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Long term outcomes of gastric mucosa-associated lymphoid tissue lymphoma treated with radiotherapy: A multi-center retrospective cohort study

Clinton D. Smith[1,2] | Sanjiv Gupta[3,4] | Yaw Sinn Chin[2,5] | Stephen R. Thompson[1,2]

[1]Department of Radiation Oncology, Prince of Wales Hospital, Sydney, Australia

[2]Prince of Wales Clinical School, Faculty of Medicine, University of New South Wales, Kensington, New South Wales, Australia

[3]Department of Radiation Oncology, Calvary Mater Newcastle, Waratah, Australia

[4]Faculty of Medicine and Public Health, University of Newcastle, Callaghan, Australia

[5]Department of Radiation Oncology, St George Hospital, Sydney, Australia

Correspondence
Clinton D. Smith, Department of Radiation Oncology, Bright Alliance Building, Prince of Wales Hospital, Barker St Randwick, New South Wales 2031, Australia.
Email: clinton.smith2@health.nsw.gov.au

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Abstract

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a rare disease. Radiotherapy remains an important definitive modality. We assessed the long term outcomes of patients with early stage gastric MALT marginal zone lymphoma (MZL) treated with definitive radiotherapy at three institutions in New South Wales, Australia. A retrospective, multi-center study of patients with gastric MALT MZ lymphoma treated with radiotherapy between 1st of March 1999 and 31st of May 2020 was conducted. Eligible patients were: age ≥18 years, treated with curative-intent radiotherapy, pathological diagnosis of MALT MZ lymphoma. There were 33 eligible patients. Complete response (CR) was reported in 30/31 (96.7%) of endoscopically assessed cases. During median follow up of 66.2 months (IQR 22–119 months), estimated 5 and 10 years local relapse free survival were 92.6% (95% CI: 83–100) and 92.6% (95% CI: 83–100); distant relapse free survival 95.8% (95% CI 88.2–100) and 64.7% (95% CI 43.4–96.4); freedom from treatment failure 92.6% (95% CI; 83.1–100) and 62.5% (95% CI; 41.7–93.7), respectively. There were six documented recurrences; one local, four distant, and both in one patient; two cases were high grade recurrences. 5 and 10 years OS were 92.4% and 73.5% respectively. There were no grade 3–5 late toxicities or treatment related deaths. Patients with gastric MALT MZL treated with definitive radiotherapy have excellent outcomes. In long term follow up a significant proportion developed distant low grade disease. Extended follow up should be considered in these patients. Treatment is well tolerated with minimal toxicity. Radiotherapy remains an important modality in the treatment of gastric MALT MZ lymphoma.

KEYWORDS
B-cell, lymphoma, marginal zone, radiotherapy, stomach neoplasms, treatment outcome

1 | INTRODUCTION

Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) are B-cell tumors that usually present at an early, localized stage, and with indolent behavior. The stomach is the most commonly affected site[1] giving rise to the disease entity: gastric MALT lymphoma.

There is overwhelming evidence that *H pylori* is a causative pathogen in the development of gastric MALT lymphoma.[2] In a systematic review, 90% of gastric MALT lymphoma cases had associated inter-current *H pylori* infection.[3] Eradication of *H pylori* has been shown to result in long term rates of control in at least 60% of patient with early stage disease.[4] Despite excellent outcomes with triple therapy, disease can and does recur in a proportion of patients. In this circumstance and in cases where the disease is not associated with *H pylori*, or does not respond to eradication therapy, radiotherapy has been used as an effective organ-preserving treatment[5] although prospective data are lacking. Retrospective studies have demonstrated excellent long term outcomes with minimal toxicity.[6–8]

In this study we present a retrospective analysis of long term outcomes of a multi-center cohort of patients with gastric MALT lymphoma treated with radiotherapy at three tertiary institutions in New South Wales, Australia and evaluate any clinico-pathological or treatment related factors associated with prognosis.

2 | METHODS

We conducted a multi-center retrospective cohort study at three New South Wales, Australian tertiary hospitals: Prince of Wales Hospital; St George Hospital; Calvary Mater Hospital. The study period was between 1st of March 1999 and 31 May 2020. The study was approved by the Hunter New England Human Research Ethics Committee as a low/negligible risk study.

2.1 | Patient selection

The electronic medical records of patients with a diagnosis of lymphoma and treated with radiotherapy were screened. Records were extracted if they had a biopsy proven diagnosis of gastric MALT MZ lymphoma which had been treated with radiotherapy. Inclusion criteria were: age greater than 18, localized disease (Lugano stage I/II) and were treated with curative intent, defined by a dose threshold ≥20 Gy. All patients had endoscopic evaluation prior to treatment, and staging with either computed tomography (CT) scan and/or F-18 Fluorodeoxyglucose positron emission tomography (FDG PET). Demographic and clinical information was extracted manually from the electronic patient records.

2.2 | Treatment and follow up

Details of any prior treatment were collected. *H pylori* status where known was recorded. Target volumes and prescribed dose were at the discretion of the treating radiation oncologist. Data was collected on radiotherapy details including modality used [parallel opposed anterior-posterior fields (AP/PA), 3-dimensional conformal radiotherapy (3D-CRT)], prescribed dose (Gy), and number of fractions. Response to treatment was determined by upper endoscopy. Complete response (CR) was achieved if there was no residual MALT lymphoma on post treatment biopsy.

Duration of follow up was until last entry in a patient's medical record or death, through to 13th of July 2021. Local recurrence was considered to have occurred if there was documented presence of disease in the stomach manifesting as either biopsy-proven gastric MALT lymphoma or diffuse large B-cell lymphoma (DLBCL) after a CR; or persisting disease after radiotherapy. Distant recurrence was considered to be biopsy-proven MALT MZL or DLBCL outside of the irradiated area, either localized or disseminated. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

2.3 | Statistical analysis

Demographic and clinicopathological characteristics were summarized with descriptive statistics. Where variables were unable to be extracted from the medical record, they are identified in Table 1 but not included in the proportions presented. Time-to-event intervals were measured from day 1 of radiotherapy until the date of the specific endpoint, last follow up, or death; whichever occurred first. Where endpoints were not met patients were censored at the date of last follow up, or death if it was a competing risk. Survival rates were calculated using the Kaplan-Meier method and curves were generated. Univariate analysis was performed by log-rank tests. Multivariate analysis was performed using Cox-proportional hazard model. Hypothesis testing was conducted at the 0.05 level of significance. All statistical calculation and output was performed using *R* Software (version 3.6.3).

3 | RESULTS

Thirty-six consecutive patients were identified, treated between 1st of March 1999 and the 30th of March 2020. Three patients were excluded: 1 patient had been treated with palliative intent; and 2 were diagnosed with stage IV disease at presentation. Thirty-three patients were included in the final analysis. A summary of clinical and demographic characteristics are provided in Table 1.

Thirty one patients (94%) had Lugano stage I disease and 2 patients (6%) had stage II disease. A large cell component, not meeting a diagnosis of diffuse large B-cell lymphoma, was reported in the specimens of 5 patients (16%). All patients were staged with either CT and/or PET: CT only in 8 patients (24%), PET only in 6 patients (18%) or both CT and PET in 19 patients (58%). Only 1 patient (3%) had an endoscopic ultrasound as part of their staging. Assessment of bone marrow was performed in 5 patients (16%). Three patients had other investigations (gallium scans) as part of their work up. MALT-IPI[9]

TABLE 1 Patient characteristics ($N = 33$)

	No. of patients (%)
Gender	
Male	17 (52)
Female	16 (48)
Median age (range)	64 (37–82)
ECOG	
0	20 (61)
1	12 (36)
2	1 (3)
Lugano stage	
I	31 (94)
II	2 (6)
Multifocality	4 (13), Missing = 1
MALT-IPI	Missing = 1
0	21 (66)
1	10 (31)
2	1 (3)
H pylori at diagnosis	
Positive	6 (18)
Negative	27 (82)
Any previous treatment	21 (64)
H pylori eradication	19 (58)
Chemotherapy	3 (9)
Surgery	1 (3)
Radiotherapy dose (Gy)	
Median (range)	30 (20–42)
< 30	8 (24)
≥ 30	25 (76)
Median no. Fractions (range)	15 (10–28)
Radiotherapy technique	
AP/PA	2 (6)
3DCRT	31 (94)

Abbreviations: 3DCRT, 3-Dimensional Conformal Radiotherapy; AP/PA, Anterior posterior, posterior, anterior; ECOG, Eastern Co-operative Oncology Group score; Gy, Gray; IPI, International Prognostic Index.

scores were low risk (score = 0) in 21 patients (66%), intermediate risk (score = 1) in 10 patients (31%) and high risk (score ≥2) in 1 patient (3%).

Twenty-one patients (64%) had received any treatment prior to radiotherapy; 17 with *H. Pylori* eradication (HPE), 2 with HPE + chemotherapy, 1 with chemotherapy, and 1 with surgery. All patients had *H. Pylori* testing prior to treatment with any modality. Of the entire cohort, 19 patients (58%) had HPE prior to RT. Of these patients, six (32%) were *H Pylori* positive prior to HPE, and thirteen (68%) were *H pylori* negative prior to HPE. Of the patients who had HPE; 3 (17%) had a partial response, 11 (61%) had stable disease and 4 (22%) had progressive disease. One patient who had HPE was not assessed for response prior to RT. Three patients (9%) received systemic agents prior to RT; one had a CR, one had stable disease, one patient was not assessed for response prior to RT. Two patients had both HPE and chemotherapy; in both cases HPE preceded chemotherapy. In one case there was stable disease after HPE and stable disease after systemic therapy. In the other there was progressive disease after HPE, and CR after chemotherapy. One patient (3%) had surgery—a wedge resection for bleeding - prior to RT.

The median time from previous treatment to radiotherapy was 5.6 months (range 1—28 months). Median prescribed RT dose was 30 Gy (range 20—42) in 15 fractions (range 10–28). Two patients received 20 Gy, five received 24 Gy, one received 27 Gy, 24 received 30 Gy and one received 42 Gy. Treatment was delivered with a 3D conformal technique in 31 patients (94%) and AP/PA technique in 2 patients (6%).

Thirty two patients had response to radiotherapy documented. Upper endoscopy was used to assess initial response in 30 patients (94%), and in 2 patients (6%) CT was used instead. Complete response was reported in 31 patients (97%). One patient had persistent disease. One patient had no response documented, having developed metastatic rectal cancer shortly after RT and had no follow up endoscopy.

3.1 | Survival/event analysis

At a median follow up of 66.2 months, there were six documented recurrences; 1 patient with local recurrence only, 3 with distant recurrence, and 2 with both. There were two high grade recurrences. The clinical details of all recurrences are presented in Table 2. All 3 distant-only recurrences were MZ lymphoma. The sites of these recurrences were: isolated left parotid (1), bilateral lung (1), and isolated sigmoid colon (1). Only one patient had a local recurrence of MZ MALT lymphoma. The other two local recurrences were patients in whom high grade transformation occurred. Both of these patients died of lymphoma.

The 5 and 10 years OS was 93% and 74% respectively. There were two deaths from lymphoma. The 5 and 10 years disease specific survival (DSS) was 96% and 87%, respectively (Figure 1A)—both deaths from NHL were in the two patients in whom high grade transformation had occurred. There were 3 local recurrences at a median of 24 months (range 11—71). The estimated 5 and 10 years local relapse free survival (LRFS) was 93% and 86% respectively. There were 5 distant recurrences at a median of 87 months (range 24—111). Of the 3 distant-only recurrences, the median time to failure was 89 months (range 87—111). The estimated 5 and 10 years distant relapse free survival (DRFS) was 96% and 65% respectively. The median time to any recurrence was 79 months (range 11—111 months). The 5 and 10 years freedom from treatment failure (FFTF) was 93% (95% CI; 83–100) and 63% (95% CI; 42–94),

TABLE 2 Patients with relapse

Patient	Sex	Age at radiotherapy	*H. Pylori* positive[a]	Previous treatment	Relapse location	Site of recurrence	High grade recurrence	Time to recurrence in months	Further treatment	Status last follow up (if dead, due to NHL/treatment?)
1	F	73	No	No	Local only	Stomach	Yes	11.1	Observation	Dead (NHL)
2	M	64	No	No	Local + distant	Disseminated	No	23.7	Chemotherapy (RCHOP)	Alive—NED
3	M	64	No	No	Local + distant	Disseminated	Yes	71.4	Chemotherapy (RCHOP)	Dead (NHL)
4	M	73	No	No	Distant only	Sigmoid colon	No	87.2	Observation	Alive—with disease
5	F	54	No	Yes; HPE	Distant only	Bilateral lung	No	88.6	Chemotherapy (RCVP)	Alive—NED
6	F	64	Yes	Yes; HPE + chemo	Distant only	Left parotid	No	111.2	Radiotherapy	Dead (NED, not treatment related)

Abbreviations: HPE, H Pylori eradication; NED, no evidence of disease; NHL, non-Hodgkin Lymphoma; RCHOP, Rituximab Cyclophosphamide Hydrocydaunorubicin (doxorubicin), Oncovin (Vincristine), Prednisone; RCVP, Rituximab, Cyclophosphamide, Vincristine, and Prednisone.
[a]Before *H Pylori* Eradication.

respectively (Figure 1B). No patients with an initial large cell component recurred. High grade recurrences occurred in 2 patients; one at 11 months and one at 71 months. Low grade recurrences occurred at a median of 88 months in 4 patients (range 24–111 months).

On univariable analysis, any previous treatment was associated with improved 5 years FFTF (100% vs. 80%, $p = 0.05$) and previous HPE had borderline significance (100% vs. 83%, $p = 0.06$)—Table 3. These variables were also significant for improved 5 years LRFS (any previous treatment, 100% vs. 83%, $p = 0.02$; and previous HPE, 100% vs. 80%, $p = 0.03$), and 5 years DSS (any previous treatment, 100% vs. 89%, $p = 0.04$; and previous HPE, 100% vs. 90%, $p = 0.05$)—see Supplementary, Table 4. No variables were statistically significant on multivariate analysis.

3.2 | Toxicity

There were 2 acute grade 3 toxicities (1 anorexia, 1 fatigue) and no severe late toxicities or treatment related deaths. There were no long term grade 2 or higher gastrointestinal complaints documented, nor any clinically significant renal function decline. There were no gastric perforations. One patient developed a second malignancy in follow up; a left upper lobe lung carcinoma which was out of field.

4 | DISCUSSION

This is the largest Australian study reporting outcomes in patients diagnosed with gastric MALT MZL treated with curative intent. In this multi-center retrospective study, patients with gastric MALT lymphoma treated with radiotherapy had excellent 5 years outcomes, with 5-year FFTF, LRFS, DRFS and OS >90%. Disease specific survival was also excellent at 5 years (96%) and 10 years (87%). Our outcomes are consistent with other published series.[5–8,10] This study confirms that these excellent outcomes also apply to an Australian population.

Of note, other series have reported 10-year FFTF in the magnitude of >85%.[10] This is in contrast to the 10-year FFTF reported herein (63%). In this study we applied a broad definition of recurrence; that being that any subsequent diagnosis of MALT MZL including any new diagnosis of MALT MZL at a distant site. We chose this definition based on previously reported data of long term failures of extranodal MZL.[11,12]

In the few patients in our series who had distant recurrence only, the failures were low grade MALT MZL only. These may have been new MALT MZL diagnoses or distant recurrence of gastric MALT MZL. A number of studies have reported late distant failures for MALT lymphomas.[7,11,12] Median time to distant failure in these series range from 47 to 62 months which is shorter than the median time to distant failure we report of 89 months. Our results reinforce that in those patients with a previous diagnosis of gastric MALT MZL, there is an increased risk of developing further distant MALT MZL in the longer term. Extended follow up seems to be required. The optimal follow up is undefined. In this series there was only one local failure which occurred after 5 years. Annual endoscopy until 5 years may be sufficient.

Although all patients in the cohort were tested for *H pylori*, only six patients were found to be positive for the causative pathogen. Despite this, more than half ($N = 19$) of patients were treated for HPE in the first instance, that is, 13 patients with *H pylori* negative disease had a trial of HPE. None of the patients who received HPE

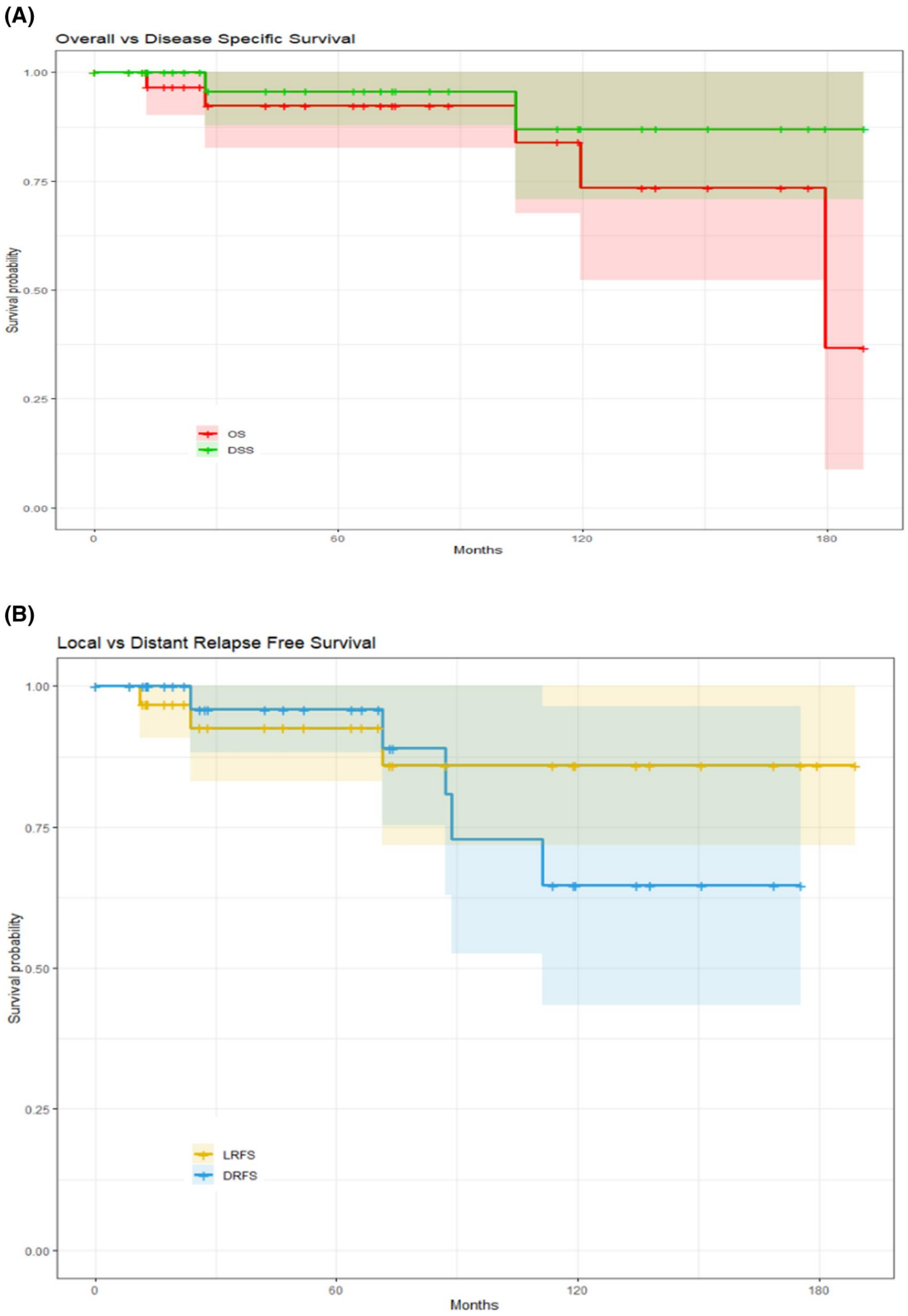

FIGURE 1 Survival curves showing (A) overall survival (OS) versus disease specific survival (DSS); and (B) Local relapse free survival (LRFS) versus distant relapse free survival (DRFS)

had a CR. Of the three patients who had a PR to HPE in our series, two patients were *H pylori* negative. Gastric MALT response rate for eradication in *H pylori* negative disease has been reported to be as high as 29%.[13] Guidelines vary on whether or not HPE can be given first-line in the *H pylori* negative setting. European Society for Medical Oncology guidelines acknowledges it as an option,[14] however it is

TABLE 3 Univariable analysis of prognostic factors for 5 years Freedom From Treatment Failure (FFTF)

Variable	Categories	# Of patients	5 years estimated FFTF (%)	*p* (log-rank test)
Age	≤64	19	93	0.7
	>64	14	92	
Lugano stage	I	31	92	0.4
	II	2	100	
Malt-IPI	0	21	94	0.5
	≥1	11	91	
H pylori positive	Yes	6	100	0.7
	No	27	91	
HPE	Yes	19	100	0.06
	No	14	83	
Any previous treatment	Yes	21	100	0.05 *
	No	12	80	
Total dose	<30	8	100	0.7
	≥30	25	91	

Abbreviations: HPE, H. Pylori eradication; IPI, international prognostic index.

not recommended in the treatment algorithm of National Comprehensive Cancer Network guidelines.[15] In our series, having had HPE treatment previously did not portend a worse prognosis and in fact was associated with better local control on univariate analysis. Thus, up-front HPE even for *H pylori* negative cases may be reasonable, with the possibility of thereby avoiding RT.

Severe adverse events are uncommon, if not rare, when radiotherapy is utilized for gastric MALT MZL.[6,10,12] In this study we demonstrate very few severe acute side effects and no severe late toxicities. Gastric perforation has historically been a significant clinical concern after radiotherapy for gastric MALT MZL. However, in our series this was not reported and similarly in recently reported series we could not find a single report of this severe toxicity.[5–8,10,12] Another understandable concern from patients is often the risk of second malignancy with radiotherapy, however there were no in-field occurrences of this in our series.

More conformal radiotherapy has been adopted over time to improve the therapeutic ratio by sparing normal tissue with the aim of minimizing toxicity. For gastric MALT MZL this was explored in a multicentre study by the International Extranodal Lymphoma Study Group[10] where 40% of patients received entire abdomen radiotherapy with a boost to the stomach. Actuarial incidence of second malignancy was 14% at 10 years. The authors concluded that the rate would likely have been reduced with more limited fields. Ultimately the authors advocated for radiotherapy to the stomach and the perigastric nodes only. Newer radiotherapy techniques including VMAT and IMRT have the advantage of better normal tissue sparing,[16] however caution needs to be exercised to ensure that this is not at the expense of a geographic miss.

Our study was limited by its small sample size and retrospective nature. As a result, analysis of predictive factors for outcomes was difficult. Notably in our series, over 20 years at three institutions there were only 33 patients that fit the criteria for inclusion. Other series in different countries have included higher patient numbers over similar time frame. This may be accounted for by geographic variation in incidence of this disease. In one study[1] the Australian age-standardized incidence rates of MZL were reported as 5 per 1,000,000 compared with—for example, - the US; 18 per 1,000,000, and the UK; 26 per 1,000,000. Although direct comparison should be evaluated with caution (due to differences in reporting, case definition and registration, etc) this may provide insight into the relatively lower numbers in our series when compared to other recently published data.[6–8] However, despite this geographic variability, there appears at least to be concordance with respect to radiotherapy outcomes.

Given the period over which we collected patient data there were advances made in how treatment was delivered. The small sample size however precluded any meaningful analysis as to the impact of these treatment advances to patient outcomes. Nevertheless, our reported outcomes are consistent with the literature and this gives confidence in radiotherapy practice in Australia for the treatment of gastric MALT MZ lymphoma.

5 | CONCLUSION

Patients with gastric MALT MZ lymphoma treated with definitive radiotherapy have excellent outcomes in terms of both local control, and survival, with minimal treatment related toxicity. Given a significant proportion of patients in long term follow up developed distant low grade disease, extended follow up should be considered. Radiotherapy remains the treatment of choice if *H pylori* eradication does not achieve a CR, and in H pylori-negative disease.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Clinton D. Smith https://orcid.org/0000-0003-2346-8899

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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