



INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

GASTRIC IRRADIATION FOR MALT LYMPHOMA A RETROSPECTIVE STUDY

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1. Introduction

MALT lymphoma is recognised in the WHO Classification as a form of B-cell non-Hodgkin's lymphoma, characterised by a heterogeneous mucosal infiltrate including lymphocytes and plasma cells. It has been associated with specific molecular events such as t(11;18) and alterations of Bcl-10, which may predict response to therapy. (Wotherspoon 2002) It typically occurs in extra-nodal sites such as stomach, lung, thyroid, salivary tissue and orbit and is often controlled locally by low dose radiotherapy. (Tsang 2001)

Low grade gastric MALT lymphoma accounts for 50% of primary gastric lymphomas. Often restricted to the stomach at presentation, it usually follows an indolent course, and is frequently associated with *Helicobacter pylori* infection. (Radaskiewicz 1992) Antimicrobial "triple" or "eradication" therapy (eg: amoxicillin, metronidazole and omeprazole) is able to eradicate the *Helicobacter* in the majority of patients, and been shown to produce remission of the associated lymphoma in 50-80% of cases, and is generally considered first line treatment for gastric MALT lymphoma. (Zucca 1996) Treatment options for patients who are *Helicobacter pylori* negative or who fail to respond to antibiotics include surgery, chemotherapy or radiotherapy. (de Jong 1999, Gospodarowicz 2000) Surgery often entails total gastrectomy as MALT lymphomas are usually multifocal. (Wotherspoon 1992) Surgery with or without radiotherapy or chemotherapy has been reported to produce a 93% 10-year relapse-free survival in a series of 16 patients with stage I disease. (Fung 1999) In one available report, single agent chemotherapy produced a 75% remission rate, but event free survival was only 50% at 5 years and 10% at 10 years. All relapses occurred in sites of prior involvement. (Hammel 1995) Endoscopic ultrasound may be of value in assessment and follow-up of gastric MALT lymphoma. (Pavlick 1997, Toyoda 2001)

A series from Memorial Sloan-Kettering Hospital has reported 100% complete response rate following irradiation for gastric MALT lymphoma in 17 consecutive patients after a median dose of 30 Gy. All patients were in ongoing remission at a median of 18 months follow-up (range 6-60 months). (Schechter 1998). A follow-up report on 51 cases indicated an 89% freedom from progression at 4 years. (Yahalom 2002). A series from Toronto also reports 100% freedom from progression in 9 cases of stage I-II gastric MALT lymphoma following radiotherapy. (Tsang 2001). Several radiotherapy series, with a surgical series for comparison, are summarised in Table 1.

Despite these reports, the literature on radiotherapy for gastric MALT remains limited. There is uncertainty about optimal radiotherapy dose and technique. (Wirth 1999) Furthermore the disease status prior to radiotherapy is not well documented in some older, retrospective studies, which diminishes their value as a guide for treatment. Optimal management of *H pylori* negative disease is not defined. (Rosin 2001) Many haematologists/oncologists are not aware of radiotherapy as an effective treatment for this condition, or have reluctance to use radiotherapy because of concerns regarding toxicity.

A survey of treatment preferences after failure of eradication therapy (De Jong 1999) reported that of 7 Dutch centres, 5 preferred RT, 1 surgery and 1 chemotherapy; of 7 other European centres, 5 preferred surgery and 2 chemotherapy; and of 5 non-European centres, 1 preferred chemo, 1 surgery and 1 RT. Haematology oriented groups - 8/10 elected conservative treatment; GE oriented groups - 5/7 surgery.

Table 1. Response rate and freedom from progression following treatment with irradiation or surgery in six gastric malt lymphoma series

Series	n	Stage	Prior HP+	Interval Eradication to RT	RT dose (Gy)	CR	FFP
Schechter 1998	17	12-I 4-II₁	5	3.5 Mo (1.5-24)	28.5-43.5	100%	100% 27 Mo median f/u
Yahalom 2002	51		21	?	30 median	100%	89% 48 Mo
Tsang 2001	9		?	?	20-30 (+/- chemo)	100%	100% 5 yr
Burgers 1988	24	All I	?	?	20 WAR 20 boost		83% 4yr
Fung 1999	16				Surgery		93% 10yr
Wirth (unpublished)	7		5		30	100%	100% 1-9 yr f/u

HP+ = H Pylori status positive, RT = radiotherapy, WAR = whole abdominal radiation

2. Study Design

This is a multi-centre retrospective review of patients treated with gastric radiation for gastric MALT lymphoma from 1980 through 2002.

3. Aims

3.1 Primary

To assess, in patients with gastric MALT lymphoma who are treated with gastric irradiation:

1. Local response rate after treatment
2. Duration of local control
3. Time to progression, progression free and overall survival
4. Patterns of failure (see below)

3.2 Secondary

1. Documented late toxicity
2. The range of techniques used for treatment
3. The impact of radiotherapy dose and volume on time to disease progression
4. The impact of tumour characteristics on time to disease progression

4. Methods

4.1 Patient selection

1. Histological diagnosis of low grade gastric MALT lymphoma or any low grade histology in the working formulation (it is presumed that these will represent MALT lymphoma in the current classification and, subject to approval and resources, an attempt will be made to review gastric histology)

Note: Patients with a “large cell” component will be included providing the diagnosis is reported as above. The presence of a large cell component will be recorded.

2. No history of lymphoma prior to the diagnosis of gastric lymphoma
3. Newly diagnosed disease, or recurrent disease after prior therapy other than radiotherapy
4. Treatment with gastric irradiation with curative intent
5. Stage I-II (Lugano modification of Ann Arbor system- appendix I) at all time points prior to radiotherapy
6. Patients form part of a consecutive series at each of the contributing centres, and commenced radiotherapy between 1/1/1980 and 31-12-2002.

5. Data recording

Data is to be extracted from medical records, and recorded in purpose designed case record forms. Data will include elements of past history, the history of gastric lymphoma, including treatment and progressions prior to radiotherapy, and progression, if any, following radiotherapy. Specific study procedures for recording and transmitting data are contained in section 9.

6. Pathology review

The primary analysis will be based on the historical pathology reports. Key features, including the presence of lympho-epithelial lesions, any large cell component and the Wotherspoon score (if recorded) will be noted. If feasible, a review of initial biopsies will be performed at either the treating centres or at a reference centre (to be decided). Central pathology review would improve the quality of the study and may facilitate correlative molecular studies. Specimens may also be suitable for biological studies, including t(11;18) translocation studies.(Jaffe 2001) (see also ethical issues in section 10).

7. End-points

7.1 Response

The main analysis of response will be based on the best histological response documented following radiotherapy. For cases in which only endoscopic results are available, analysis of response will be based on the best endoscopic response documented following radiotherapy.

Pathologic response criteria:

CR: normal mucosa

CRu: residual abnormality but no diagnostic features of MALT/NHL

PR: improved, but residual NHL apparent

SD: no appreciable change

PD: increasing extent or worsening grade

Endoscopic response criteria:

CR: normal mucosa

CRu: non-specific abnormality (including ulceration)

PR: appearance suggests residual lymphoma – improved appearance cf pre-treatment

SD: no change

PD: worse appearance

7.2 Treatment failure

7.2.1 Gastric failure:

Persistent or recurrent disease on gastric biopsy at least six months after eradication therapy, at least 3 months after the completion of conventional cytotoxic therapy (chemo and/or XRT), or any time after surgery. If reported according to Wotherspoon criteria, this would be a histology score of 4 or 5. In those patients who have achieved a CR (biopsy with a score of 0 or 1 recorded as CR or CRu) relapse would be defined as a later biopsy with a score of 4 or 5. A diagnosis of gastric failure in the absence of histological evidence (ie endoscopic or clinical only) will be categorised as possible failure.

The status of gastric disease prior to each treatment will be categorised as either: 1. Residual disease or 2. Progressive disease

7.2.2 Regional failure:

Persistent or recurrent disease involving peri-gastric, coeliac, paraaortic or mesenteric nodes or contiguous involvement of adjacent organs

7.2.3 Distant failure

Disease involving supra-diaphragmatic nodes or haematogenous spread to extra-nodal sites.

The diagnosis of extra-gastric failure will be based on standard clinical and radiological criteria (new or enlarging lymph node > 1.5 cm, splenic or hepatic nodules, or biopsy evidence of disease).

7.2.4 Late toxicity

Late toxicity will be scored as the presence/absence of evidence of organ dysfunction within the presumed area of irradiation.

7.2.5 Second malignancy

Second malignancies will be recorded and scored as in-field/marginal or out of field.

7.2.6 Time to failure event

Time to event will be measured from commencement of radiotherapy to date of first event. In cases of persistent disease, time to event will be measured from commencement to conclusion of radiotherapy.

A study close-out date will be determined at the time of analysis in order to prevent bias in the reporting of results. This will generally be taken to be the earliest of the dates of last contact of the patients who are still alive and being followed up. If patients have further treatment for presumed disease progression in the absence of these criteria, they will be censored from that point on for the end-point of disease control in all time to event analyses.

Events, censoring, and patients included in time to event analyses are defined as follows:

Time-to-event outcome	Events	For	Censored by
Duration of local control	Gastric failure	Patients with a complete response	Death, regional or distant failure
Time to progression at any site	Gastric, regional nodal, or distant failure, Persistent disease	All patients	Death without prior failure
Progression-free survival	Gastric, regional nodal, distant failure, Persistent disease, Death	All patients	Nil
Overall survival	Death	All patients	Nil
Time to late toxicity	Late toxicity	All patients	Death

8. Statistical considerations

8.1 Statistical analyses

All patients meeting inclusion requirements for the study will be accounted for in the analysis. In statistical analyses two sided p-values and 95% confidence intervals will be reported.

Descriptive summary data for patient and tumour characteristics, treatment techniques, gastric tumour response and patterns of failure will be reported in tabular form. Fisher's exact test will be used to evaluate statistical significance of differences in dichotomous variables, Pearson chi-square for non-ordered variables, and Cochran-Armitage test for trend for ordered categorical variables. Gastric tumour response rates will be calculated as the percentage of all patients with 95% confidence intervals calculated using the exact binomial distribution.

All time to event analyses will use the Kaplan Meier product limit method of survival analysis. The Mantel-Cox logrank test will be used to compare subgroups (eg. *H. pylori* status, surgery, chemotherapy). Cox proportional hazard regression will be used to investigate radiotherapy dose/volume and tumour characteristics association with duration of local control, time to progression at any site, progression free and overall survival adjusting for significant confounding. Cumulative incidence of the various types of failure will be estimated according to the method of Kalbfleisch and Prentice, based on the progression-free survival curves.

8.2 Sample size considerations

We estimate there will be approximately 150 patients in this series. An overall rate of complete local response to treatment of 95% would be estimated with a standard error of 2%. This corresponds to a 95% confidence interval of 90% – 98% if 142 of the patients in the series had a complete response to treatment.

Estimation of standard error for actuarial 5 year rates of local control and progression free survival assume that patients were accrued at a uniform rate over the time period of this study, follow up of patients is 1 year, and events follow an exponential distribution. We estimate that 140 patients will achieve a complete response and that a 5 year local control rate of 90% will have a standard error of 2.6% and 95% confidence intervals of 85% - 95%. In a sample of 150 patients, a 5 year progression free survival rate of 80% will be estimated with a standard error of 3.4% and will have 95% confidence intervals of 73% - 87%.

9. Study management

PHASE 1.

Collection of data for eligible patients at each participating institution. Data collected on each patient should be recorded on the approved case record forms (CRF). CRFs may be completed by the site investigator or data manager. The site investigator is responsible for ensuring that all blank data spaces on each form are completed.

PHASE 2.

A copy of the completed CRF should be retained by the site investigator for reference, and the original paper copy sent to the clinical trial coordinator (CRFs may be sent in batches rather than individually). A copy of the original pathology report, and pathology report prior to radiotherapy, is to be sent with the CRF, or details of the biopsies including the pathology department and laboratory numbers should be sent to allow future request of pathological material should pathology review be activated as part of the present study. Pathology reports will be identified only by an ID number and patient initials corresponding to the case record forms.

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PHASE 3.

Analysis of data at Peter MacCallum Cancer Centre

PHASE 4.

Presentation and publication of data

Recommendations for future studies

10. Ethical issues

Patient privacy and confidentiality will be respected. All information provided will be confined to the personnel involved in conducting the study. No identification of individual patients will be made in any presentation or publication. CRFs will be identified by patient initials and unit record numbers from participating institutions. Patients' identities will only be made known to the trial personnel if necessary to coordinate pathology review. Pathology review would only be undertaken after a future protocol amendment, detailing procedural and ethical issues, is submitted to the ethics committees of participating centres, and approval for pathology review has been given by these committees. Patient consent will be sought prior to pathology review according to the requirements of the ethics committee operating in the relevant institution.

11. Publication of results

Authorship on publications and presentations will comprise the study personnel who have made a significant contribution to the scientific content of the study and have reviewed and approved the manuscript according to the Uniform Requirements for manuscripts submitted to medical journals, International Committee of Medical Journal Editors, 2000. The principal investigator will be the first author on publications reporting the main aims of the study. Presentations and publications will not be made without the knowledge and consent of all authors.

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APPENDIX 1

STAGING

EI1. Mucosal / submucosal, no lymph nodes

EI2. Muscularis / serosa, no lymph nodes

EII1. Any depth of invasion (including adjacent organs) with regional nodes

EII2. As for EII1, but with non-regional infradiaphragmatic nodes

EIII. Supradiaphragmatic nodes / another localised GI organ, spleen

IV. diffuse or disseminated extra-gastric involvement

APPENDIX II

HISTOLOGICAL SCORING SYSTEM

Grade	Description
0	Normal
1	Chronic active gastritis(CAG)
2	CAG with florid follicle formation
3	Suspicious lymphoid infiltrate in LP, probably reactive
4	Suspicious lymphoid infiltrate in LP, probably lymphoma
5	Low grade B-cell lymphoma of MALT