As in any retrospective review of non-Hodgkin’s lymphoma, the various classification systems in this study complicated direct comparisons between different eras. Accepting this inherent difficulty, we grouped patients into low-grade and intermediate- to high-grade subgroups on the basis of accepted histopathological similarities. The intermediate- to high-grade subgroup included histologies such as DLBCL, diffuse small cleaved lymphoma, immunoblastic lymphoma, and diffuse histiocytic lymphoma; the low-grade subgroup included primarily follicular subtypes and MALT lymphoma. There were no cases of mantle cell lymphoma. Fifteen patients had intermediate- to high-grade lymphoma, and 15 patients had low-grade lymphoma (including 6 with pure MALT lymphoma). One patient had been initially treated surgically for MALT lymphoma, which recurred as both MALT lymphoma and DLBCL. This case likely represented transformation of the low-grade tumour. This patient was considered to have intermediate- to high-grade disease in our analysis.

Patients were staged according to the Cotswold update of the Ann Arbor staging system. In accordance with the existing literature on gastric lymphoma, weight loss was not considered a ‘B symptom’ because many patients present with mechanical obstruction. In all, 28 (90%) patients had stage I or II disease: 19 at stage IAE, 1 at stage IBE, and 8 at stage IIAE. The remaining 3 patients had stage IV disease, on the basis of the extent of bone marrow involvement. Tumour dimensions could be determined accurately in 15 instances from radiographs or surgical reports. Sizes ranged from 2 to 15 cm, with the median being 4 cm.

The decision to perform surgery in this patient population was based primarily on historical preference of the referring physician. Most patients with gastric lymphoma were treated before 1990 by subtotal or total gastrectomy followed by adjuvant therapy. Fifteen patients underwent surgical resection as definitive local treatment: 12 had surgery plus adjuvant therapy as their initial treatment and 3 underwent surgical resection alone (followed by salvage RT for recurrence). Subtotal gastrectomy was the most commonly performed surgical procedure (11 of 15 patients). Planned adjuvant therapy following surgery consisted of RT for 6 patients and chemoradiotherapy for 6 others. Sixteen patients received RT as the primary local treatment with or without chemotherapy or antibiotics; a further 3 patients received RT as salvage therapy after a recurrence at the site of the primary surgical resection. Hence, all 31 patients in the series received RT (Table 1).

There were 2 basic field sizes in this series: involved-field RT (IFRT) and whole-abdomen RT (WART). The former type was used to describe localised radiation fields that encompassed the entire stomach (or surgical bed) and the surrounding first-echelon lymph nodes. Seventeen patients were treated with IFRT. In contrast, WART was a component of treatment in 14 patients,
of whom 8 also received a boost to an involved site. Common indications for WART included a disease stage greater than IAE (7 patients), non-MALT low-grade lymphoma (4 patients), and recurrent disease (2 patients).

Hyperfractionated RT (twice daily) was used in 9 patients and once-daily fractions were used in the remaining patients. Six of 14 patients treated with WART fields received hyperfractionated RT (80 cGy per fraction twice daily) in an attempt to limit late complications. The mean dose was 32 Gy and the median dose was 30 Gy (range, 20-40 Gy); 21 patients received doses of less than 35 Gy and 10 received more than 35 Gy to the primary site. All 31 patients completed RT as planned; however, 4 patients required unplanned treatment breaks. Two patients required more than a 5-day treatment break: 1 had pneumonia (10 days) and 1 had thrombocytopenia (19 days). An additional patient who had been treated with comprehensive lymphatic irradiation had a 40-day planned treatment break between WART and mantle irradiation.

**Table 1. Patient characteristics.**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tumour grade</th>
<th>Sex/age (y)</th>
<th>Stage</th>
<th>Initial treatment</th>
<th>Dose (Gy)</th>
<th>Fractionation (No. of times daily)</th>
<th>Field size</th>
<th>Chemotherapy</th>
<th>Status</th>
<th>Site of recurrence</th>
<th>Second malignancy</th>
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<td>1</td>
<td>Low</td>
<td>F/70</td>
<td>IAE</td>
<td>Surgery</td>
<td>30.0</td>
<td>IFRT</td>
<td>None</td>
<td>DWD</td>
<td>Died</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>M/50</td>
<td>IAE</td>
<td>Surgery</td>
<td>25.0</td>
<td>WART</td>
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</tr>
<tr>
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<td>IAE</td>
<td>Surgery</td>
<td>30.4</td>
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<td>DWD</td>
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<td>na</td>
<td>na</td>
</tr>
<tr>
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<td>M/65</td>
<td>IAE</td>
<td>Surgery</td>
<td>30.4</td>
<td>WART</td>
<td>None</td>
<td>DWD</td>
<td>Died</td>
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<td>na</td>
</tr>
<tr>
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<td>M/75</td>
<td>IAE</td>
<td>Surgery</td>
<td>30.0</td>
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<td>Surgery</td>
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<td>WART</td>
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<td>na</td>
<td>NSCLC</td>
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<td>M/40</td>
<td>IAE</td>
<td>Surgery</td>
<td>40.0</td>
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<tr>
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<td>M/64</td>
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<td>34.2</td>
<td>IFRT</td>
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<td>IAE</td>
<td>Surgery</td>
<td>40.0</td>
<td>WART</td>
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<td>WART</td>
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<td>WART</td>
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<td>M/54</td>
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<td>Surgery</td>
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<td>IFRT</td>
<td>ProMACE/CytoBOM†</td>
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<td>Abx-RT at recurrence</td>
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<td>na</td>
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<td>RT alone</td>
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<td>M/62</td>
<td>IAE</td>
<td>RT alone</td>
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<td>21</td>
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<td>IV</td>
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<td>30.4</td>
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<td>na</td>
</tr>
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<td>30.0</td>
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<td>M/80</td>
<td>IAE</td>
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<td>RT alone</td>
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<td>WART</td>
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<td>DTC</td>
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<td>M/48</td>
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<td>Abx-chemo/RT at recurrence</td>
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<td>IFRT</td>
<td>COP/Leukaran/Rituxan x 4</td>
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<td>Waldeyer’s</td>
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<td>26</td>
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<td>M/61</td>
<td>IV</td>
<td>Chemo/RT</td>
<td>30.4</td>
<td>2 WART</td>
<td>Leukaran + prednisone</td>
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<td>M/71</td>
<td>IAE</td>
<td>Chemo/RT</td>
<td>35.0</td>
<td>IFRT</td>
<td>CHOP x 6</td>
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<td>na</td>
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<td>28</td>
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<td>M/73</td>
<td>IAE</td>
<td>Chemo/RT</td>
<td>25.0</td>
<td>IFRT</td>
<td>Velban</td>
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<td>M/51</td>
<td>IAE</td>
<td>Chemo/RT</td>
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<td>IFRT</td>
<td>COP x 1</td>
<td>DWD</td>
<td>Generalised</td>
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</table>

* Radiation therapy given for recurrence after surgery.
† ProMACE/CytoBOM (initial) & CHOP x 6 (recurrence)

Abbreviations: Int = intermediate; MALT = mucosa-associated lymphoid tissue; Abx = antibiotics; RT = radiation therapy; Chemo = chemotherapy; IFRT = involved-field radiation therapy; WART = whole-abdomen radiation therapy; COPP = cyclophosphamide, Oncovin, procarbazine, and prednisone; CHOP = cyclophosphamide, vincristine, and prednisone; COP = cyclophosphamide, Oncovin, and prednisone; DID = died of intercurrent disease; DWD = died of disease; DTC = died of treatment complication; NSCLC = non–small-cell lung cancer; na = not applicable.
Chemotherapy was a component of treatment for 13 patients, 11 of whom had intermediate- to high-grade disease at diagnosis. Patients received a median of 6 cycles of chemotherapy. Seven patients received at least 4 cycles, with the most common regimen being CHOP. Other, non–anthracyline-based regimens—such as cyclophosphamide, vincristine, and prednisone (CVP); or cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone (COPP)—were used when it was deemed necessary for patient tolerance. Four patients with intermediate- to high-grade lymphoma received fewer than 4 cycles of chemotherapy (Table 1). Five patients with intermediate- to high-grade lymphoma (all of whom were older than 70 years) did not receive any chemotherapy.

In 4 of the 6 documented MALT lymphoma cases, \textit{H pylori} eradication therapy was attempted before or coincident with RT. Antibiotics were not routinely used if the biopsy result for \textit{H pylori} was negative.

Patterns of failure were documented on the basis of radiographic and clinical descriptions. In-field failures were defined as tumour recurrences within the irradiated field. Out-of-field recurrences were defined as those occurring in a single nodal or extranodal site separate from the irradiated field. Marginal failure included failures contiguous to radiation fields, and generalised disease was defined as disseminated, multisite failure.

Acute gastrointestinal toxicity was retrospectively analysed from weekly progress notes from the attending radiation oncologist. Late toxicity was recorded according to clinical follow-up notes and telephone conversations. Toxicity values were assigned using the Radiation Therapy Oncology Group (RTOG) acute- and late-toxicity scoring system for gastrointestinal complications.\textsuperscript{21}

All patients had at least 1 year of potential follow-up from the start of definitive treatment (surgery or radiation). The median overall follow-up duration was 41 months (range, 3 months to 24 years). The follow-up duration for living patients was 43 months. One patient was lost to follow-up approximately 3 years after subtotal gastrectomy and adjuvant RT. Kaplan-Meier curves were generated for local control, cause-specific survival, and overall survival.\textsuperscript{22} Fisher’s exact test was used to compare treatment-related variables. Statistical analyses were performed using the SAS system version 8 (SAS Institute, Cary, NC, United States).

**RESULTS**

Overall survival for the entire group was 49% at 5 years and 24% at 10 years. Cause-specific survival (CSS) at 5 and 10 years was 79% and 62%, respectively. There was no statistically significant difference in CSS between surgically treated patients and those treated with RT as the sole local therapy at 5 years (87% and 69%, respectively; \(p = 0.39\)). The overall 5-year relapse-free survival rate was 84%. No patient experienced an in-field failure or a marginal failure following RT. Three patients relapsed in a single out-of-field nodal or extranodal site, and 3 others relapsed with generalised disease. Of those relapsing with generalised disease, 2 had had intermediate- to high-grade tumours and 2 had stage II AE disease at presentation (Table 1). None of the 3 patients who had received radiation for salvage of initial surgical failure experienced a recurrence.

Field size was not significantly associated with CSS. Three of 17 patients who had been treated with involved fields and 4 of 14 patients who had been treated with whole-abdomen fields experienced a cause-specific death (18% and 29%; \(p = 0.67\)). Four of 6 patients with MALT lymphoma and 13 of 24 patients with non-MALT lymphomas received IFRT (67% and 54%; \(p = 0.66\)). There was also no significant correlation between surgical resection and field size or radiation dose. Of the 6 recurrences following RT, none were within the radiation field or at the margin. Two cases, in patients who had received IFRT, recurred in the non-irradiated low abdomen and pelvic nodes, and a third recurred with generalised disease. Two patients who had been treated with WART experienced recurrences with generalised disease, and a third had a recurrence in Waldeyer’s ring.

There was no evidence of a radiation dose-response relationship, because there were no in-field failures despite doses as low as 20 Gy. The mean dose among those experiencing any type of recurrence was about 34 Gy, compared with an overall mean dose of 32 Gy. Three of the recurrences occurred in patients treated with up to 40 Gy of radiation; 2 of these cases were generalised and one was out-of-field.

Patients with low-grade lymphoma fared better than those with intermediate- to high-grade lymphoma. The 5-year CSS in patients with stage I or II low-grade lymphoma was similar to that in patients who had stage I or II disease with intermediate- to high-grade tumours (88% and 80%; \(p = 0.14\)). All 6 patients with MALT
lymphoma who had been treated with conservative therapy alone (radiation with or without *H pylori* eradication) showed no evidence of local or distant disease progression at the last follow-up visit.

There was no significant difference in RTOG acute gastrointestinal toxicity scores between patients treated with IFRT and WART (Table 2). Overall, slightly less than half of the patients experienced either grade 0 or 1 acute gastrointestinal toxicity, whereas 14 experienced grade 2 acute toxicity. Late gastrointestinal toxicity was relatively rare. One patient experienced moderate diarrhoea, which was consistent with an RTOG late toxicity score of 2, and 1 patient experienced mild chronic diarrhoea and had a toxicity score of 1. There were no cases of acute perforation associated with rapid treatment response. One late case of fatal gastrointestinal bleed occurred 6 months after RT in a patient with severe pretreatment oesophageal varices. Another fatal gastrointestinal bleed occurred 2 weeks after RT in a patient with a 15-cm tumour. A man with diffuse histiocytic lymphoma, hypertension, and a history of 3 abdominal surgeries, including exploratory laparotomy before treatment, developed a gastrocutaneous fistula after 40 Gy of radiation and 3 cycles of CHOP. He had a particularly aggressive tumour, which recurred as a 20-cm mass in the lower abdomen just after the fistula developed.

Non-cutaneous second malignancies occurred in 5 (16%) of the 31 patients. The latency period was about 6 years (range, 2-15 years). Only one of the 5 cases of second malignancy occurred within the previously irradiated field. Two patients each developed prostate and lung cancer. One of the prostate cancers occurred in a WART field 15 years after treatment, and the other occurred well outside an involved field. One man developed an adenocarcinoma of the right breast about 7.5 years after WART. The superior aspect of his treatment field stopped several centimetres below the nipple, but scatter beyond the field edge may have involved breast tissue. He was well at the last follow-up visit after a modified radical mastectomy. Three of the 5 patients have died as a result of their second cancers.

**DISCUSSION**

Primary gastric lymphoma has historically been a surgically treated disease. Surgical proponents have cited high cure rates for local disease, the ability to determine precise histology, and the prevention of gastric perforation or haemorrhage as possible advantages. In light of our data and the German Multicenter Study, both of which show equivalent survival rates for nonsurgical treatment and surgery plus RT, a re-evaluation of these potential advantages seems warranted.

Cure rates achieved by surgery followed by RT or chemotherapy, or both, have traditionally been high. Researchers of the Department of Radiation Oncology at the Princess Margaret Hospital, University of Toronto, Canada, reviewed 149 patients with early-stage gastric lymphoma who were treated between 1967 and 1996. The subset of patients treated at the hospital before 1985 — typically with surgery and adjuvant RT — had a CSS of 88%. Sano et al reported an 85.6% CSS in 50 early-stage patients treated with total gastrectomy, systematic lymphadenectomy, and chemotherapy for nodal metastases. Similarly, Bartlett reported a 10-year overall survival of 88% with a primarily surgical approach.

Recent experience with stomach-conserving therapy has shown similar outcomes. Patients treated after 1985 at the Princess Margaret Hospital typically received chemoradiation for DLBCL, and RT alone for MALT lymphoma; only 19 of 45 patients underwent surgical resection. Using this treatment protocol, Gospodarowicz et al reported an overall 5-year CSS of 95.5%. In the subset of Princess Margaret Hospital patients with low-grade lymphoma treated after 1985, the CSS was 100%. Most retrospective reviews have shown survival rates of 70% to 90% with variable follow-up durations.

Our data compare favourably to those from other studies with respect to local disease control; however, our series saw more generalised and regional failures than did others. This finding may be explained in part by the chemotherapy that was delivered to patients who experienced a tumour recurrence. Four of the 6 treatment failures occurred in patients with intermediate- to high-grade lymphoma, and all 4 failures were observed in those who had received attenuated or no chemotherapy. There were no failures in the 7 patients with

<table>
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<th>Field size</th>
<th>RTOG acute gastrointestinal toxicity* score</th>
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<tr>
<td></td>
<td>0 1 2 3</td>
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<tr>
<td>Involved-field radiation therapy</td>
<td>5 4 7 1</td>
</tr>
<tr>
<td>Whole-abdomen radiation therapy</td>
<td>4 2 7 1</td>
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</table>

* Fatal gastrointestinal bleed 2 weeks after radiation therapy.
intermediate- to high-grade disease who had received 4 cycles of chemotherapy and RT. Our current recommendation for intermediate- to high-grade gastric lymphoma includes 4 to 6 cycles of doxorubicin-based chemotherapy (usually CHOP) followed by radiation.

Historically, surgery was required for accurate diagnosis. Modern endoscopic techniques have improved radiologists’ ability to reliably obtain biopsy samples; reported accuracy rates range from 62% to 98.5%. Endoscopy has become the preferred method of diagnosis in many settings, thereby rendering more extensive surgery unnecessary.

Finally, the risk of gastric perforation and haemorrhage has been espoused in the pro-surgery literature as a reason to avoid primary chemotherapy and RT. In our series, there were no cases of haemorrhage or perforation during treatment that suggested rapid tumour regression as a cause. One patient with a very large tumour died of gastrointestinal bleeding 2 weeks after therapy, but it was unknown whether the haemorrhage was related to persistent disease or treatment. Other stomach-conserving therapy experiences have also shown a low incidence of perforation or haemorrhage. Gobbi et al reported no cases of perforation among 76 patients treated for primary gastric lymphoma. Brooks et al reported early perforation in 2 of 58 patients. An experience from Stanford showed treatment-related bleeding or perforation in 25% of patients with gastrointestinal lymphoma. The Stanford series, however, included a large proportion of patients with intestinal lymphoma, and haemorrhage or perforation usually occurred in the setting of tumour progression rather than an immediate response to RT. We suspect that the risk of perforation or haemorrhage with low-grade lymphoma is minimal and that, in the absence of full-thickness stomach-wall involvement, the risk of perforation in intermediate- to high-grade lymphoma is probably low as well.

There are minimal data in the literature to guide the selection of radiation dose for gastric lymphoma. Clinicians have been forced to extrapolate from retrospective dose-response data in patients with non-Hodgkin’s lymphoma. Preliminary studies from Stanford showed no evidence of a dose-response relationship in intermediate- to high-grade lymphomas between 30 and 50 Gy. A more recent Canadian series reported impressive outcomes using 30 to 35 Gy after complete response to chemotherapy in early-stage non-Hodgkin’s lymphoma. At the University of Florida, excellent tumour control was associated with doses of 30 Gy for both low-grade and intermediate- to high-grade lymphomas, and a complete response to chemotherapy was achieved. Higher doses were recommended only for tumours greater than 6 cm and for partial responders to chemotherapy.

To our knowledge, dose-response has not been studied specifically in gastric lymphoma. Although nearly half of the patients in our series underwent surgical resection — and thus had only a microscopic tumour burden — we found no in-field failures using a median dose of about 30 Gy. Most recurrences occurred in patients with intermediate- to high-grade disease and were out-of-field or generalised, which suggests that insufficiently effective chemotherapy may have been the cause.

MALT lymphoma has recently been treated with primary RT to doses of 30 to 34 Gy, and with encouraging success. Disease-free survival rates have ranged from 75% to 100% with variable follow-up durations. Our own experience with MALT lymphoma and definitive RT mirrors the existing literature, with no documented in-field disease progression.

Eradication of *H pylori* may induce complete clinical responses in selected patient populations. For example, the presence of perigastric lymph nodes has been shown to be a negative predictive factor in patients treated for *H pylori* eradication. *H pylori* eradication therapy alone may be insufficient for high-grade MALT lymphomas. Stage IIE disease and stage I disease involving the muscularis mucosa or serosa are thought to respond poorly to antibiotics as well. Although eradication of *H pylori* remains an acceptable initial treatment for patients with flat mucosal lesions, high rates of persistent monoclonality and reports of delayed treatment failures mandate close surveillance and probably delayed RT in many cases. Given the effectiveness of relatively low-dose radiation in this disease, it is reasonable to proceed directly to RT in symptomatic patients after a short trial of antibiotics.

Five patients (16%) developed second malignancies following treatment in the current study. The precise role of radiation in the genesis of second malignancies remains controversial. Possible explanations for the excess incidence of second malignancies include chemotherapy, radiation, vigilant follow-up, and expression...
of an inherent sensitivity toward carcinogenesis. Shenkier et al. described an excess of pretreatment malignancies as evidence for an inherent predisposition to carcinogenesis. It is well accepted that patients with lymphoma typically have genetic abnormalities (such as translocations of the \textit{bcl-2} gene, dysregulation of cell-cycle proteins, and mutations of \textit{p53}), which may predispose them to other malignancies.

Because low-grade gastric lymphomas tend to have a favourable prognosis, cure rates are high and a significant proportion of patients remain at risk of developing long-term complications. The situation may be analogous to that of survivors of Hodgkin’s lymphoma: diligent follow-up of this high-risk group reveals an increased occurrence of late toxicity and second malignancies.

The carcinogenic effects of chemotherapy and radiation must also be considered. In a recent epidemiological study of 19,046 survivors of Hodgkin’s lymphoma, the development of lung cancer was associated with alkylating agents (relative risk, 4.2) and radiation doses of more than 5 Gy (relative risk, 5.9).\textsuperscript{38} Statistically significant increases started 1 to 4 years after treatment with alkylating agents and 5 years after RT. Tobacco use increased the risk by more than 20 times.

The dose-response relationship between radiation and carcinogenesis remains uncertain. Animal and human data suggest a decrease in the incidence of malignancy at higher radiation doses (such as those within radiation fields), most likely because of increased cell killing of potentially mutagenic cells.\textsuperscript{39} In our series, all but 1 case of second malignancy occurred outside the treatment field; these cases were thus exposed to doses of less than 30 Gy. If radiation had been responsible for the increased incidence of second malignancies, then it is likely that scatter radiation at the field edge played a dominant role. As radiation treatments become more conformal using 3-dimensional conformal RT and intensity-modulated RT, the amount of low-dose scatter to normal tissues can be expected to increase. Further studies are warranted to ensure a subsequent increase in second malignancies does not occur.

Appropriate field sizes and RT doses must be selected with tumour control, acute toxicity, and potential late complications in mind. With respect to tumour control, 3 of the 6 recurrences in our series were not generalised failures and were hence potentially avoidable with more effective regional treatment. In particular, there were 2 intra-abdominal recurrences in patients with intermediate- to high-grade lymphomas that had been treated with IFRT; these failures might have been avoided either by treating WART fields or by using more effective chemotherapy.

The absence of in-field recurrence in either IF or WART patients suggests that the moderate doses of RT used in WART are very effective at controlling subclinical disease. Similarly, the absence of out-of-field recurrences in patients treated with at least 4 cycles of CHOP chemotherapy suggests that adequate chemotherapy is very effective in treating subclinical disease. Whereas moderate-dose extended-field RT or sufficient chemotherapy may be effective in controlling subclinical disease, data from randomised clinical trials are needed to determine the appropriate number of cycles of CHOP chemotherapy and the relative therapeutic ratio of this treatment, compared with that of extended-field RT.

**CONCLUSION**

Primary gastric lymphoma should be considered an ideal disease for effective organ-sparing therapy. Conservative therapy appears equivalent to surgical resection in terms of disease control and survival, and it offers potential for improved quality of life. Future studies should focus on defining the optimal characteristics of combined modality therapy in patients with intermediate- to high-grade gastric lymphoma and in refining doses and field sizes in low-grade gastric lymphoma.

Currently at the University of Florida, we recommend IFRT alone, of up to 30 Gy, for stage I and II MALT lymphomas. WART may be considered for stage II low-grade lymphoma in selected settings. We recommend 4 or more cycles of CHOP chemotherapy followed by IFRT — of up to 30 Gy after a complete response and of 40 Gy after partial response — for patients with intermediate- to high-grade gastric lymphoma.

**REFERENCES**


3. de Jong D, Boot H, van Heerde P, et al. Histological grading in...


