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Radiation therapy for localized duodenal low-grade follicular lymphoma

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ABSTRACT

The aim of this study was to evaluate the initial treatment results and toxicities of radiation therapy for patients with early stage low-grade follicular lymphoma (FL) arising from the duodenum. We reviewed 21 consecutive patients with early stage duodenal FL treated with radiation therapy between January 2005 and December 2013 at the Cancer Institute Hospital, Tokyo. The characteristics of patients were: median age 62 years (range, 46–79 years), gender (male, 6; female, 15), clinical stage (I, 20; II_1, 1), histological grade (I, 17; II, 4). All patients were treated with radiation therapy alone. The median radiation dose was 30.6 Gy (range, 30.6–39.6) in 17 fractions. The involved-site radiation therapy was delivered to the whole duodenum. The median follow-up time was 43.2 months (range 21.4–109.3). The 3-year overall survival (OS), relapse-free survival (RFS) and local control (LC) rates were 94.7%, 79.3% and 100%, respectively. There were four relapses documented outside the treated volumes: two in the gastrointestinal tract (jejunum, terminal ileum), one in an abdominal lymph node (mesenteric lymph node) and one in the bone marrow. None died of the disease; one death was due to acute myeloid leukemia. No toxicities greater than Grade 1 were observed during treatment and over the follow-up time. The 30.6 Gy of involved-site radiation therapy provided excellent local control with very low toxicities. Radiation therapy could be an effective and safe treatment option for patients with localized low grade FL arising from the duodenum.

KEYWORDS: duodenal follicular lymphoma, radiotherapy, indolent lymphoma

INTRODUCTION

Primary follicular lymphoma (FL) arising in the gastrointestinal tract is a rare situation. Although the gastrointestinal tract is the most common site for extranodal lymphomas, FL only account for 1–3% of gastrointestinal non-Hodgkin's lymphomas [1].

The gastrointestinal FL is recognized as a variant of FL in the 2008 edition of WHO classification [2]. It shares common features with nodal FL in regards to morphology and immunophenotype, such as the expression of CD10 and BCL-6 markers [3].

In an extensive literature review of 249 patients, Yamamoto *et al.* reported that the gastrointestinal FLs had a tendency of low histological grade (Grade 1, 84.4%; Grade 2, 11.3%; Grade 3, 4.3%), low clinical stage of either Stage I (66.3%) or II (26.9%), and more favorable outcome than that of nodal FL [4].

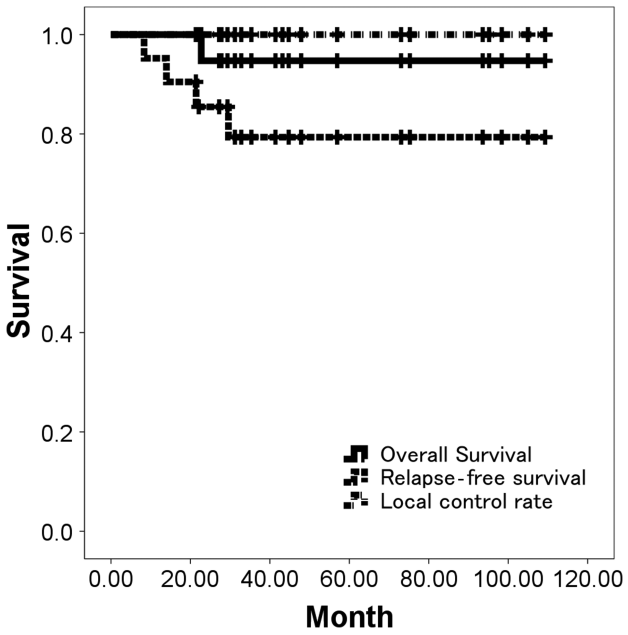

Fig. 1. Overall survival, relapse-free survival and local control rate for 21 patients.

The duodenum is the most frequent site for gastrointestinal FL [3–4]. In a retrospective study of 125 patients, Takata *et al.* reported that the most common involved site was the second portion of the duodenum, and it was associated with better progression-free survival than other FLs of the gastrointestinal tract [5].

Although recent studies have elucidated clinicopathological aspects of the disease, the clinical manifestations, prognosis and treatment have not been fully addressed. There is no consensus regarding the initial management. However, radiotherapy is considered the most powerful and effective treatment for localized low-grade non-Hodgkin's lymphoma [6].

The purpose of this study is to report our initial experience of 21 patients treated with primary radiation therapy and to explore the clinical course, prognosis and curability of the duodenal FL.

MATERIALS AND METHODS

Study design

This historical cohort study was approved ethically by the institutional review board (Approval No. 2015–1127) and scientifically by the scientific review board (Approval No. 1663) of the Japanese Foundation for Cancer Research. Records of patients with localized FL of the duodenum treated with definitive radiation therapy between January 2005 and December 2013 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research were reviewed. Information concerning patient characteristics, detailed initial treatment, acute and late toxicities, relapses and salvage treatment, and outcomes were collected with chart review.

Diagnosis and staging

A diagnostic biopsy was obtained through endoscopic exam in all patients before initial treatment. All biopsy specimens were fixed in formalin, followed by hematoxylin and eosin (H&E) staining and immunohistochemical staining, including CD20 and bcl-2 markers. If the initial diagnosis was performed by an outside hospital or clinic, all patients were re-examined by upper endoscopy with biopsy at our hospital.

Clinical staging was performed by physical examination, complete blood count, endoscopic examination, bone marrow biopsy and diagnostic imaging of CT and PET-CT scan. Staging was done according to the Lugano staging classification for primary gastrointestinal tract lymphoma.

Initial treatment: radiation therapy

All patients were treated with radiation therapy to the involved site. The radiation dose, using 15-MV photons, was delivered in a schedule of 30.6 Gy in 17 fractions for a non-bulky lesion and 39.6 Gy in 22 fractions for a bulky lesion, respectively. The clinical target volume (CTV) included the whole duodenum, and the planning target volume (PTV) was delineated by adding a 1-cm margin to the CTV. The 3D conformal radiation therapy was planned to the PTV using the three-field technique or four-field technique (AP–PA field plus opposed lateral or oblique field). Respiratory and peristaltic motions of the duodenum were evaluated by fluoroscopy with oral contrast media. The individual radiation fields were confirmed to include sufficient margin for the internal movement of the duodenum through the conventional simulator using fluoroscopy. No chemotherapy and/or antibody therapy was administered as an initial regimen.

Follow-up and statistical analysis

Patients were followed every 2–3 months for the first year, and every 6 months for the following year. Endoscopic examination was performed 3 months post-treatment.

The 3-year OS, relapse-free survival (RFS) and local control (LC) rates were analyzed statistically in all patients. Overall survival was defined as the period from the first day of radiotherapy until the date of death due to any cause. RFS was defined as the period from the first day of radiotherapy until the date of first documented recurrence or the date of death due to any cause, whichever occurred earlier. The LC rate was defined as the period from the first day of radiotherapy until the date of the first documented local relapse. All statistical analyses were calculated by the Kaplan–Meier method, with statistical difference tested by log-rank test. A P value of <0.05 was considered to be statistically significant. All the statistical analyses were performed with Predictive Analytic Software (PASW), version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Baseline characteristics and staging

A total of 21 patients were retrospectively reviewed. The patient baseline characteristics are described in Table 1. Many of the patients (71%) were asymptomatic at presentation and were incidentally diagnosed by upper endoscopic exam. Eight patients (38%) had a medical history of solid tumor of the gastrointestinal tract (esophageal cancer, gastric cancer and colon cancer) and underwent routine upper endoscopic exam for either preoperative workups or postoperative surveillance. The other causes of initial endoscopy were follow-up of non-malignant diseases (peptic ulcer, gastroenteritis) in three patients (14%), annual health examination in two patients (10%), further evaluation of gastrointestinal bleeding in one patient (5%) and workups for elevated tumor marker (CA19-9) in one patient (5%). All patients with medical history

Table 1. Patient baseline characteristics

Characteristics	Patients (*n*)
Age (year)	
Median 62 (Range 46–79)	
Gender	
Male	6
Female	15
Stage (Lugano)	
I	20
II_1	1
Histological grading (WHO)	
1	17
2	4
Immunohistochemical feature	
CD20 and BCL-2 positive	21
International Prognostic Index (IPI) Score	
Low	21
Follicular Lymphoma International Prognostic Index (FLIPI) score	
Low	19
Intermediate	2
Primary site of tumor location	
2nd portion	15
3rd portion	3
2nd and 3rd portion	2
2nd and 4th portion	1
Symptom	
Jaundice	1
Heartburn	1
Chest pain	1
Anemia	1
Abdominal discomfort	2
No symptom	15

of gastrointestinal solid cancer (38%) were in complete remission prior to definitive treatment of duodenal FL.

The clinical staging procedures of all patients are listed in Table 2. The PET/CT scan results are shown in Table 3. The FDG-PET/CT was performed in 19 patients, and only 7 cases (37%) showed positive results in the primary site.

Table 2. Multiple modality performed in staging procedure

	Patients (*n*)
Chest CT	18
Abdominal CT	18
PET/CT	19
Gallium Scan	2
Upper endoscopy	21
Capsular endoscopy	2
Colonoscopy	14
Bone marrow biopsy	21

Table 3. The results of the initial PET/CT study

	Patients (*n*)
PET/CT	
primary site positive	7
primary site negative	12

Survivals and failure patterns

The median follow-up duration of all patients was 43.2 months (range, 21.4–109.3 months). The 3-year OS, DFS and LC rates were 94.7%, 79.3% and 100%, respectively (Fig. 1). None died of the disease; the death of one patient was related to acute myeloid leukemia, which developed 7.6 months after definitive treatment of FL.

No incidence of local relapse is reported at this time. There were four recurrences, and the failure sites are listed in Table 4. All of the recurrent sites were outside the treated volume. One recurrence was bone marrow invasion by FL cells. The patient died due to acute myeloid leukemia, and FL recurrence was diagnosed incidentally in the process of post bone marrow transplant evaluation. The other recurrent sites were within the abdominal cavity: mesenteric lymph node, terminal ileum and jejunum. No symptom was associated with the recurrence. The recurrence was diagnosed by routine endoscopic exam or PET/CT scan. Salvage therapy of immunochemotherapy, namely, rituximab, cyclophosphamide, vincristine (oncovin) and prednisone (R-COP) was planned. Successful results were seen in three cases, where the patients completed the second line treatment, and all of them maintain second complete remission. In the analysis of recurrence, there were no differences by gender, clinical stage, histological grade, International Prognostic Index (IPI) score, Follicular Lymphoma International Prognostic Index (FLIPI) score or past medical history of gastrointestinal solid cancer [7, 8].

Toxicity

The acute and late toxicities are listed in Table 5. Most of the acute toxicities were minor and acceptable. Many patients experienced anorexia of Grade 1 (95%). No acute toxicities greater than Grade 2 were reported. The late toxicities were also not significant, and

Table 4. Sites of first failure

Sites	Patients (*n*)
Bone Marrow	1
Mesenteric Lymph Node	1
Terminal Ileum	1
Jejunum	1

Table 5. Acute and late toxicities

Grade	1	2	3	4	5
Acute toxicities					
Fatigue	4	0	0	0	0
Anorexia	20	0	0	0	0
Nausea	3	0	0	0	0
Vomiting	1	0	0	0	0
Gastritis	2	0	0	0	0
Diarrhea	4	0	0	0	0
Late toxicities					
Fatigue	2	0	0	0	0
Anorexia	5	0	0	0	0

limited to Grade 1. Mild anorexia was most frequently observed (24%) for late toxicity, and these patients recovered.

DISCUSSION

FL is a common subtype of lymphoma in the USA and European countries, but it is observed less in Asian countries [9]. However, unlike nodal FL, almost 50% of the cases of gastrointestinal FL were reported from Japan [4]. Endoscopy has a high detection rate of gastrointestinal FL [5, 10, 11]. Most Japanese patients are covered with the national health insurance system have easy access to endoscopic exam for various clinical reasons or annual health examination [12]. The frequency of the endoscopic exam may have caused the demographic discrepancy between nodal FL and gastrointestinal FL.

Earlier detection of gastrointestinal FL is possible by endoscopy. The disease has a distinguishable endoscopic appearance characterized by small whitish polypoid nodules up to 2 mm in diameter, and this is described as 'multiple polypoid lesions', 'multiple small polyps', 'multiple nodules' or 'multiple granules'. More detailed endoscopic images are enabled by high-resolution imaging, allowing identification of the microscopic features of enlarged villi, opaque whitish spots, and coiled vascular pattern within the villi [10, 11].

In our study, many patients were asymptomatic at presentation and were incidentally diagnosed by upper endoscopic exam at an early stage. Case reports of FL of the duodenum are rarely reported in the literature, and there is no information on whether early detection and treatment will lead to improvements in survival. Recent studies have suggested that the disease is a distinct entity, separate from nodal FL and represents a favorable outcome [4, 5, 13]. There is no common standard treatment strategy, and the initial management of this disease in controversial. This study represents our single institution experience of localized duodenal FL treated with radiation therapy.

In regard to patient baseline characteristics, our study showed a female predominance in the population, which is similar to previous reports [1, 3, 14]. The most frequently involved anatomical site was the second portion of the duodenum. Low histological grade and low FLIPI score were presented. Many of the patients were asymptomatic.

In our study, excellent LC was achieved with definitive radiation therapy. However, recurrences were observed in four cases, and all of them were outside the irradiated volume. Only one case presented bone marrow invasion. The patient was unable to undergo salvage therapy due to the progression of acute myeloid leukemia, which was related to the cause of death. The remaining three relapses were observed in the gastrointestinal tract (two) or abdominal lymph node (one). They were limited to the abdomen, and no involvement of adjacent organs or supradiaphragmatic lesions were observed. Consistent with previous reports [5, 13], our study showed a low rate of relapses outside the abdomen.

Although duodenal FL shares common features with nodal FL in regards to morphology and immunophenotype, recent reports on pathological findings have suggested that the two types of FL are distinct. Yoshino *et al.* reported that the disease extent was confined to the submucosal layer in their findings about duodenal FL [3]. To explain the low tendency of disease dissemination outside the gastrointestinal tract, Bende *et al.* reported that the gastrointestinal FL expressed surface IgA and specific mucosal adhesion molecules, such as α4β7, which are rarely found in nodal FL. IgA is an immunoglobulin class that is the main effector of the mucosal immune system, and it is less frequently found in nodal FL. α4β7, a mucosal homing receptor, binds to ligand MAdCAM-1 which is an adhesion molecule that is selectively expressed on mucosal endothelium. The majority of nodal FL did not express α4β7 integrin. In contrast, intestinal FL and low-grade Mucosa-Associated Lymphoid Tissue (MALT) lymphomas were strongly positive [15]. Moreover, several other similarities between duodenal FL and low grade MALT lymphoma were found recently.

Other clinicopathological findings, such as the lack of a follicular dendritic cell network [16, 17], deviation of immunoglobulin heavy chain (VH) usage [18], and patterns of gene expression [19] suggest that duodenal FL and low-grade MALT lymphoma have similar characteristics. Tari *et al.* also speculated that the gastrointestinal FL has an intermediate characteristic between nodal FL and low-grade MALT lymphoma based on his clinical findings of 28 gastrointestinal FLs [20]. In general, low-grade MALT lymphoma has a tendency to remain localized for a long period, and excellent clinical outcomes are achieved with local therapy such as surgery and radiation therapy. In our study, we consider that localized duodenal FL is also indolent, and that radiation therapy may be a favorable treatment option.

The treatment strategy for early stage gastrointestinal FL is controversial. Historically, several therapeutic options such as surgery, chemotherapy, radiation therapy, or watchful waiting (no therapy) have been performed as initial management. Since the long-term outcome in a large population is unclear, there is no standardized treatment strategy for early stage gastrointestinal FL.

In the largest case report of 63 patients with early stage duodenum FL, four main treatment strategies of watch and wait, radiation therapy, rituximab monotherapy or various chemotherapy treatments were applied. Of these 63 patients, 19 underwent radical radiation therapy and have achieved 100% complete regression. Patients received a focal dose of 30–45.3 Gy via an abdominal bath of 24.5–30 Gy. Although, complete regression was also achieved in the remaining therapies, LC was superior with radiation therapy compared with other treatments [13].

In our initial treatment, we had satisfactory results for LC with low toxicity. All 21 patients achieved complete remission in LC, and acute toxicities were minor. These findings suggest that radiation therapy is potentially curative in localized low-grade FL of the duodenum. However, there are several issues regarding the optimal dose, the optimal target and the optimal timing for starting radiation therapy.

In our study, the curative radiation dose was derived from a traditional treatment strategy of early stage low-grade lymphoma as 30–36 Gy, and we achieved excellent LC with 30.6 Gy in 17 fractions. However, in an effort to evaluate a lower dose to low–grade lymphomas, the UK has conducted a randomized study to compare the standard dose (40–45 Gy in 20–23 fractions) with a lower dose (24 Gy in 12 fractions). There was no difference in the overall response rate, progression-free survival, or overall survival between the standard and lower dose [21]. Although, this trial included relapsed or resistant disease, 69% of the patients were to receive radical radiation therapy as first-line therapy, and these results suggest that low-grade lymphomas may be treated with a smaller dose. Therefore, the optimal dose to treat duodenal FL may be less than the traditional dose of 30 Gy.

Regarding the target of radiation therapy, we have defined the duodenum as the involved site and irradiated the whole duodenum. However, there is no clear histological distinction between the duodenum and jejunum. In addition, the disease has a tendency to involve multiple sites in other parts of the gastrointestinal tracts. Takata *et al.* have reported that 85% of the duodenal FL had multiple involvements of the small intestine, predominantly the jejunum [5]. The gastrointestinal FL expresses α4β7 integrin, a mucosal homing receptor, which binds to ligand MAdCAM-1, which is selectively expressed on mucosal endothelium. The interaction of α4β7/MAdCAM-1 may explain the multifocal distribution of gastrointestinal FL in the intestinal lumen, but no further distribution beyond it.

The initial staging of whether the disease is single or multifocal is important for determining the treatment strategy. If the tumor is multifocal, chemotherapy or antibody therapy will be considered. However, our staging process may have underestimated the distribution of the disease, because only selected patients underwent endoscopic evaluation of the whole intestine. Instead, our patients received a PET/CT scan to evaluate disseminated diseases [22, 23]. Only 7 cases (37%) showed positive results in the primary site through PET/CT, in our study. Therefore, we speculate that the sensitivity of PET/CT for gastrointestinal FL is low. This may be explained by the indolent nature and small proportion of the disease. For these reasons, PET/CT may not be sufficient to evaluate the disease distribution in the gastrointestinal tract. Therefore, the endoscopic evaluation of the entire intestinal tract may be necessary for appropriate clinical staging.

Relapses occurred in the small intestine for two cases (terminal ileum and jejunum). The cause of the failures may be related to insufficient evaluation prior to treatment, or insufficient radiation volume. However, since we did not evaluate the whole intestine through endoscopy at initial clinical staging, the cause of the recurrence is uncertain. Considering the possibilities of multifocal disease distribution through the intestinal tract, the whole intestinal tract could be the target area for radiation. However, due to the fact that extended radiation volumes are related to an increase of toxicities, the limited target to the duodenum should be a favorable clinical target volume in practice.

The optimal timing for initiating the treatment is uncertain, especially in asymptomatic patients. Kiess and Yahalom suggested that observation is the most sensible management strategy for localized gastrointestinal FL with no symptoms [24]. Schmatz reported that 7 out of 24 patients (29%) achieved complete regression in the watch and wait therapy group, and two patients developed nodal dissemination. The watch and wait group had no difference in survival or time to progression when compared with the definitive treatment group [12]. These results support the watch and wait policy that has been adopted in asymptomatic patients. However, transformation of duodenal FL to a more aggressive lymphoma was reported by Miyata-Takata *et al.* in a single case report [25]. Histological transformation is well known in nodal FL [26, 27], but less observed in duodenal FL. Since duodenal FL is a rare disease, the frequency of histological transformation, risk factors and time to transformation are unknown. Taking into account the possibility of transformation to a high-grade lymphoma, a definitive treatment for duodenal FL may be necessary, even in asymptomatic patients. However, the optimal timing to deliver definitive treatment needs further study.

The duodenal FL is rare, and several important aspects of this lymphoma have still not been addressed. However, definitive radiation therapy provided excellent local control and presented as an effective treatment option. The limitation of this study are short follow-up periods, and long-term outcomes and toxicities are not evaluated. A long-term follow-up will be necessary to evaluate the efficacy of radiation therapy for duodenal FL.

CONCLUSION

In this study, duodenal FL was well controlled by 30.6 Gy of involved site radiation therapy. Several relapses were documented, and all of the relapses occurred outside the irradiated volume. Involved site radiation therapy could be an effective and safe treatment option for patients with localized low-grade FL arising from the duodenum.

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