Advances in Radiation Oncology (2021) **6**, 100648

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Incidence and Dosimetric Predictors of Radiation-Induced Gastric Bleeding After Chemoradiation for Esophageal and Gastroesophageal Junction Cancer

Margaret Montovano, MA,[a,b] Minsi Zhang, MD, PhD,[a] Patrick Oh, MD,[a] Maria Thor, PhD,[c] Christopher Crane, MD,[a] Ellen Yorke, PhD,[b] Abraham J. Wu, MD,[b,*,1] and Andrew Jackson, PhD[b,1]

[a]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; [b]Rutgers New Jersey Medical School, Newark, New Jersey; and [c]Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York

Received 2 July 2020; revised 19 November 2020; accepted 5 January 2021

Abstract

Purpose: To determine the incidence and predictors of gastric bleeding after chemoradiation for esophageal or gastroesophageal junction cancer.

Methods and Materials: We reviewed patients receiving chemoradiation to at least 41.4 Gy for localized esophageal cancer whose fields included the stomach and who did not undergo surgical resection. The primary endpoint was grade ≥3 gastric hemorrhage (GB3+). Comprehensive stomach dose-volume parameters were collected, and stomach dose-volume histograms were generated for analysis.

Results: A total of 145 patients met our inclusion criteria. Median prescribed dose was 50.4 Gy (range, 41.4-56 Gy). Median stomach Dmax was 53.0 Gy (1.0-62.7 Gy), and median stomach V40, V45, and V50 Gy were 112 cm^3 (0-667 cm^3), 84 cm^3 (0-632 cm^3), and 50 cm^3 (0-565 cm^3), respectively. Two patients (1.4%) developed radiation-induced GB3+. The only dosimetric factor that was significantly different for these patients was a higher stomach Dmax (58.1 and 58.3 Gy) than the cohort median (53 Gy). One of these patients also had cirrhosis, and the other had a history of nonsteroidal anti-inflammatory drug use. Five other patients had GB3+ events associated with documented tumor progression. A Cox proportional hazards model based on stomach Dmax with respect to the development of GB3+ was found to be statistically significant. Time-to-event curves and dose-volume atlases were generated, demonstrating an increased risk of GB3+ only when stomach Dmax was >58 Gy ($P < .05$).

Conclusions: We observed a low rate of GB3+ events in patients who received chemoradiation to a median dose of 50.4 Gy to volumes that included a significant portion of the stomach. These results suggest that when prescribing 50.4 Gy for esophageal cancer, there is no need to minimize the irradiated gastric volume or dose for the sake of preventing bleeding complications. Limiting stomach maximum

Sources of support: This work was supported by the National Institutes of Health/National Cancer Institute (P30 CA008748) and R25CA020449. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures: Dr Wu has received research funding from CivaTech Oncology, Inc, personal fees from AstraZeneca, and travel grants from AlphaTau Medical. He serves on the scientific advisory board for Simphotek, Inc. Dr Crane has received personal fees from Celgene Corp., and travel grants from Varian Medical Systems, Elekta, and Ion Beam Applications.

Data Sharing Statement: Research data are available upon request from corresponding author.

* Corresponding author: Abraham J. Wu, MD; E-mail: wua@mskcc.org

[1] A.J.W. and A.J. contributed equally to this work.

https://doi.org/10.1016/j.adro.2021.100648

doses to <58 Gy may also avoid bleeding, and particular caution should be taken in patients with other risk factors for bleeding, such as cirrhosis.

Introduction

Esophageal cancer, including both squamous cell carcinoma and adenocarcinoma, is an aggressive and deadly malignancy affecting more than 450,000 people annually worldwide. It ranks sixth among all cancers in mortality rates, with a 5-year survival ranging from 15% to 25%.[1] Radiation therapy, in combination with systemic chemotherapy and surgery, is an integral part of treatment for esophageal cancer. Current guidelines recommend neoadjuvant chemoradiation followed by esophagectomy for patients with locally advanced esophageal cancer. The standard radiation dose for esophageal cancer in the United States is 50.4 Gy in 28 fractions.[2] Because the distal esophagus and gastroesophageal (GE) junction are very common sites of presentation of esophageal adenocarcinoma, irradiating esophagus cancer will often include a significant portion of the stomach in the planning target volume (PTV), thus exposing the gastric mucosa to full doses. However, there is a lack of data characterizing the incidence of radiation-induced gastric bleeding and assessing dosimetric parameters associated with its development.

Gastric toxicity is a feared complication of radiation treatment for upper gastrointestinal malignancies. As a result, stomach doses ≥45 to 50 Gy are usually avoided to prevent severe gastric toxicities, such as hemorrhage, ulceration, and perforation.[3,4] Although these complications have long been recognized, there is a lack of data in the current literature describing the tolerance of the stomach to radiation and dose-volume parameters associated with the development of gastric toxicity. Although a limited number of prior studies have demonstrated dose-toxicity relationships of gastric complications in patients with intrahepatic and pancreatic malignancies,[5-9] there are no studies to describe dosimetric parameters associated with the risk of gastric toxicities in patients undergoing radiation therapy for esophageal cancer. Because the portion of the stomach that is irradiated in esophageal cancer (ie, proximal stomach/cardia) is different from that typically irradiated in hepatobiliary malignancies (body/pylorus), the incidence and predictors of gastric bleeding may differ.

Our objective was to characterize the incidence of radiation-induced gastric bleeding and to identify predictive dosimetric parameters in patients with esophageal cancer. We therefore retrospectively analyzed dose-volume histograms (DVHs) of the stomach in a large series of patients with esophageal cancer treated with chemoradiation without surgery, thus leaving their stomachs intact.

Methods and Materials

Patient characteristics

The institutional review and privacy board approved this study, and patient confidentiality was maintained as required by the Health Insurance Portability and Accountability Act. The records of all patients who received chemoradiation for stage I to III esophageal or GE junction cancer between 2007 and 2015 at our institution were reviewed. Although our standard dose for both preoperative and definitive-intent chemoradiation is 50.4 Gy, we included all patients who received a prescription dose of at least 41.4 Gy because this represents a standard baseline dose for preoperative chemoradiation. We limited our analysis to patients whose PTVs overlapped with the stomach and who did not undergo esophagogastric resection after RT. Although our standard institutional practice is to recommend surgery after preoperative chemoradiation for locally advanced distal esophageal cancer, these patients either were not surgical candidates or declined surgery.

This yielded a cohort of 145 patients who had available dosimetric data. Patient medical records, including all physician notes and endoscopy reports, were reviewed to identify posttreatment gastric toxicities. Our primary endpoint, the development of grade >3 gastric bleeding (GB3+), was defined per Common Terminology Criteria for Adverse Events version 4.0 as a hemorrhage that required transfusion or radiologic, endoscopic, or elective operative intervention.

Treatment planning

In our standard simulation process, patients are immobilized, arms up, in an alpha cradle mounted in a platform that indexes to the treatment couch. They receive intravenous and oral contrast. In addition to a computed tomography (CT) planning scan under gentle free-breathing (2-2.5 mm slice thickness) they receive a 4-dimensional CT to assess target breathing motion. GTV is contoured based primarily on the CT simulation and diagnostic positron emission tomography CT imaging, with reference to the endoscopic reports. Standard clinical target volume expansions were 3 to 4 cm longitudinally (oriented along the

esophageal mucosa) but were limited to 1 to 2 cm distally if the tumor involved the stomach, and elective nodal regions were also included according to published guidelines.[10] Standard PTV expansion was 0.5 cm.

Over the time spanned by this study, two different planning systems were used: an in-house system described by Mohan et al. was used until mid-2014, and Eclipse (Varian Medical Systems) with calculations done with the Anisotropic Analytical Algorithm was used thereafter.[11] Cases planned in the in-house system were transferred to Eclipse, and dose distributions were recalculated with Anisotropic Analytical Algorithm. All patients were treated on Varian linear accelerators, mostly with 6 MV fixed gantry direction sliding-window intensity modulated radiation therapy. The planning goal was for at least 95% of the PTV to be covered by the prescription dose and for the maximum plan dose not to exceed 110% to 112% of prescription dose and to be located within the PTV. Patients were instructed to fast for at least 2 hours before simulation and each fraction of radiation therapy.

The entire outer wall of the stomach, from the GE junction to the pylorus, was contoured. During the study timeframe, the only relevant constraint on gastric dose was to keep the mean dose to the stomach outside the PTV <30 Gy, meaning that there was no specific constraint on the part of the stomach within the PTV. As noted, hotspots in the stomach were to be limited to no more than 110% of prescription dose.

Statistical analysis

Stomach DVHs were generated for 143 of 145 patients. Two patients were not exportable for full DVH analysis. Stomach dose-volume parameters, including stomach volume, absolute and relative mean dose, absolute and relative maximum dose, and volume of the stomach receiving 40, 45, and 50 Gy were collected (V40, V45, and V50). The absolute PTV size and volume of PTV/stomach overlap was also collected for all patients.

For statistical analysis, a Cox proportional hazards model based on absolute maximum stomach dose was generated. Time-to-event curves were generated using Dmax = 58 Gy (Dmax in 2 patients with GB3+) to dichotomize patients, and a log-rank test was used to compare the curves. Dose-volume atlases of GB3+ were subsequently generated.[12,13] We then calculated the probability that the true rate of GB3+ events was >5% in patients whose treatments violated candidate DVH thresholds.

Results

Of the 145 patients who met our inclusion criteria, the median age at diagnosis was 71 years (range, 37-95). The majority of patients were male (77.9%). The median follow-up time was 16.8 months (1-118 months) after end of radiation therapy. All patients had histologically confirmed malignancy via endoscopic biopsy, with the majority (78.6%) having adenocarcinoma; the remaining patients had squamous cell carcinoma. Of the patients with available clinical staging information at diagnosis (n = 142), 11 (7.6%) were stage I, 36 were stage II (24.8%), and 95 (65.5%) were stage III. The majority of tumors were located at the gastroesophageal junction (37.2%) or distal esophagus (51%). In addition, 137 (94.5%) patients underwent induction chemotherapy before radiation therapy, and 144 of 145 patients received concurrent chemotherapy. The most common chemotherapy regimen was carboplatin/paclitaxel. Patient demographics and characteristics are described in Table 1.

Definitive chemoradiation was the intended therapy in 77 (53.1%) patients. The remaining 68 (46.9%) patients were intended to receive preoperative chemoradiation but ultimately did not receive surgery, typically because they either had a clinical complete response and declined surgery, or because they were marginal candidates for surgery due to comorbidities or performance status. One hundred forty-four of 145 patients underwent intensity modulated radiation therapy, and the remaining 1 patient had 3-dimensional conformal radiation therapy. The median dose delivered was 50.4 Gy (range, 41.4-56 Gy). The majority of patients (n = 111) received 50.4 Gy delivered in 28 fractions. In addition, 16 patients being treated with definitive intent also received a simultaneous integrated GTV boost to 56 Gy in 28 fractions. Of the remaining patients, 5 received a dose of 48.6 Gy, 8 received a dose of 45 Gy, 2 received a dose of 43.2 Gy, and 3 received a dose of 41.4 Gy.

Median stomach volume and stomach/PTV overlap were 323 cm^3 (47-1107 cm^3) and 69 cm^3 (0.2-563 cm^3), respectively. Median stomach maximum dose (Dmax) and mean dose (Dmean) were 53.0 Gy (1.0-62.7 Gy) and 30.5 Gy (0.5-51.4 Gy), respectively. The median stomach V40, V45, and V50 Gy were 112 cm^3 (0-667 cm^3), 84 cm^3 (0-632 cm^3), and 50 cm^3 (0-565 cm^3), respectively. Stomach dose parameters for our patient cohort are described in Table 2.

In total, 7 patients (4.8%) developed grade $\geq$3 gastric bleeding. Five of these patients, however, had endoscopically confirmed progression (n = 3) or recurrence (n = 2) of the primary esophageal tumor extending into the stomach, which was clinically determined to be the source of bleeding. Of these 5 patients, 4 received a prescription dose of 50.4 Gy and 1 received 56 Gy. In all 5 of these cases, the gastric mucosa was observed to be otherwise normal at the time of bleeding by endoscopic evaluation. The 2 (1.4%) remaining cases of G3+ bleeding events were therefore presumed to be radiation induced. Both of these patients were prescribed a dose to

Table 1 Patient demographics

Characteristics	n
Age, y	
Median	71
Range	37-95
Sex	
Male	113
Female	32
Histology	
Squamous cell carcinoma	31
Adenocarcinoma	114
Location	
Proximal esophagus	2
Mid-esophagus	15
Distal esophagus	74
GE junction	54
Clinical stage	
IA	6
IB	5
IIA	2
IIB	34
III	4
IIIA	71
IIIB	11
IIIC	9
Unspecified	3
Chemotherapy	
Induction only	0
Concurrent only	7
Induction + concurrent	137
None	1
RT intent	
Preoperative	68
Definitive	77
Dose delivered	
41.4 Gy	3
43.2 Gy	2
45 Gy	8
48.6 Gy	5
50.4 Gy	111
56 Gy	16
RT technique	
IMRT	144
3CDRT	1
Cirrhosis	
Yes	3
No	142

Abbreviations: 3CDRT = three-dimensional conformal radiation therapy; GE = gastroesophageal; IMRT = intensity modulated radiation therapy; RT = radiation therapy.

the tumor of 56 Gy in 28 fractions. Thus, among patients who received a dose ≥50.4 Gy (n = 127), the rate of radiation-induced gastric bleeding was 1.6%.

The 2 patients with presumed radiation-induced gastric bleeding events are described in Table 3. One of these patients had endoscopically confirmed radiation-induced erosive gastropathy and a history of cirrhosis with thrombocytopenia. The second patient had a history of extensive nonsteroidal anti-inflammatory drug (NSAID) use and did not undergo endoscopic evaluation, but was deemed to have likely radiation-induced bleeding due to the absence of other likely causes (this patient was without evidence of recurrent malignancy at the time of bleeding). The absolute stomach Dmean and Dmax values for these patients were 25.1 and 27.9 Gy and 58.1 and 58.3 Gy, respectively. V40, V45, and V50 were 47 and 178 cm^3, 37 and 124 cm^3, and 25 and 83 cm^3, respectively. The only stomach dosimetric parameter that was greater in both of these patients compared with the median value for our overall cohort was Dmax (58.1 and 58.3 Gy vs 53 Gy).

A Cox proportional hazards model based on stomach Dmax with respect to the development of GB3+ was found to be statistically significant. Time to event curves were generated using a cutoff of 58 Gy to dichotomize patients, given this was the Dmax observed in both events (Fig 1). A log-rank test comparing the 2 curves was also statistically significant although only 2 GB3+ complications were observed in our cohort. Nine patients had stomach Dmax >58 Gy, including both patients considered to have radiation-induced gastric bleeding. Of the 7 patients with stomach Dmax >58 Gy who did not experience bleeding events, 2 had known anticoagulant use and 3 had known NSAID use. No patients with stomach Dmax <58 Gy experienced bleeding complications.

Dose-volume atlases of the incidence of GB3+ were subsequently generated to determine the probability that the true rate of GB3+ was >5% for DVHs passing over candidate dose-volume constraints (Fig 2). As illustrated in Figure 2, dose appeared to be more important than volume in predicting the probability of gastric bleeding events. For treatments violating the candidate constraint Dmax <58 Gy, the probability that the true rate of GB3+ was >5% is 99%. To facilitate subsequent use, the dose-volume atlas of the incidence of GB3+ is available in the Appendix.

Discussion

Contemporary data on dosimetric parameters associated with radiation-induced gastric toxicities is scarce, but stomach doses ≥45 to 50 Gy are traditionally avoided in clinical practice. For example, a historic guideline for normal tissue constraints suggests 50 Gy as the threshold for stomach toxicity when the entire organ is irradiated, and 45 Gy has been the standard dose for adjuvant or preoperative radiation therapy to the stomach.[3,4] To our knowledge, this is the first report to investigate stomach dosimetric parameters associated with the development of gastric bleeding after radiation therapy in patients with esophageal cancer. Our cohort is also distinctive in being

Table 2 Stomach dose-volume histogram parameters

Parameters	Median	Mean	Range
PTV (cm^3)	691	772	168-2017
Stomach volume (cm^3)	323	374	47-1106
PTV/stomach overlap (cm^3)	69	86	0.2-563
Absolute maximum stomach dose (Gy)	53.0	51.6	10.1-62.7
% Maximum stomach dose	106	104	2-121
Absolute mean stomach dose (Gy)	30.5	29.6	0.50-51.46
% Mean stomach dose	61	59	1-102
V40 (cm^3)	112	123	0-667
V45 (cm^3)	84	103	0-632
V50 (cm^3)	50	73	0-565

Abbreviation: PTV = planning target volume.

limited to patients who did not undergo esophagus or gastric surgery after radiation therapy because such surgery would otherwise obscure the potential long-term effect of gastric radiation.

Notably, we observed a very low rate (1.4%) of radiation-induced gastric bleeding when treating patients with esophageal cancer to a median dose of 50.4 Gy. Furthermore, this low rate was observed even though no significant attempt was made to restrict the volume of stomach included in the PTV or limit the radiation dose to stomach within PTV. Tumor progression, in fact, was a much more frequent cause of gastric bleeding. These results suggest that the standard dose of 50.4 Gy is safe for esophageal cancer, even if the PTV includes a significant portion of the stomach and the patient does not undergo surgical resection. These results also support the value of endoscopy to evaluate bleeding; otherwise, this may be erroneously attributed to radiation toxicity rather than tumor progression.

The only significant predictor of GB3+ was maximum stomach dose. Our results demonstrated that there was an increased risk of GB3+ only when stomach Dmax exceeded >58 Gy ($P \leq .05$). Dose-volume atlases of GB3+ generated from our data additionally demonstrate that dose may be more predictive than volume in determining the true probability of gastric bleeding (Fig 1). Together, these results suggest that 50.4 Gy is a safe dose for esophageal cancer and that limiting the maximum point dose to the stomach to <58 Gy may limit what is already a very rare incidence of radiation-induced gastric bleeding.

A limited number of previous studies have characterized the incidence of radiation-induced gastric toxicities in patients treated for gastrointestinal cancers, mainly in intrahepatic and pancreatic malignancies. These studies have reported an incidence of radiation-induced gastric bleeding higher than that of our patient cohort, ranging from 10.6%[5] to 18%.[7] A recent retrospective report

Table 3 Summary of radiation-induced grade >3 gastric bleeding events

	Patient A	Patient B
Age at diagnosis, y	72	61
Prescribed tumor dose, Gy	56	56
Tumor location	Distal esophagus	Distal esophagus
Tumor histology	Squamous cell carcinoma	Adenocarcinoma
Concurrent chemotherapy	Paclitaxel/capecitabine	Cisplatin/fluorouracil
Clinical stage at diagnosis	IIIA	IIIB
Other GI risk factors	Aspirin use	Cirrhosis, thrombocytopenia
Time to event, wk	124	17
Presentation	Symptomatic iron deficiency anemia	Anemia/melena
Treatment	Transfusion	Transfusion
Rebleed	No	Yes
Stomach max dose, cGy	5809	5840
Stomach mean dose, cGy	2511	2785
Stomach/PTV overlap	20	85
Stomach V40	47	178
Stomach V45	37	124
Stomach V50	25	83

Abbreviations: GE = gastroesophageal; PTV = planning target volume.

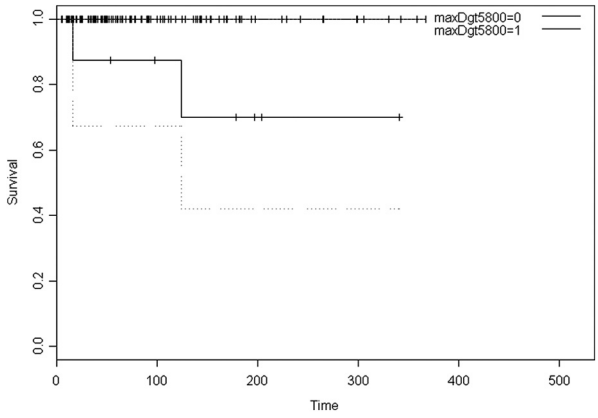

Figure 1 Freedom from grade >3 gastric bleeding events: patients split at max dose >58 Gy ($P < .05$; log-rank test).

analyzing the incidence of radiation-induced gastric toxicity for esophageal cancer specifically, however, found that although gastric mucosal damage was identified in 35% patients, only 3 of 256 (1.2%) patients experienced a grade >3 gastric toxicity.[14] That report, however, did not specifically evaluate stomach dosimetric parameters associated with the development of gastric toxicity. Together with our report, these data suggest a lower incidence of radiation-induced gastric bleeding after chemoradiation in patients with esophageal cancer versus those with intrahepatic and pancreatic

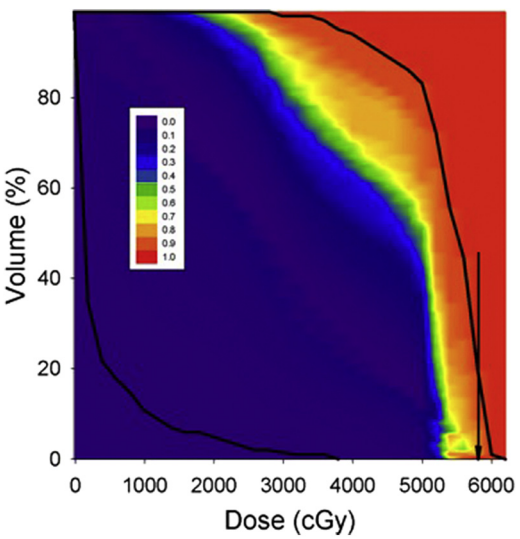

Figure 2 Color map of probability that true rate of grade >3 gastric bleeding event is >5%. Color coded map of probability that the true rate of grade ≥3 gastric hemorrhage is > 5% (for dose-volume histograms [DVHs] passing above the % volume and dose constraint at the colored point). Nine DVHs have Dmax >58 Gy (black arrow), 2 with complications, 134 have Dmax <58 Gy, none with complications. The black envelope represents the outer boundary of the treated DVHs. Colors above and below the envelope represent the a-priori probability in the absence of any data and the probability for the entire cohort, respectively.

malignancies, a difference for which an underlying mechanism should be explored.

We speculate that because radiation therapy for esophageal cancer involves irradiating the proximal stomach, as opposed to the distal stomach and duodenum as for hepatobiliary malignancies, different anatomic regions of the stomach may have different radiation tolerances. In a previous report analyzing dosimetric parameters associated with gastric bleeding in patients with pancreatic cancer, Nakamura et al found that V50 of a composite structure containing the stomach and duodenum was the best predictor of the development of radiation-induced gastric bleeding, compared with V50 of the stomach alone. Maximum dose to the stomach and stomach/duodenum, however, was not predictive of gastric complications in their patient cohort. In contrast to our results, they concluded that irradiating a lower volume of the stomach with a higher dose is safer than radiating a high volume of the stomach with a lower maximum dose.[7] Furthermore, 2 other previous reports found PTV size to be predictive of grade >3 toxicity in chemoradiation therapy for pancreatic cancer, although stomach DVHs were not analyzed.[8,9] These results suggest that the proximal stomach may have a higher tolerance to radiation-induced mucosal injury than the distal stomach.

Perhaps these findings could in part be explained by underlying histologic differences in corresponding anatomic regions of the stomach. The proximal fundus and body of the stomach contain oxyntic glands filled with parietal and chief cells responsible for acid secretion, and the distal antrum contains mucinous pyloric glands responsible for alkaline mucus and protein secretion.[15,16] Differentiated parietal and chief cells of the oxyntic glands have been shown to be more radiosensitive than mucus neck cells, thus supporting the hypothesis that the distal stomach may be more sensitive to radiation.[15]

It is also important to consider baseline risk factors for gastric bleeding events, especially when comparing patients undergoing radiation for esophageal or hepatobiliary malignancies. Both patients who experienced probable radiation-induced gastric bleeding in our patient cohort had well-known risk factors for gastric bleeding: NSAID use and cirrhosis. Liver cirrhosis is a known independent risk factor for gastric bleeding and has also been shown to be highly predictive of radiation-induced gastric bleeding in multiple previous studies. It has been shown that in the setting of liver cirrhosis, the gastric mucosa displays functional abnormalities, such as diminished mucus production and inhibited epithelial proliferation that limit its ability to heal, and the presence of portal hypertension further contributes to diminished healing of the gastric mucosa in these patients.[5,6] Perhaps this could, in part, explain the difference in time to gastric bleeding events in our 2 patients with radiation-induced gastric bleeding. The patient with cirrhosis and resultant thrombocytopenia experienced bleeding 17 weeks after

radiation, and the patient with NSAID use did not experience bleeding until 124 weeks after radiation (Table 3). Because cirrhosis is a common comorbidity in patients with primary intrahepatic malignancies, it must be adjusted for when comparing the incidence of radiation-induced gastric bleeding in these patients to those with esophageal cancer. In a previous study analyzing dosimetric factors associated with radiation-induced gastric bleeding in patients with intrahepatic malignancies, however, Feng et al found that maximum stomach dose was predictive of gastric bleeding, even when adjusted for the presence of cirrhosis.[6]

Although our study is the first to describe dosimetric parameters associated with gastric bleeding events in patients with esophageal cancer, it has notable limitations. As a retrospective, single-institution study, our results are from a small cohort of patients and may not be representative of the population as a whole. Only 2 patients had apparent radiation-induced bleeding events, so the proposed limit of stomach Dmax <58 Gy may be considered provisional and ideally should be validated in other data sets.

Another inherent limitation of such analysis is that stomach volume and dose measurements are subject to variability because the stomach can change position and shape anatomically and thus confound dose calculations. However, it was our practice to instruct patients to fast for 2 to 3 hours before treatment, and it is likely that over the course of 28 fractions and 5 to 6 weeks, daily variation in stomach position and filling would have been essentially random and therefore, on average, not likely to have systematically biased our dosimetric assumptions.

Additionally, our cohort of 145 patients was not entirely uniform. After excluding patients who underwent surgery, 77 of our patients were intended to receive definitive chemoradiation and 68 were intended to receive surgery but ultimately did not, typically because they either had a clinical complete response and declined surgery or because they were marginal candidates for surgery. Despite this heterogeneity, it seems unlikely that the specific reason for lack of surgery would change the risk of experiencing radiation-induced gastric bleeding events. We also note that it is not always clear at the outset whether a surgical candidate will remain a candidate after undergoing chemoradiation, and some surgical candidates decline surgery if they have achieved an apparent complete response to chemoradiation. Indeed, approximately half of the patients in our cohort were intended to receive preoperative radiation but never received surgery. This is why we prefer a dose 50.4 Gy regardless of definitive or preoperative intent and why it is important to understand the risk of gastric bleeding if the patient does not ultimately undergo surgery.

Finally, chemotherapy regimen or dose was not controlled or adjusted for in our analysis, and chemotherapy itself can be associated with gastrointestinal mucosal damage or have differing radiosensitizing effects depending on the exact regimens and doses chosen. Because there were very few RT-associated bleeding events, our data do not allow us to compare whether different chemotherapy regimens modify the risk of bleeding.

Our results have several important clinical implications. Most importantly, we found a very low incidence of radiation-induced gastric bleeding in a large cohort of patients with distal or GE junction tumors who received chemoradiation to a median dose of 50.4 Gy to a volume that included portions of the stomach. The fact that tumor progression was a more common cause of gastric bleeding after RT further suggests that deliberately limiting the volume or dose of stomach within the PTV would be counterproductive, given that symptomatic tumor progression in the stomach is more common than radiation-induced bleeding. We also suggest that radiation sensitivity of the stomach may differ according to the anatomic region, with the proximal stomach likely more radioresistant than the body or distal stomach.

Conclusions

Our results suggest that a dose of 50.4 Gy is safe for treatment of esophageal cancer even if the volume overlaps stomach and that there is no compelling reason to minimize the gastric volume or dose purely on the basis of preventing future bleeding events, particularly because tumor progression into the stomach was a more common cause for gastric bleeding. Practically, we suggest contouring and considering the proximal 2 cm of the stomach as esophagus for treatment planning purposes so that PTV coverage is not unduly compromised by dosimetric constraints on the stomach. This practice would also be consistent with the eighth edition American Joint Committee on Cancer definition of esophageal cancer, which recommends staging GE junction tumors as esophageal cancers if the epicenter of the tumor is no more than 2 cm beyond the GE junction.[17] Our dosimetric analysis does suggest that limiting maximum point doses to <58 Gy may prevent gastric bleeding events, however. Ultimately, additional study will be helpful to derive more robust dosimetric predictors of gastric toxicity, and to elucidate a potential difference in intrinsic radiosensitivity between different regions of the stomach.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2021.100648.

References

1. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol*. 2013;19:5598-5606.
2. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. *Clin Oncol*. 2002;20:1167-1174.
3. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21:109-122.
4. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725-730.
5. Chon YE, Seong J, Kim BK, et al. Gastroduodenal complications after concurrent chemoradiation therapy in patients with hepatocellular carcinoma: Endoscopic findings and risk factors. *Int J Radiat Oncol Biol Phys*. 2011;81:1343-1351.
6. Feng M, Normolle D, Pan CC, et al. Dosimetric analysis of radiation-induced gastric bleeding. *Int J Radiat Oncol Biol Phys*. 2012;84:e1-e6.
7. Nakamura A, Shibuya K, Matsuo Y, et al. Analysis of dosimetric parameters associated with acute gastrointestinal toxicity and upper gastrointestinal bleeding in locally advanced pancreatic cancer patients treated with gemcitabine-based concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;84:369-375.
8. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2007;68:801-808.
9. Ito Y, Okusaka T, Kagami Y, et al. Evaluation of acute intestinal toxicity in relation to the volume of irradiated small bowel in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. *Anticancer Res*. 2006;26:3755-3759.
10. Wu AJ, Bosch WR, Chang DT, et al. Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer. *Int J Radiat Oncol Biol Phys*. 2015;92:911-920.
11. Mohan R, Barest G, Brewster LJ, et al. A comprehensive three-dimensional radiation treatment planning system. *Int J Radiat Oncol Biol Phys*. 1988;15:481-495.
12. Jackson A, Yorke ED, Rosenzweig KE. The atlas of complication incidence: A proposal for a new standard for reporting the results of radiotherapy protocols. *Semin Radiat Oncol*. 2006;16:260-268.
13. Katsoulakis E, Jackson A, Cox B, Lovelock M, Yamada Y. A detailed dosimetric analysis of spinal cord tolerance in high-dose spine radiosurgery. *Int J Radiat Oncol Biol Phys*. 2017;99:598-607.
14. Monma S, Kato K, Shouji H, et al. Gastric mucosal injury and hemorrhage after definitive chemoradiotherapy for locally advanced esophageal cancer. *Esophagus*. 2019;16:402-407.
15. Schubert M, Peura D. Control of gastric acid secretion in health and disease. *Gastroenterology*. 2008;134:1842-1860.
16. Feldman M, Friedman LS, Brandt LJ. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology Diagnosis, Management. Chapter 51: Gastritis and gastropathies*. 9th ed. Philadelphia, PA: WB Saunders; 2015:857.
17. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. *J Thorac Oncol*. 2017;12:36-42.