



Overview

Lymphomas of the Upper GI Tract: The Role of Radiotherapy

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Abstract

The most common site of extra-nodal non-Hodgkin's lymphoma (NHL) is the gastrointestinal tract, of which the stomach is the most common site. With the exception of extra-nodal marginal zone lymphoma of gastric mucosa-associated lymphoid tissue (MALT), where excellent long term results can be achieved by radiotherapy, the published literature lacks high quality studies evaluating the role, optimal dose and technique of such treatment in the management of gastrointestinal lymphoma. Non-randomised studies support organ preservation and a role for local radiotherapy in gastric lymphoma.

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Key words: Lymphoma; MALT; radiotherapy; stomach

Statement of Search Strategies Used and Sources of Information

A search of published studies was carried out in September 2011 using Google Scholar, PubMed, PubMed Central and Scopus.

Introduction

The most common site of extra-nodal non-Hodgkin's lymphoma (NHL) is the gastrointestinal tract, and up to 5–10% of all gastrointestinal malignancy is thought to be due to lymphoma. Primary gastrointestinal NHL is a group of heterogeneous diseases (Table 1). Although most arise primarily in the gut, a significant minority of lymphomas involving the gut will appear as a result of secondary dissemination from other nodal or extra-nodal sites. Between 1992 and 1996, 371 primary gastrointestinal NHL patients were registered in the German Multicenter Study GIT NHL 01/92 [1]. In total, 74.8% of patients had gastric NHL. Within the intestine, the small

bowel and the ileo-caecal region were involved in 8.6 and 7.0% of the cases, respectively. Multiple sites of gastrointestinal tract involvement were observed in 6.5% of cases. About 90% of the gastrointestinal NHL were limited stage i.e. I/II. Although high-grade tumours accounted for most cases, there were distinct patterns in several sites such as the stomach, where 40% were of extra-nodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma). One third of large cell lymphomas had low-grade components.

The specific treatment of intestinal lymphomas, in particular with radiotherapy, with notable exceptions (i.e. gastric MALT lymphoma), is poorly described within the literature. The largest experience is reported by the German study group [2] who described 56 patients with primary intestinal lymphoma, excluding gastric lymphoma, in a prospective, non-randomised multicentre study. Initial surgical resection was recommended, then chemotherapy. Radiotherapy was advised for stages 111E and IVE (Table 2).

Investigation of primary gastrointestinal NHL has been further hampered by lack of consensus regarding staging systems. The most commonly used staging system for primary gastrointestinal NHL is the Lugano staging system (Table 2) [3]. The lymphomas most commonly seen in the intestine are listed in Table 1 [4].

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Table 1

Lymphomas of the gastrointestinal tract [4]

B cell lymphoma
MALT lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Burkitt lymphoma
Immunodeficiency-associated B-cell proliferations
T cell lymphoma
Enteropathy-type T-cell lymphoma
Other peripheral T-cell lymphomas
Hodgkin's lymphoma

MALT, mucosa-associated lymphoid tissue.

The challenge for the radiation oncologist is thus patient selection, with an inadequate, largely descriptive, literature base as a guide; difficulties with tumour localisation and thus choice of volumes and poor tolerance of the intra-abdominal viscera to radiation. The modest available literature fails to clearly define radiation fields and no study includes quality assurance. Historically there are concerns that delivering radiotherapy to intestinal lymphomas has a risk of major harm rather than benefit due in particular to gastrointestinal bleeding or perforation. In general, therefore, chemotherapy and surgery have remained the mainstays of treatment. Increasingly, however, clinical practice is for surgery to have a more limited role other than obtaining histological diagnosis,

Table 2

The Lugano system of Staging of primary gastrointestinal lymphoma

I Involvement of a gastrointestinal (GI) organ
I1 Lymphoma restricted to the mucosa and submucosa
I2 Lymphoma extending beyond the submucosa
II Involvement of a GI organ with involvement of infradiaphragmatic lymph nodes and/or extension of growth beyond the involved organ
II1 Involvement of a GI organ together with regional lymph nodes (II1) and/or another neighbouring organ (II1E) below the diaphragm (perigastric lymph nodes of less than 1 cm diameter on imaging studies are considered not to be involved)
II2 Involvement of a GI organ and lymph node involvement extending beyond the regional lymph nodes (below the diaphragm) (II2), possibly with further local involvement of an organ (II2E)
III Involvement of a GI organ and lymph node involvement above and below the diaphragm, possibly with further local involvement of an organ (III E), of the spleen (IIIS), or both (IIISE)
IV Diffuse or disseminated involvement (of non-GI organs) with or without lymph node involvement

The suffix "E" is applied only when there is direct infiltrative growth of the primary tumour into a neighbouring organ or tissue.

and radiation therapy is more widely used, particularly for gastric lymphoma.

Is Surgery Necessary for Primary Gastrointestinal Non-Hodgkin's Lymphoma?

Surgery may be required for diagnostic purposes, such as laparoscopic lymph node biopsy, and can be both diagnostic and therapeutic; for example, by removing a localised obstructing small bowel tumour. A prospective observational study of all histological subtypes of NHL of the gastrointestinal tract was initiated in Münster in 1992 (GIT NHL 01/1992) and included 185 patients with stage I or II gastric lymphoma; 106 of these patients underwent purely non-surgical treatment, i.e. radiotherapy and/or chemotherapy.

The subsequent, second prospective observational study of malignant NHL of the gastrointestinal tract (GITNHL02/1996) included 393 patients with localised primary gastric lymphoma who were treated with radiotherapy and/or chemotherapy only or additional surgery between December 1996 and December 2003. The survival rate at 42 months for patients treated with surgery was 86% compared with 91.0% for patients without surgery. In both these non-randomised studies there was no disadvantage for an organ-preserving treatment. Therefore, current non-randomised data suggest that primary gastric resection should be reserved for treatment failure [5].

Extra-nodal Marginal Zone Lymphoma of Mucosa-associated Lymphoid Tissue

The most frequent and best characterised primary lymphoma seen in the gut is the MALT lymphoma, most of which arise in the stomach, but can arise in any part of the gastrointestinal tract. Histologically, the infiltrate is usually composed of reactive B-cell follicles and an inter-/perifollicular diffuse infiltrate of neoplastic marginal zone cells.

Gastric MALTomas are the most common and well-studied MALTomas. These tumours are clearly associated with *Helicobacter pylori* infection [6], with the organism present in more than 90% of pathological specimens of MALTomas. These are relatively benign neoplasms and may remain localised and not progress for several years.

One diagnostic catch is the rare co-existence of a gastric adenocarcinoma at the time of diagnosis of low-grade lymphoma [7] and an increased incidence of gastric cancer in patients with lymphoma affecting the stomach [8], although the role of *H. pylori* infection resulting in the latter remains controversial. A recent consensus statement indicates that *H. pylori* infection is a necessary, but not sufficient, causal factor for non-cardia gastric adenocarcinoma [9].

In the GIT NHL 01/1992 observational study, seven of the patients with gastric lymphoma who were treated conservatively developed locally recurrent tumours. After

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