Favorable radiation field decrease in gastric marginal zone lymphoma

Experience of the German Study Group on Gastrointestinal Lymphoma (DSGL)

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Abstract

Purpose Long-term impact of stage-adapted field reduction in a large cohort of gastric marginal zone lymphoma (gMZL) patients treated conservatively with curative radiation therapy (RT).

Patients and methods Prospective analysis of paper records of 290 patients with stage IE–IIE gMZL, treated in 78 radiotherapeutic institutions in Germany from 1992–2013. Stage-adapted radiation fields decreased from extended field (EF) to involved field (IF) over the course of three consecutive prospective trials of the German Study Group on Gastrointestinal Lymphoma (DSGL). Treatment results were compared between the three cohorts.

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Results Overall collective with median age of 60 years, slight male predominance (m:f = 1.1:1) and ratio of disease stage I:stage II = 2.1:1. Median follow-up 6.4 years in total: 13.0 years in the first gastrointestinal study (GIT 1992), 8.2 years in the second (GIT 1996) and 4.7 years in the third study (DSGL 01/2003). Stage-adapted radiation field decrease together with further technological development led to reduced relative frequencies of acute/chronic adverse effects and until now was accompanied by lower disease recurrence. The third study design with smallest field size (IF in stage I, locoregional EF in stage II) achieved the best survival outcome at the 5-year follow-up (overall survival 92.7%, event-free survival 89.5% and lymphoma-specific survival 100.0%). Disease relapse observed in 10 patients. Cumulative incidence of disease-specific death was 1.7% of the followed patients. Primary disease stage associated with lymphoma-specific survival.

Conclusion Stage-adapted reduction towards IF in gMZL resulted in favorable adverse effects, local control and survival rates. These results support further decreases in modern RT of gMZL.

Keywords Indolent gastric lymphoma · Non-Hodgkin lymphoma · Extended field · Involved field · Radiation therapy

Erfolgreiche Strahlenfeldverkleinerung bei gastralem Marginalzonenlymphom

Erfahrungen der Deutschen Studiengruppe Gastrointestinale Lymphome (DSGL)

Zusammenfassung

Zielsetzung Langzeiteffekt der stadienadaptierten Strahlenfeldverkleinerung bei kurativer Radiotherapie (RT) in einer großen Kohorte von Patienten mit gastralem Marginalzonenlymphom (gMZL).

Patienten und Methoden Prospektive Analyse der Papierakten von 290 Patienten mit gMZL im Stadium IE–IIE, behandelt in 78 radiotherapeutischen Institutionen in Deutschland von 1992–2013. Stadienadaptierte Strahlenfeldreduktion vom „extended field“ (EF) zum „involved field“ (IF) im Verlauf der drei konsekutiven prospektiven Studien der Deutschen Studiengruppe Gastrointestinale Lymphome (DSGL). Behandlungsergebnisse wurden zwischen den drei Studienkohorten verglichen.

Ergebnisse Gesamtkollektiv mit medianem Alter von 60 Jahren; Geschlechterverhältnis m:w = 1,1:1 und Stadienverhältnis I:II = 2,1:1. Medianes Follow-up insgesamt 6,4 Jahre: 13,0 Jahre in der ersten gastrointestinalen Studie (GIT 1992), 8,2 Jahre in der zweiten (GIT 1996) und 4,7 Jahre in der dritten Studie (DSGL 01/2003). Die stadienadaptierte Strahlenfeldverkleinerung zusammen mit der technischen Weiterentwicklung führte zu reduzierten relativen Häufigkeiten der akuten/chronischen Nebenwirkungen und ist bislang begleitet von einer niedrigeren Rezidivrate. Das Konzept der dritten Studie mit der kleinsten Feldausdehnung (IF im Stadium I, lokoregionales EF im Stadium II) erreichte die besten Überlebensraten nach einem Follow-up von 5 Jahren (Gesamtüberleben 92,7%, ereignisfreies Überleben 89,5% und lymphomspezifisches Überleben 100,0%). Lymphomrezidive wurden bei 10 Patienten beobachtet. Die kumulative Inzidenz der krankheitsspezifischen Todesrate bei den nachbeobachteten Patienten betrug 1,7%. Das primäre Krankheitsstadium war assoziiert mit dem lymphomspezifischen Überleben.

Schlussfolgerung Die stadienadaptierte Feldverkleinerung zum IF bei gMZL resultiert in günstigen Nebenwirkungen, lokaler Kontrolle und Überlebensraten. Diese Ergebnisse bekräftigen die weitere Deeskalation der modernen RT von gMZL.

Schlüsselwörter Indolentes Magenlymphom · Non-Hodgkin-Lymphom · Extended field · Involved field · Radiotherapie

Introduction

The development of modern radiation techniques over the past 25 years has considerably changed the use of radiation therapy (RT) to treat gastric marginal zone lymphoma (gMZL) [1–8]. Radiotherapy is now a central, well-tolerated treatment option with curative potential in gMZL [9, 10]. In this multi-institution study the details of predominantly single-modality RT used to treat gMZL between 1992 and 2013 were evaluated in the context of three consecutive prospective gastrointestinal (GIT) study designs: GIT 1992 [11, 12], GIT 1996 [13] and DSGL 01/2003 of the German Study Group on Gastrointestinal Lymphoma (DSGL). Merely stage IIE patients in the first study received RT after prior chemotherapy with six cycles of COP (cyclophosphamide, vincristine and prednisolone) [11]. The reduction of RT volume and its therapeutic tolerability is demonstrated. Additionally, its effects on treatment outcome in terms of tumor control, survival results and relapse patterns during long-term follow-up were investigated.

Patients and methods

Patients

The medical paper records of 290 patients with biopsy-proven stage IE or IIE indolent gMZL, who were treated conservatively at 78 radiotherapeutic institutions in Germany between 1992 and 2013, were analyzed prospectively with the follow-up data closure date of April 9, 2018. All patients received curative RT, primarily as the initial oncologic treatment strategy, but the design of the first study required that stage IIE patients be pretreated with six cycles of COP chemotherapy [11]. The primary pathological diagnosis of gMZL was confirmed by a central histopathological review. Institutional review board approval was obtained for the three studies. Protocols were approved by the ethical board of the physicians' chamber of Westfalia-Lippe and the Westfalian Wilhelms-University of Münster, and by local ethics committees of the other participating centers. Each patient gave written informed consent for the study.

Data compiled included clinical characteristics, ECOG (Eastern Cooperative Oncology Group) performance status, lymphoma stage, treatment, acute and chronic adverse effects, follow-up examinations, disease relapse and location, and salvage treatments. Follow-up assessment was completed through additional reviews of all patient charts.

Treatment strategy

Patients underwent endoscopy and computed tomography staging before treatment. After pathologic confirmation of early stage extranodal gMZL, patients were referred to the radiation oncologist for RT with curative intent if the disease was *Helicobacter pylori* (*H. pylori*) independent. Where testing was positive for *H. pylori* in stage IE gMZL (or stage II1 gMZL in patients aged more than 65 years), RT was the treatment if antibiotic therapy failed, defined as progressive disease or no change. The interval from *H. pylori* eradication to RT was at least 12 months in case of no change after eradication therapy. Protocol RT was stratified according to disease stage [11, 13], as extended field (EF), reduced extended field (red. EF), or involved field (IF) with continuously decreasing field size throughout the three cohorts. The dose was 40 Gy in the area of the tumor, 30 Gy in terms of prophylactic extended region. Patients were generally treated with anterior–posterior opposing fields or three-dimensional (3D) conformal RT, whereas in the final study the application of intensity-modulated RT (IMRT) has just been started (Table 1).

Follow-up

Esophagogastroduodenoscopy was used for routine evaluation of potential radiogenic toxicity and initial response 8 weeks after treatment completion [10]. It was repeated along with topographic mapping biopsy, abdominal ultrasound, physical examination, serum and hematology laboratory controls and renal function every 3 months for the first 2–3 years, semi-annually for up to 5 years, and annually thereafter. At each point, disease response was classified as either a complete response, complete response uncertain, partial response, no change, or progressive disease, according to GELA (Groupe d' Etude des Lymphomes de l' Adulte) criteria. Relapse was stated when a new manifestation of lymphoma appeared at least 1 month after the first follow-up where a complete response was proven. Failure in the stomach or in the regional lymph nodes was considered a locoregional failure or relapse, and relapse at any other site was considered a distant failure. An early relapse occurred less than one year/a late relapse at least one year after treatment, respectively [14]. Transformation to aggressive lymphoma was considered to be recurrent disease.

Table 1 Study design and radiation technique in indolent gastric marginal zone lymphoma (gMZL)

	GIT 1992		GIT 1996		DSGL 01/2003		
Stage	IE	IIE	IE	IIE	IE	II1E	II2E
Chemotherapy	–	6xCOP	–	–	–	–	–
Radiation therapy	EF 30 Gy + Boost ad 40 Gy	EF-mediast 30 Gy + Boost ad 40 Gy	Red. EF 30 Gy + Boost ad 40 Gy	EF 30 Gy + Boost ad 40 Gy	IF 40 Gy	Red. EF 30 Gy + Boost ad 40 Gy	EF 30 Gy + Boost ad 40 Gy
AP/PA opposing fields	*n* = 56 (98.2%)		*n* = 29 (22.3%)		*n* = 1 (1.0%)		
3D-CRT	*n* = 1 (1.8%)		*n* = 101 (77.7%)		*n* = 101 (98.0%)		
IMRT	–		–		*n* = 1 (1.0%)		

COP cyclophosphamide, vincristine, prednisone, *EF* extended field (whole abdomen with pelvis), EF-mediast (whole abdomen + mediastinum), *Red. EF* reduced EF (abdomen without pelvis), *IF* involved field (stomach + perigastric nodes + adjacent paraaortic nodes + proximal duodenum), *AP/PA* anterior–posterior/posterior–anterior, *3D-CRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy

Statistical analysis

Baseline patient characteristics and RT treatment were described using medians and ranges. Categorical data were described using absolute and relative frequencies in contingency tables. Acute and chronic adverse effects were evaluated using contingency tables, and χ^2 was used to compare the severity of adverse effects between the three studies. Study endpoints were event-free survival (EFS), overall survival (OS) and lymphoma-specific survival (LSS). EFS was defined as the time from the first day of curative radiation treatment until the date of progression, relapse at any site, death or final follow-up/OS until death or final follow-up/LSS until death caused by the primary disease or its oncologic treatment, respectively. Survival curves were estimated using Kaplan–Meier methods. Influence of treatments and disease factors were assessed using the log-rank test to compare survival curves. The number and types of relapses after primary treatment were also examined. Statistical analyses were performed using IBM® SPSS® Statistics (Version 25.0) (IBM, Armonk, NY, USA). All calculated p values were two-sided descriptive measures. Factors with $p \leq 0.05$ were considered statistically significant.

Results

Median age at diagnosis across all three patient cohorts was 60 years (range 24–84 years) and 68% (197/290) of patients had stage IE disease. The basic characteristics of the all three cohorts together are shown in Table 2. Eastern Cooperative Oncology Group performance status was 0–1 in 94.5% of patients. For staging examinations, each patient underwent a computed tomography scan, esophagogastroduodenoscopy and colonoscopy.

The applied radiation techniques express historical technological developments from opposing fields (used in 98.2% of those participating in the first study) to three-dimensional conformal RT (used in 77.7% of those in the second study and 98.0% of those in the third (DSGL 01/2003) study; Table 1). One patient in the third study was already treated with intensity-modulated RT. The dose of normofractionated radiation delivered to each tumor was 40 Gy ± 10% except for one patient in the first study who received an underdosage of 15%. The adjuvant radiation dose in extended field was 30 Gy ± 10%. In the first study the 14 patients with stage II disease (4.8% of the entire cohort) were treated with RT after previous chemotherapy with six cycles of COP chemotherapy. Radiation field sizes in the three study designs are shown in Table 1. After RT, a complete response was detected in 288 (99.3%) patients. Two patients died before radiation therapy was completed: 1 due to a cardiac event and 1 due to progression and change towards aggressive lymphoma (first study; Table 2).

Within the total collective of 290 patients, long-term follow-up data from 179 patients could be obtained. In the remaining 111 patients follow-up data after radiation treatment could not be ascertained, even after intensive research by personally contacting hospital departments, further attending physicians, family doctors and population registration offices. In the three studies about the same proportion of patients was lost to follow-up (35, 41 and 36%, respectively) due to changes of residence, closure of medical practices (Table 3). There were no further deaths according to the relevant information provided by registration authorities. The patients with randomly occurring lost to follow-up at the end of treatment were not included in the survival analysis, whereas the other 179 patients are shown in the Kaplan–Meier graphs of OS, EFS and LSS with censoring at the latest timepoint with information available, as required by biostatistical recommendation. Of the follow-up patients 34/179 died, cause of death was not related to gMZL in 31/34 patients (Fig. 1). The 3 patients who died from gMZL-related causes were participants of the first study and had primary stage II gMZL. Of these, 2 died from distant recurrence (1 indolent, 1 aggressive relapse), and the other developed early progressive disease (under primary RT) that transformed to aggressive lymphoma. Death occurred during salvage chemotherapy. No deaths were associated with RT. Follow-up results and survival analysis for these 179 patients, including an estimate of the confidence interval, is shown in Table 3. Over the course of the three studies, 5- and 10-year OS rates and 5- and 10-year EFS rates increased. Follow-up ended in the third study after 10 years, but of the remaining two, the first showed a tendency to greater 15-year OS and 15-year EFS rates. The three studies did not differ in OS ($p = 0.463$; Fig. 2a) or EFS ($p = 0.387$; Fig. 2b) rates.

Because of the 3 gMZL-related deaths in the first study, LSS was reduced to 93.9% (95% CI 85.6–100.0%) for the 5-, 10-, and 15-year rates. In contrast, these rates remained at 100% during follow-up for the second and third studies. The three studies yielded significantly different LSS rates ($p = 0.026$; Fig. 2c). Individually, a statistical abnormality was detected between the first and second studies ($p = 0.044$), but not between the second and third studies ($p = 0.072$). In the first study, LSS differentiation by stage showed that the 5-, 10-, and 15-year LSS rates for stage II were 80.8% (95% CI 56.89–100.0%), whereas for stage I, it remained at 100% throughout follow-up. In this evaluation, LSS rates were significantly different ($p = 0.008$) between stages I and II (Fig. 2d).

Of all followed patients, 10 experienced relapse, of which 6 patients relapsed within the radiation field (in the stomach) initially, and 4 patients relapsed outside, respec-

Table 2 Patient characteristics and acute toxicity (CTC) among indolent gastric marginal zone lymphoma (gMZL) in all studies ($n = 290$)

		GIT 1992	GIT 1996	DSGL 01/2003	Total
Patients with indolent gMZL		$n = 57$	$n = 130$	$n = 103$	$n = 290$
Age, median (range) in years		60 (24–76)	61 (29–84)	59 (26–80)	60 (24–84)
Sex					
Female		$n = 28$ (49.1%)	$n = 63$ (48.5%)	$n = 50$ (48.5%)	$n = 141$ (48.6%)
Male		$n = 29$ (50.9%)	$n = 67$ (51.5%)	$n = 53$ (51.5%)	$n = 149$ (51.4%)
Ann-Arbor Stage					
I		$n = 43$ (75.5%)	$n = 87$ (67.0%)	$n = 67$ (65.0%)	$n = 197$ (68.0%)
II					
II1		$n = 8$ (14.0%)	$n = 28$ (21.5%)	$n = 25$ (24.3%)	$n = 61$ (21.0%)
II2		$n = 6$ (10.5%)	$n = 15$ (11.5%)	$n = 11$ (10.7%)	$n = 32$ (11.0%)
Complete remission		$n = 55$ (96.5%)[a]	$n = 130$ (100%)	$n = 103$ (100%)	$n = 288$ (99.3%)[a]
ECOG score					
0		$n = 25$ (43.9%)	$n = 77$ (59.2%)	$n = 68$ (66.0%)	$n = 170$ (58.6%)
1		$n = 30$ (52.5%)	$n = 43$ (33.1%)	$n = 31$ (30.1%)	$n = 104$ (35.9%)
2		$n = 2$ (3.6%)	$n = 10$ (7.7%)	$n = 4$ (3.9%)	$n = 16$ (5.5%)
Acute toxicity (CTC)[b]					
Drop in hemoglobin	0	$n = 42$ (73.7%)	$n = 112$ (86.2%)	$n = 91$ (88.3%)	$n = 245$ (84.5%)
	1–2	$n = 10$ (17.5%)	$n = 18$ (13.8%)	$n = 11$ (10.7%)	$n = 39$ (13.4%)
	3–4	$n = 2$ (3.5%)	$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 2$ (0.7%)
Leukocytopenia	0	$n = 15$ (26.3%)	$n = 56$ (43.1%)	$n = 74$ (71.8%)	$n = 145$ (50.0%)
	1–2	$n = 33$ (57.9%)	$n = 68$ (52.3%)	$n = 24$ (23.3%)	$n = 125$ (43.1%)
	3–4	$n = 6$ (10.5%)	$n = 6$ (4.6%)	$n = 4$ (3.9%)	$n = 16$ (5.5%)
Thrombocytopenia	0	$n = 34$ (59.6%)	$n = 95$ (73.1%)	$n = 89$ (86.4%)	$n = 218$ (75.2%)
	1–2	$n = 19$ (33.3%)	$n = 30$ (23.1%)	$n = 13$ (12.6%)	$n = 62$ (21.4%)
	3–4	$n = 1$ (1.8%)	$n = 5$ (3.8%)	$n = 0$ (0.0%)	$n = 6$ (2.0%)
Elevated bilirubin	0	$n = 52$ (91.2%)	$n = 123$ (94.6%)	$n = 99$ (96.1%)	$n = 274$ (94.5%)
	1–2	$n = 2$ (3.5%)	$n = 7$ (5.4%)	$n = 3$ (2.9%)	$n = 12$ (4.1%)
	3–4	$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 0$ (0.0%)
Elevated transaminases	0	$n = 48$ (84.2%)	$n = 122$ (93.8%)	$n = 97$ (94.1%)	$n = 267$ (92.1%)
	1–2	$n = 6$ (10.5%)	$n = 7$ (5.4%)	$n = 5$ (4.9%)	$n = 18$ (6.2%)
	3–4	$n = 0$ (0.0%)	$n = 1$ (0.8%)	$n = 0$ (0.0%)	$n = 1$ (0.3%)
Loss of appetite	0	$n = 26$ (45.6%)	$n = 53$ (40.8%)	$n = 49$ (47.6%)	$n = 128$ (44.1%)
	1–2	$n = 24$ (42.1%)	$n = 69$ (53.1%)	$n = 48$ (46.5%)	$n = 141$ (48.6%)
	3–4	$n = 4$ (7.0%)	$n = 8$ (6.1%)	$n = 5$ (4.9%)	$n = 17$ (5.9%)
Weight loss	0	$n = 32$ (56.1%)	$n = 64$ (49.2%)	$n = 57$ (55.3%)	$n = 153$ (52.8%)
	1–2	$n = 21$ (36.8%)	$n = 60$ (46.2%)	$n = 44$ (42.7%)	$n = 125$ (43.0%)
	3–4	$n = 1$ (1.8%)	$n = 6$ (4.6%)	$n = 1$ (1.0%)	$n = 8$ (2.8%)
Nausea	0	$n = 20$ (35.0%)	$n = 30$ (23.9%)	$n = 34$ (33.0%)	$n = 84$ (29.3%)
	1–2	$n = 22$ (38.6%)	$n = 67$ (51.5%)	$n = 50$ (48.5%)	$n = 139$ (47.9%)
	3–4	$n = 12$ (21.1%)	$n = 33$ (24.6%)	$n = 18$ (17.5%)	$n = 63$ (21.4%)
Diarrhea	0	$n = 27$ (47.4%)	$n = 83$ (63.8%)	$n = 83$ (80.6%)	$n = 193$ (66.6%)
	1–2	$n = 11$ (19.3%)	$n = 37$ (28.5%)	$n = 17$ (16.5%)	$n = 65$ (22.4%)
	3–4	$n = 16$ (28.0%)	$n = 10$ (7.7%)	$n = 2$ (1.9%)	$n = 28$ (9.6%)
Constipation	0	$n = 52$ (91.1%)	$n = 123$ (94.7%)	$n = 94$ (91.2%)	$n = 269$ (92.7%)
	1–2	$n = 1$ (1.8%)	$n = 5$ (3.8%)	$n = 7$ (6.8%)	$n = 13$ (4.5%)
	3–4	$n = 1$ (1.8%)	$n = 2$ (1.5%)	$n = 1$ (1.0%)	$n = 4$ (1.4%)

Table 2 (Continued)

		GIT 1992	GIT 1996	DSGL 01/2003	Total
Neurotoxicity	0	$n=53$ (92.9%)	$n=130$ (100%)	$n=101$ (98.0%)	$n=284$ (97.9%)
	1–2	$n=1$ (1.8%)	$n=0$ (0.0%)	$n=1$ (1.0%)	$n=2$ (0.7%)
	3–4	$n=0$ (0.0%)	$n=0$ (0.0%)	$n=0$ (0.0%)	$n=0$ (0.0%)

ECOG Eastern Cooperative Oncology Group, *CTC* Common Toxicity Criteria
Given are the numbers available with missing data being the difference between total numbers and given numbers
[a]$n=2$ patients died in the first study during RT, both not achieving CR (1 nontherapy-associated cardiac event, 1 progression as aggressive lymphoma receiving chemotherapy)
[b]Acute toxicity (CTC), missing patients: GIT 1992 $n=3$ (5.3%), GIT 1996 $n=0$ (0.0%), DSGL 01/2003 $n=1$ (1.0%), in total $n=4$ (1.4%) of whom: 2 patients received only half of their planned radiation doses (1 died during primary therapy of a nontherapy-associated cardiac event, 1 other died after progression as aggressive lymphoma during primary therapy receiving chemotherapy); 2 other patients had incomplete documentation forms and the responsible radiotherapeutic institutions had no further information

tively (Table 4). Five out of the 10 relapsing patients, and 3 out of the 6 local relapses, belonged to the first study. During the course of the 3 studies, the total recurrence rate fell from 13.5 to 3.0%, and the local recurrence rate from 8.1 to 1.5%, respectively. On further follow-up, 3 developed a second relapse (2 distant, 1 local), and of those, 1 suffered a third relapse (distant). In total, 14 recurrence events were recorded.

Investigation revealed that the primary RT among patients with recurrence included a significant protocol violation (underdosage by 15% or inadequate RT field size) in 2 patients, 1 who developed local relapse and 1 who developed distant relapse. Of those who developed more than one relapse, an indolent lymphoma had formed as the first relapse. In 2 of these 3, an indolent lymphoma again formed as a second relapse. The other developed an aggressive lymphoma in both the second and third relapses.

Of the 14 recurrence events, 11 occurred within the first five years, and 3 occurred much later (13.8, 14.5 and 18.2 years after the beginning of primary RT). Salvage therapy after the first relapse was successful, resulting in complete remission. Of the patients with a second relapse, 1 died from that event (indolent lymphoma in the multilocular craniofacial region and mediastinum), 1 again achieved continuing

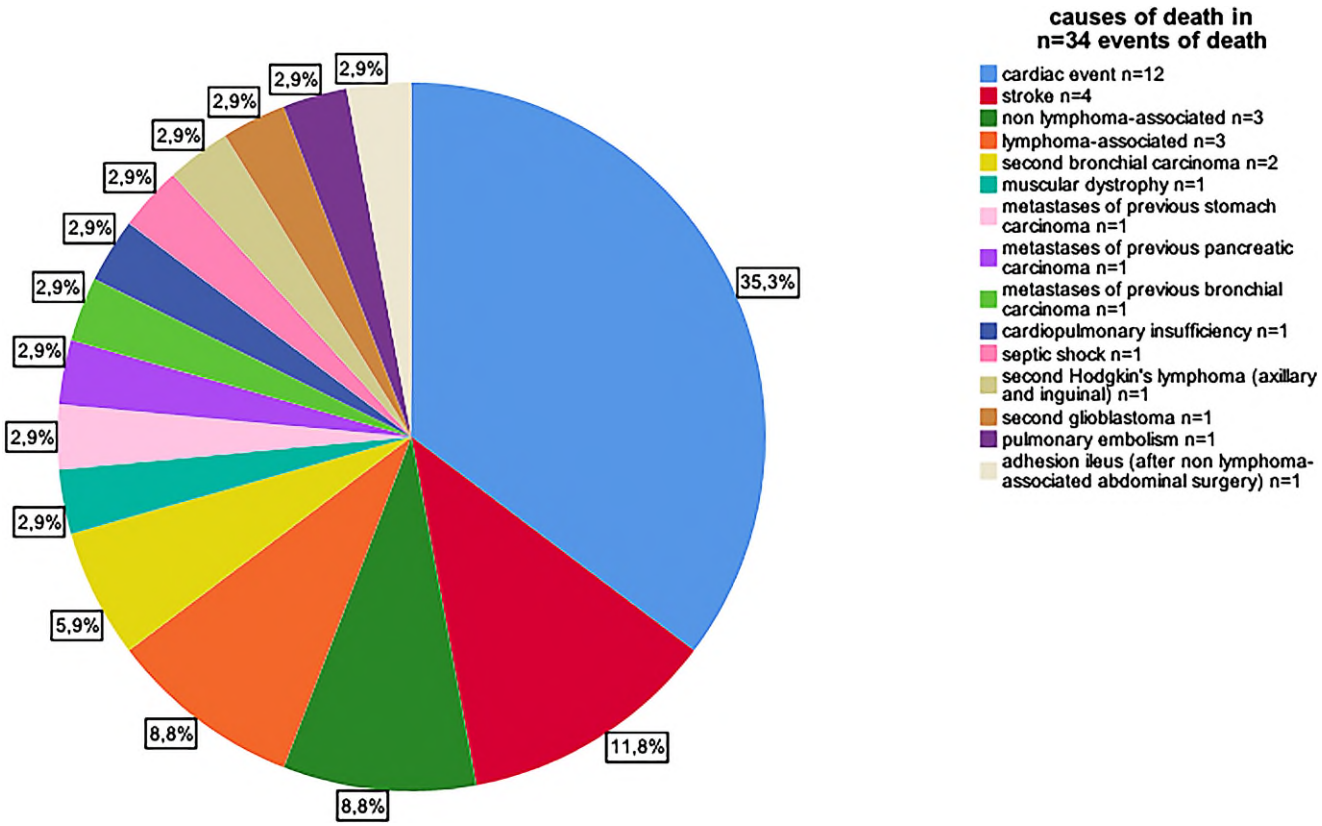

Fig. 1 Causes of death in $n=34$ patients

Table 3 Follow-up results/events and long-term impairment of organ function (LENT SOMA) among indolent gastric marginal zone lymphoma (gMZL) in all studies ($n = 179$)

		GIT 1992	GIT 1996	DSGL 01/2003	Total
Follow-up patients with gMZL (of total)		$n = 37$ (64.9%)	$n = 76$ (58.6%)	$n = 66$ (64.1%)	$n = 179$ (61.7%)
Median observation time in years (months)		13.0 (156)	8.2 (98.5)	4.7 (56)	6.4 (77)
Events (progression/relapse/death)		$n = 13$ (35.1%)[a]	$n = 21$ (27.6%)[b]	$n = 7$ (10.5%)[c]	$n = 41$ (22.9%)
Progression		$n = 1$ (2.7%)	$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 1$ (0.6%)
Relapse in total		$n = 5$ (13.5%)	$n = 3$ (3.9%)	$n = 2$ (3.0%)	$n = 10$ (5.6%)
Local		$n = 2$ (5.4%)	$n = 2$ (2.6%)	$n = 1$ (1.5%)	$n = 5$ (2.8%)
Distant		$n = 2$ (5.4%)	$n = 1$ (1.3%)	$n = 1$ (1.5%)	$n = 4$ (2.2%)
Local and distant		$n = 1$ (2.7%)	$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 1$ (0.6%)
Early relapse		$n = 2$ (5.4%)	$n = 0$ (0.0%)	$n = 1$ (1.5%)	$n = 3$ (1.7%)
Late relapse		$n = 3$ (8.1%)	$n = 3$ (3.9%)	$n = 1$ (1.5%)	$n = 7$ (3.9%)
Death in total		$n = 11$ (29.7%)	$n = 18$ (23.7%)	$n = 5$ (7.6%)	$n = 34$ (19.0%)
Related to treatment		$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 0$ (0.0%)
DOD		*n = 3 (8.1%)*	$n = 0$ (0.0%)	$n = 0$ (0.0%)	$n = 3$ (1.7%)
Other diseases		$n = 8$ (21.6%)	$n = 17$ (22.4%)	$n = 3$ (4.6%)	$n = 28$ (15.6%)
Not lymphoma associated		$n = 0$ (0.0%)	$n = 1$ (1.3%)	$n = 2$ (3.0%)	$n = 3$ (1.7%)
Overall survival (with 95% CI)					
Five-year		85.8% (74.2–97.3)	87.2% (79.4–95.0)	92.7% (85.6–99.8)	–
Ten-year		75.2% (60.1–90.3)	73.2% (61.4–85.0)	87.9% (76.5–99.2)	–
Fifteen-year		71.0% (54.5–87.5)	66.4% (52.5–80.3)	–	–
Event-free survival (with 95% CI)					
Five-year		74.4% (60.0–88.9)	84.4% (76.0–92.8)	89.5% (81.4–97.5)	–
Ten-year		66.9% (50.6–83.2)	70.9% (59.1–82.6)	84.5% (72.3–96.7)	–
Fifteen-year		62.8% (45.6–80.1)	58.5% (41.8–75.2)	–	–
Lymphoma-specific survival (with 95% CI)					
Five-year		93.9% (85.6–100)	100%	100%	–
Ten-year		93.9%	100%	100%	–
Fifteen-year		93.9%	100%	–	–
Impaired Organ function (LENTSOMA)[d]					
Liver	0	$n = 33$ (89.2%)	$n = 72$ (94.7%)	$n = 64$ (97.0%)	$n = 169$ (94.4%)
	1–2	$n = 1$ (2.7%)	$n = 3$ (4.0%)	$n = 1$ (1.5%)	$n = 5$ (2.8%)
Kidney	0	$n = 32$ (86.5%)	$n = 69$ (90.8%)	$n = 63$ (95.5%)	$n = 164$ (91.6%)
	1–2	$n = 2$ (5.4%)	$n = 6$ (7.9%)	$n = 2$ (3.0%)	$n = 10$ (5.6%)
Bladder	0	$n = 33$ (89.2%)	$n = 74$ (97.4%)	$n = 65$ (100.0%)	$n = 172$ (96.1%)
	1–2	$n = 1$ (2.7%)	$n = 1$ (1.3%)	$n = 0$ (0.0%)	$n = 2$ (1.1%)
Stomach and bowel	0	$n = 32$ (86.5%)	$n = 72$ (94.7%)	$n = 63$ (95.5%)	$n = 167$ (93.2%)
	1–2	$n = 2$ (5.4%)	$n = 3$ (4.0%)	$n = 2$ (3.0%)	$n = 7$ (3.9%)

DOD died of disease, *early relapse* relapse within the first year after start of treatment, *late relapse* relapse after the first year of treatment, *CI* confidence interval, *LENT SOMA* Late Effects on Normal Tissue Subjective Objective Management

[a] $n = 13$ patients developed events within the first study, of whom $n = 2$ patients died from relapse and $n = 1$ died from progress (see *n = 3 patients DOD indicated in italics*, in the first study)

[b] $n = 21$ patients developed events within the second study, of whom no patient died from relapse or progress

[c] $n = 7$ patients developed events within the third study, of whom no patient died from relapse or progress

[d] Impaired organ function (LENT SOMA), missing patients: GIT 1992 $n = 3$ (8.1%), GIT 1996 $n = 1$ (1.3%), DSGL 01/2003 $n = 1$ (1.5%), in total $n = 5$ (2.8%) died during the first 90 days after the start of radiation therapy, therefore by definition no long-term impairment of organ function could be observed

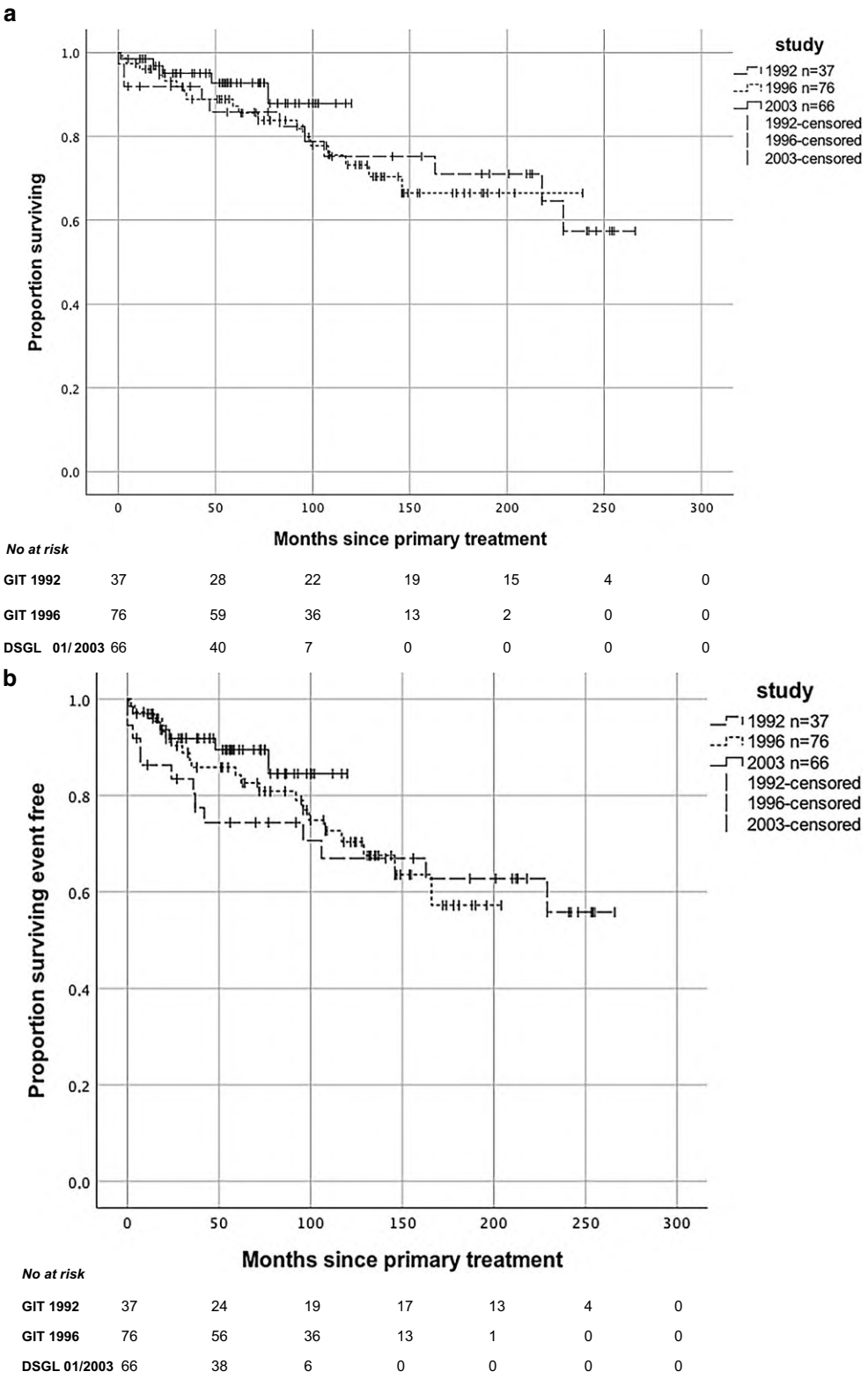

Fig. 2 **a** Overall survival (OS), *p = 0.463, Number of deaths* *n* = 11 (GIT 1992), *n* = 18 (GIT 1996), *n* = 5 (DSGL 01/2003). *Median follow-up time* 13.0 years (GIT 1992), 8.2 years (GIT 1996), 4.7 years (DSGL 01/2003). **b** Event-free survival (EFS), *p = 0.387, Number of events* *n* = 13 (GIT 1992), *n* = 21 (GIT 1996), *n* = 7 (DSGL 01/2003). *Median follow-up time* 13.0 years (GIT 1992), 8.2 years (GIT 1996), 4.7 years (DSGL 01/2003)

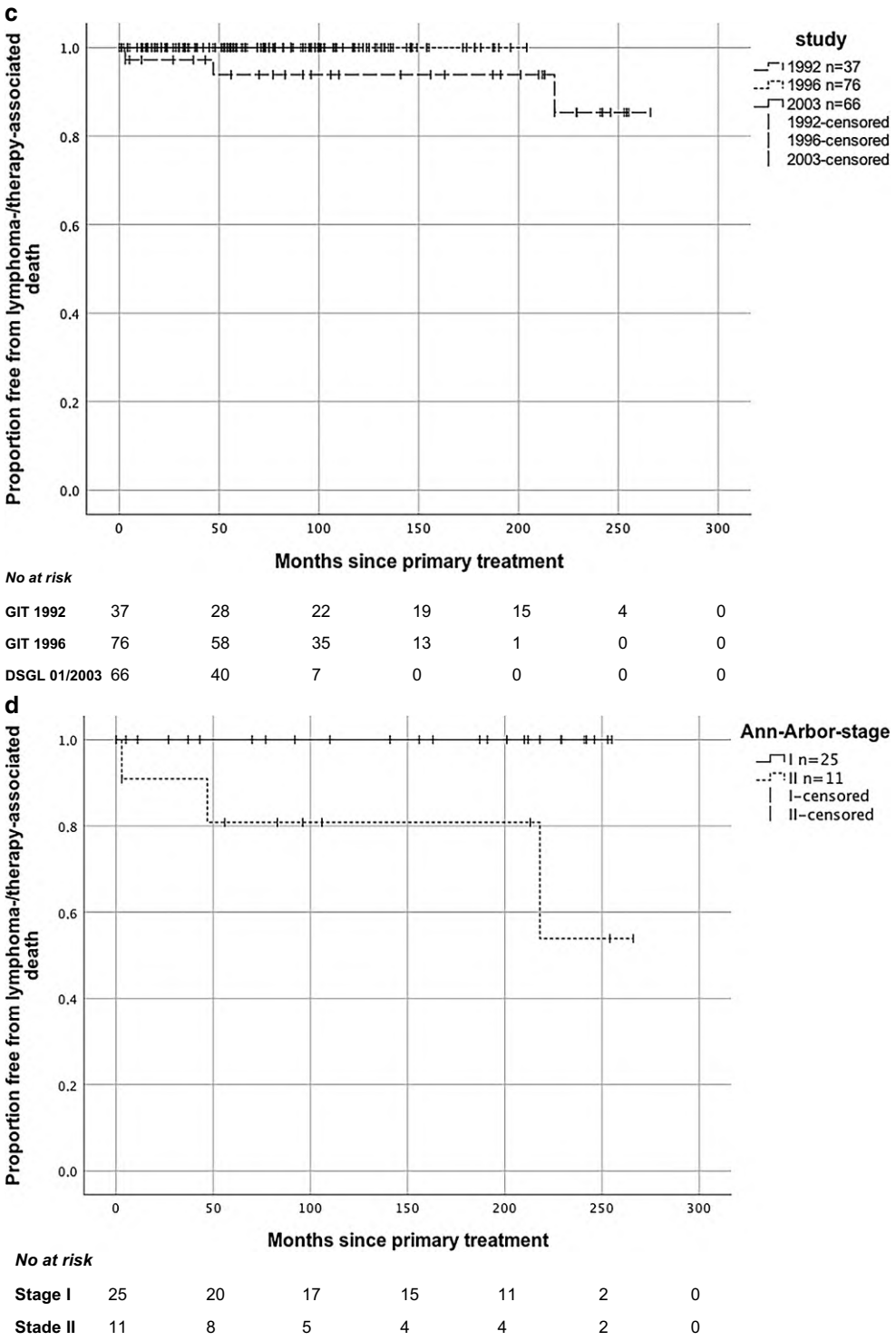

Fig. 2 (continued) **c** Lymphoma-specific survival (LSS), *p = 0.026, Number of deaths related to lymphoma or therapy* $n = 3$ (GIT 1992), $n = 0$ (GIT 1996), $n = 0$ (DSGL 01/2003), *Median follow-up time* 13.0 years (GIT 1992), 8.2 years (GIT 1996), 4.7 years (DSGL 01/2003). **d** Lymphoma-specific survival (LSS) study GIT 1992, stage-dependent (I and II), *p = 0.008, Number of lymphoma-specific deaths* $n = 3$, *Median follow-up time* 13.0 years

complete response with *H. pylori* eradication (indolent lymphoma in the stomach), and 1 was salvaged successfully with multimodal surgery–chemotherapy–RT for 3.7 years until the third relapse (aggressive lymphoma in the lung). This event caused death.

The two relapse patients who died of lymphoma were part of the first study. A third relapsing patient, also part of the first study, died during follow-up (6.9 years after the beginning of primary RT), but unlike the others, death was caused by metastases of a previous non-small cell lung cancer.

Table 4 Relapse characteristics ($n = 10$)

		GIT 1992	GIT 1996	DSGL 01/2003	Total
Follow-up patients with relapses		$n = 5$ (13.5%)	$n = 3$ (3.9%)	$n = 2$ (3.0%)	$n = 10$ (5.6%)
Sex					
Female		$n = 2$	$n = 0$	$n = 2$	$n = 4$
Male		$n = 3$	$n = 3$	$n = 0$	$n = 6$
Age in years		30, 33, 35, 69, 71	52, 65, 72	71, 45	Median: 58.5 Range (30–72)
Ann-Arbor Stage					
I		$n = 2$	$n = 3$	$n = 1$	$n = 6$
II					
II1		$n = 2$	$n = 0$	$n = 0$	$n = 2$
II2		$n = 1$	$n = 0$	$n = 1$	$n = 2$
ECOG					
0		$n = 3$	$n = 3$	$n = 0$	$n = 6$
1		$n = 2$	$n = 0$	$n = 1$	$n = 3$
2		$n = 0$	$n = 0$	$n = 1$	$n = 1$
RT protocol					
Deviation[a]	No	$n = 0$	$n = 2$	$n = 2$	$n = 4$
	Yes	$n = 3$	$n = 1$	$n = 0$	$n = 4$
Violation[b]	Yes	$n = 2$	$n = 0$	$n = 0$	$n = 2$
Relapse location					
Local		$n = 2$	$n = 2$	$n = 1$	$n = 5$
Distant		$n = 2$	$n = 1$	$n = 1$	$n = 4$
Local + distant[c]		$n = 1$	$n = 0$	$n = 0$	$n = 1$
First relapse histology					
Indolent		$n = 4$	$n = 3$	$n = 1$	$n = 8$
Aggressive		$n = 0$	$n = 0$	$n = 1$	$n = 1$
Indolent-aggressive		$n = 1$	$n = 0$	$n = 0$	$n = 1$
First relapse interval[d] in months		7, 7, 24, 36, 42	19, 20, 166	3, 15	Median: 19.5 Range (3–166)
First relapse timing [e]					
Early		$n = 2$	$n = 0$	$n = 1$	$n = 3$
Late		$n = 3$	$n = 3$	$n = 1$	$n = 7$
First salvage therapy					
Surgery		$n = 1$	$n = 2$	$n = 0$	$n = 3$
Eradication		$n = 0$	$n = 1$	$n = 0$	$n = 1$
Radiotherapy		$n = 1$	$n = 0$	$n = 0$	$n = 1$
Immunotherapy		$n = 0$	$n = 0$	$n = 1$	$n = 1$
Multimodal		$n = 3$	$n = 0$	$n = 1$	$n = 4$
First salvage CR[f]					
Persistent		$n = 3$	$n = 2$	$n = 2$	$n = 7$
Temporary		$n = 2$	$n = 1$	$n = 0$	$n = 3$
Re-relapse interval[g] in months		11, 150	36	–	Median: 36 Range (11–150)

Acute toxicities

Of the 290 patients treated with RT, RT-related *acute toxicities*, using the Common Terminology Criteria for Adverse Events, Common Toxicity Criteria (CTC) (Version 4.03) reporting system [15], could be obtained in 286. Half the prescribed radiation dose was administered to 2 patients, of whom 1 died due to a cardiac event, and 1 died after a change in therapy after tumor progression and a conversion to aggressive lymphoma. The remaining 2 patients could not be evaluated for toxicity because data are not available (Table 2).

Table 4 (Continued)

	GIT 1992	GIT 1996	DSGL 01/2003	Total
Re-salvage therapy				
Radiotherapy	$n=1$	–	–	$n=1$
Multimodal	$n=1$	$n=1$	–	$n=2$
Second salvage CR[h]				
Persistent	$n=0$	$n=1$	–	$n=1$
Temporary	$n=1$	$n=0$	–	$n=1$
No	$n=1$	$n=0$	–	$n=1$
Death				
No	$n=2$	$n=3$	$n=2$	$n=7$
Yes	$n=3$	$n=0$	$n=0$	$n=3$
DOD				
No	$n=1$	–	–	$n=1$
Yes	$n=2$	–	–	$n=2$

RT radiation therapy, *DOD* died of disease, *CR* complete remission, *ECOG* Eastern Cooperative Oncology Group
[a]*Protocol deviation* means dose deviation >5 and <10%
[b]*Protocol violation* means dose deviation ≥10% or false radiation field size
[c]*Local* at first relapse and *distant* at second/third relapse
[d]*Relapse-interval* between start of RT and first relapse
[e]*Relapse timing early* = within the first year after start of treatment/*late* = after the first year after start of treatment
[f]*First salvage CR* = de novo complete remission after first salvage therapy
[g]*Re-relapse-interval* = between first salvage therapy and second relapse
[h]*Second salvage CR* = de novo complete remission after second salvage therapy

Laboratory blood values

Acute *hematotoxicity* grades 3 and 4 decreased with each successive study. In the entire cohort, the most frequent hematotoxic side effect of any grade was related to leukocytopenia. Reductions in the relative frequencies of anemia ($p=0.005$), leukocytopenia ($p=0.001$) and thrombocytopenia ($p=0.001$) of any grade were statistically significant between studies. Acute *hepatotoxicity* grades 3 and 4 related to transaminases occurred rarely in the second study (1/130 patients, 0.8%). The trends towards lower relative frequencies of elevated bilirubin ($p=0.057$) and the transaminases AST and ALT ($p=0.062$), regardless of grade, were not statistically significant between the three cohorts.

Clinical adverse reactions

Across all studies, the most frequent gastrointestinal side effects of any grade were nausea followed by loss of appetite, weight loss, and diarrhea; constipation was rare. *Gastrointestinal acute toxicities* grades 3 and 4 decreased clearly across the three studies, being 59.6% (34/57), 45.4% (59/130), and 26.2% (27/103), respectively. Reduction in the relative frequency of diarrhea ($p=0.001$) was significant. Development of the relative frequency of nausea with an intermittent increase between the first and the second study, and a decrease (in particular of grades 3 and 4) towards the third study were statistically significant ($p=0.037$). *Neurologic acute toxicity* grades 3 and 4 were not evident.

Chronic toxicities

Of the 179 followed patients, *chronic toxicities*, according to the LENT SOMA (Late Effects on Normal Tissue, Subjective Objective Management) scoring system [16], were obtainable in 174 patients (Table 3). The trends towards lower relative frequencies of *impaired organ functions* of the liver ($p=0.332$), kidneys ($p=0.367$), gastrointestinal tract ($p=0.362$) and urinary bladder ($p=0.247$) of any grade were not statistically significant between the studies. Chronic RT-associated side effects in organ functions were limited to grades 1 or 2 and were rare in the followed patients across all three studies.

Of the entire cohort, during the maximum 22-year follow-up period, 4 patients developed second malignancies outside the radiation field. These occurred from 2.8 to 13.1 years after RT ($n=2$ for bronchial carcinoma, $n=1$ for Hodgkin's lymphoma, $n=1$ for glioblastoma). All received specific oncologic treatment (chemotherapy in Hodgkin's lymphoma, standard multimodal treatment for the glioblastoma and RT for the others), but all experienced progression and died from their second malignancies within 2 to 7 months.

Discussion

The three prospective studies aimed at optimizing the radiation field size in gMZL. To our knowledge, this is the largest cohort of patients with early stage gMZL treated conservatively with curative radiation therapy. The three studies subgroups with median follow-ups of 13.0, 8.2 and 4.7 years allow an extensive analysis of the course of this rare disease. Stage-adapted radiation therapy of indolent gastric lymphoma has been established worldwide as a curative primary therapy because of the option for stomach-maintenance and the success in lymphoma regression [11–13, 17, 18]. After locoregional radiation therapy in this patient collective, of which 4.8% received previous chemotherapy, the outcome is excellent with an exceptionally high complete response rate of 99.3% and low disease-specific death rate of 3 patients. Progressive disease occurred in 1 patient, but relapse occurred in 5.6% (10/179) of the followed patients. Local relapse was more frequent than distant (1.5:1), similar to previous reports [19, 20]. The total and in particular the local recurrence rate being at their highest in the first study might be due to the further development of radiation technique towards a predominantly three-dimensional conformal RT within the second and third study. Local relapses were always non-transformed MZL, distant relapses were equally transformed or non-transformed lymphoma. All first recurrences were successfully salvaged, most commonly resulting in continuing de novo complete remission, and second relapse occurred in 3 patients, again after long disease-free intervals. Disease-specific survival remains high due to effective salvage therapies and a small proportion of progression to further advanced disease.

In this collective the stage of gMZL was identified as a significant factor associated with disease-specific survival, given that stage II patients were the only ones who died of disease. Lymphoma stage was a strong prognostic factor, as it was in other studies [21].

Radiation therapy as definitive treatment approach in gMZL is well-tolerated, no RT-associated deaths occurred in the entire cohort. Relevant acute toxicity was related to hematotoxicity and gastrointestinal toxicity and significantly improved with RT field reduction. Moderate chronic RT-associated side effects rarely appeared and tended to occur with lower relative frequencies in the course of the successive studies. The impairment of organ function was reduced as the RT field size decreased. Three deaths were caused by metastases from previous cancers, and four deaths were caused by out-of-field second malignancies that developed during follow-up.

This cohort is similarly composed and shows acute and chronic adverse effects that are consistent with that found in the literature [9, 18, 20, 22–24]. Results confirm that excellent outcomes result when early stage gMZL is treated with RT, as reported in the literature. In the final study (DSGL 01/2003), the 5-year OS, EFS, and LSS are comparable, and the 10-year OS is more favorable than reported for other studies of gastric lymphoma. Reportedly, the 5-year OS is 90.3–94%, 10-year OS is 70.0–87%, 5-year EFS is 74.0–89.0%, 10-year EFS is 57.0–92.0%, 5-year LSS is 99.0–100%, 10-year LSS is 98% [9, 19, 20, 22, 24]. In a group of 244 patients with stage I or II extranodal MZL with heterogeneous disease sites (about 50% in the stomach), initially treated with RT alone, the reported risk of relapse for the stomach was relatively low compared to other sites; the risk of relapse after RT was significantly lower compared with other strategies [25].

The rate of transformation to aggressive lymphoma in our followed subgroup is 1.7%, relatively low compared with the literature [9, 19, 22]. Our follow-up results show that relapse occurs primarily within 5 years, and it also confirms that relapse can be late, given 3 relapse events occurred between 13.8 and 18.2 years respectively after the beginning of RT, emphasizing the importance of lifelong follow-up [19, 26]. Over the past two decades considerable interest has focused on the prescribed RT dose in indolent non-Hodgkin lymphomas in different anatomical sites. The clinical trials in the United States, Canada and the United Kingdom including smaller sample sizes in varied locations have already been conducted with very effective lower radiation doses of at median 24 or 30 Gy [7, 9, 19, 25, 27], whereas in Australia, Germany and the Netherlands large studies particularly in gastric indolent lymphoma were continued with highly effective doses of a median 40 Gy [13, 20, 28]. The use of very low-dose radiotherapy in indolent lymphoma has also been studied recently [27, 29] with limited but very encouraging tumor response rates. With its excellent lymphoma response rate, our study revealed no pattern between applied RT dose and in-field failure in gMZL.

The primary limitation of this study is the proportion (38%) of patients randomly lost to follow-up directly after radiation treatment. This is associated with a long follow-up period, particularly in the first study (GIT 1992). The varied follow-up periods across the three studies were incorporated in survival analyses, which must be considered when comparing results. The strengths of this analysis include the large cohort of gMZL patients treated with definitive radiation therapy, the centrally confirmed diagnoses by experienced hematopathologists, the standardized radiation therapy approach with follow-up examinations, and the length of observation time. The large sample size and length of follow-up period provide detailed information about the efficacy and long-term outcome of historically considerably reduced RT fields in gMZL.

Conclusion

Early stage gMZL can be treated successfully with stage-adapted small-volume RT, which results in minimal toxicity and excellent long-term lymphoma control. Despite the low yet longer-term risk of disease recurrence, the natural course is predominantly indolent, and the OS of gMZL remains high after salvage therapy. These results are encouraging for further decreases in modern radiation treatment of gMZL, as application of the involved site radiation therapy (ISRT), recommended by the International Lymphoma Radiation Oncology Group, and evaluation of the optimal lower end of radiation dose (potentially below the actual international standard dose of 30 Gy).

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Compliance with ethical guidelines

Conflict of interest G. Reinartz, R.P. Pyra, G. Lenz, R. Liersch, G. Stüben, O. Micke, K. Willborn, C.F. Hess, A. Probst, R. Jany, J. Schultze, C. Rübe, C. Hirt, W. Fischbach, M. Bentz, S. Daum, C. Pott, M. Tiemann, P. Möller, A. Neubauer, M. Wilhelm, N. Willich, W.E. Berdel and H.T. Eich declare that they have no competing interests. R. Fietkau reports grants, personal fees and non-financial support from Merck Serono, personal fees and non-financial support from Fresenius Kabi, personal fees and non-financial support from Novocure, grants, personal fees and non-financial support from MSD, grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Brainlab, personal fees and non-financial support from Sennewald GmbH, personal fees and non-financial support from Bristol-Myers Squibb, outside the submitted work.

Ethical standards The trials were conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research after approval of the Ethical Board of the physicians' chamber of Westfalia-Lippe and the Westfalian Wilhelms-University of Münster. The studies were reviewed by the local Ethical Committees (institutional review boards) of the involved trials sites.

Appendix

In addition to the authors listed on the manuscript, the supporting institutions were as follows: Aalen Radiotherapy, Aschaffenburg Radiotherapy Practice, Augsburg Radiotherapy Joint Practice, Aurich Norden Medical Care Center, Bad Saarow Helios Hospital, Bocholt Radiotherapy Practice, Bochum Catholic Hospital, Bonn University Hospital, Braunschweig Municipal Hospital, Bremen-Mitte Hospital, Celle General Hospital, Dessau Municipal Hospital, Dortmund Knappschafts-Hospital, Düsseldorf University Hospital, Düsseldorf Marienhospital, Essen University Hospital, Essen Alfried Krupp Hospital, Essen Radiotherapy Practice, Flensburg St. Franziskus Hospital, Frankfurt Nordwest Hospital, Fulda Hospital, Gießen Wilhelm Conrad Röntgen Hospital, Görlitz Radiotherapy Practice, Hagen General Hospital, Halle/Saale University Hospital, Hamburg St. Georg Radiotherapy Practice, Hamburg Altona Radiotherapy Practice, Hanau Hospital, Hannover Medical University, Hannover Diakovere Friederikenstift Hospital, Heidenheim Hospital, Herford Hospital, Jena University Hospital, Karlsruhe Vincentius Hospital, Kassel Municipal Hospital, Kassel Radiotherapy Practice, Kempten Hospital, Koblenz Radiological Institute, Köln University Hospital, Krefeld Helios Hospital, Lippstadt Dreifaltigkeits-Hospital, Lübeck University Hospital, Ludwigshafen Klinikum Ludwigshafen, Magdeburg University Hospital, Mannheim University Hospital, Minden Hospital, Mönchengladbach Maria Hilf Hospital, Mühlheim a.d. Ruhr Protestant Hospital, München Klinikum rechts d. Isar University Hospital, Neubrandenburg Dietrich Bonhoeffer Hospital, Neuss Lukas-Hospital, Nordhorn Radiotherapy Practice, Osnabrück Paracelsus Hospital, Osnabrück Radiotherapy Practice, Ostfildern Medius Hospital, Paderborn Brüderkrankenhaus St. Josef Hospital, Pinneberg Radiotherapy Joint Practice, Recklinghausen Knappschafts-Hospital, Rendsburg District Hospital, Rostock University Hospital, Schwerin Helios Hospital, Siegen St. Marien Hospital, Stuttgart Marienhospital, Trier Mutterhaus der Borromäerinnen Hospital, Vechta Medical Care Center, Wuppertal Radiotherapy Practice.

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