

## RADIATION DOSE–VOLUME EFFECTS IN THE STOMACH AND SMALL BOWEL

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**Published data suggest that the risk of moderately severe ( $\geq$ Grade 3) radiation-induced acute small-bowel toxicity can be predicted with a threshold model whereby for a given dose level, D, if the volume receiving that dose or greater (VD) exceeds a threshold quantity, the risk of toxicity escalates. Estimates of VD depend on the means of structure segmenting (e.g., V15 = 120 cc if individual bowel loops are outlined or V45 = 195 cc if entire peritoneal potential space of bowel is outlined). A similar predictive model of acute toxicity is not available for stomach. Late small-bowel/stomach toxicity is likely related to maximum dose and/or volume threshold parameters qualitatively similar to those related to acute toxicity risk. Concurrent chemotherapy has been associated with a higher risk of acute toxicity, and a history of abdominal surgery has been associated with a higher risk of late toxicity. © 2010 Elsevier Inc.**

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### 1. CLINICAL SIGNIFICANCE

The stomach and small bowel are contiguous, hollow visceral digestive organs. The stomach produces gastric acid and other factors that convert ingested food products into absorbable nutrients and initiate peristaltic activity. There is less absorption of nutrients in the stomach than in the small bowel. The small bowel has three sections (the duodenum, jejunum, and ileum) with a large surface area through which water, carbohydrates, amino acids, and lipids are absorbed into the portal circulation.

The stomach and small bowel are often incidentally irradiated when targeting tumors in the upper gastrointestinal (GI) tract, inferior lung, and retroperitoneum. The small bowel is also incidentally irradiated during radiation therapy (RT) to the pelvis.

### 2. ENDPOINTS

Nausea and vomiting can occur immediately or within hours after RT to the stomach or small bowel. Days to weeks after the first treatment, RT-induced injury to the stomach ranges from self-limited mucosal inflammation causing dyspepsia to ulceration and bleeding that can be life threatening. RT-induced small-bowel mucositis can be expressed as

cramping and diarrhea from interference with nutrient absorption, typically developing 1 to 2 weeks after the start of RT. Weight loss can be a secondary consequence.

The small bowel is also susceptible to late obstruction occurring weeks or months post-RT. In the bowel walls, RT-induced fibrosis can cause adhesions that limit bowel mobility and obstruct flow through the gut, sometimes requiring emergency surgery.

Symptoms of chronic post-RT stomach injury may include long-term dyspepsia and ulceration (1). Chronic small-bowel injury from RT can include persistent diarrhea. In addition to obstruction, late small-bowel injury can manifest as ulceration, fistula, perforation, and bleeding. Although a majority of symptoms occur within 3 years post-RT, patients remain at risk indefinitely. Patients who recover from initial complications are also at risk for future complications. Malabsorption of nutrients can occur as a late effect of RT, though the dose–volume associations for this are not well characterized (2).

The Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, grade numerous types of GI toxicity. In general, Grade 1 toxicities are radiographic findings of negligible clinical

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consequences and are rarely scored in reports of RT-induced toxicity. Grade 2 to 4 toxicities generally reflect injury of moderate, severe, or life-threatening severity, respectively.

### 3. CHALLENGES IN DEFINING VOLUMES

The stomach is a thick-walled muscular organ with a volume of 1.5 to 2 L in adults. Although the stomach usually is easily seen on treatment planning scans, oral contrast can aid in its definition. The stomach wall can vary in position based upon its contents. To minimize variability in the volume and location of the stomach, patients should avoid large meals or carbonated beverages before simulation and treatment.

It is sometimes challenging to differentiate small bowel from vessels, nodes, and large bowel on planning CT images. Although oral contrast given before imaging can aid visualization, high-density contrast can affect dose calculations that account for tissue heterogeneity. If treatment beams pass through contrast-containing small bowel seen on the planning CT, one option is to calculate dose without heterogeneity correction; a medical physicist should be involved in the planning process when there is uncertainty regarding the overall impact of heterogeneity correction in this setting. Alternatively, some planning systems allow for contrast to be segmented as a structure that can be assigned water density, thus still allowing for heterogeneity correction that accounts for other structures of variable density (*e.g.*, bone or lung) present within treatment fields. Different methods of delineating the small-bowel volume have contributed to variant dose-toxicity relationship observations, as discussed later here.

Except for sections of the small bowel that are largely immobile (*e.g.*, duodenum and regions with postsurgical adhesions), there are day-to-day variations in the bowel location. The capacity for small-bowel mobility within the peritoneal space may be constant throughout a course of conventionally fractionated treatment (3). Martin *et al.* observed that relative to supine, a prone position with a belly board significantly reduced the volume of small bowel receiving 80% to 100% of the prescribed dose during pelvic treatment for gynecologic cancer (4).

### 4. REVIEW OF DOSE-VOLUME DATA

Emami *et al.* estimated doses with a 5% or 50% risk at 5 years (TD5/5 and TD50/5, respectively) for late stomach or small-bowel toxicities but did not offer estimates to predict acute toxicities (5). The TD 5/5 estimate for gastric ulceration or perforation after whole-organ irradiation, 50 Gy, has endured as a broad dose limit guideline when fields encompass a large portion of stomach, albeit with rather limited support from actual published data. The TD50/5 estimate for irradiation of the entire stomach (65 Gy) is entirely unchallenged, likely because there are few scenarios in which a dose of that magnitude is administered to the stomach—except possibly for a primary unresectable gastric malignancy, in which case the effects of the tumor itself would render separate evaluation of normal tissue toxicity problematic.

The TD5/5 estimate for 1/3 small-bowel irradiation, 50 Gy, remains a commonly applied dose limit when small portions of the small bowel are treated with conventional fractionation, and recently published data are fairly consistent with this estimate. The TD50/5 estimate for partial small-bowel irradiation, 60 Gy, is largely unchallenged, as are the whole-organ irradiation TD5/5 and TD50/5 estimates (40 Gy and 55 Gy, respectively). In this section, the available data relating RT dose to acute and late toxicity risk are reviewed.

#### *Acute RT-induced toxicity to the stomach*

Very few published experiences allow for the separation of acute effects on the stomach alone from combined stomach/small-bowel effects. A Japanese study of patients with stomach lymphoma treated with cytoxan, daunorubicin, vincristine, and prednisone followed by 40.5 Gy to the primary site and regional nodes yielded a 4% (2/52) rate of Grade  $\geq 3$  acute nausea (6). No hemorrhage or perforation of the stomach was reported. In the Gastrointestinal Tumor Study Group (GITSG) study of unresectable pancreatic cancer, patients receiving 60 Gy AP-PA RT had a 36% incidence of nausea (grade not specified). Volumetric data regarding the portion of stomach included in the fields are not reported. Adding intravenous 5-FU increased the nausea incidence to 48% (7).

In a randomized clinical trial of 8 Gy single fraction lower hemi-body RT (including stomach), Sykes *et al.* observed a 66% rate of moderate-severe nausea with dexamethasone and chlorpromazine vs. a 6% rate with ondansetron (8 mg *p.o.* 1 to 2 h pre-RT and maintenance dose of 8 mg *p.o. b.i.d.*) (8). In a more recent Canadian study of patients receiving  $\geq 20$  Gy in  $\geq 15$  fractions to an area of  $\geq 80$  cm<sup>2</sup> (in the coronal plane) from T11 to L3 (inclusive), adding dexamethasone to ondansetron improved complete nausea control rates compared to ondansetron alone (23% vs. 12%,  $p = 0.02$ ) and lowered average nausea scores ( $p = 0.03$ ) (9). Stomach and small bowel dose-volume histograms were not reported.

#### *Late radiation-induced toxicity to the stomach*

Early reports include the analysis of testicular cancer patients treated with para-aortic RT at Walter Reed Army Medical Center in the 1940s and 1950s (10). The volume of stomach in the field was not quantified. The gastric ulceration rates were 4% (6/161) vs. 16% (9/56) after doses <50 Gy vs.  $\geq 50$  Gy. Likewise, the perforation rates were 2% (3/161) vs. 14% (8/56) after doses <50 Gy vs.  $\geq 50$  Gy.

Cosset *et al.* reported late gastric complications (ulcer of stomach/duodenum, severe gastritis, obstruction) in European Organization for Research and Treatment of Cancer (EORTC) trials of RT for Hodgkin's disease (11). Among 516 patients treated, severe toxicities included the following: ulcers ( $n = 25$ ), severe gastritis ( $n = 2$ ), and small-bowel obstruction and/or perforation ( $n = 9$ ). Nearly all patients received close to 40 Gy. Among 345 patients receiving 39 to 41 Gy over 5 weeks, patients with higher fraction sizes were more likely to develop complications (4% after weekly

doses of  $5 \times 2$  Gy, 9% after  $4 \times 2.5$  Gy, and 22% after  $3 \times 3.3$  Gy). There was no documentation of the volume of stomach irradiated.

Goldstein *et al.* noted radiological abnormalities of the distal stomach in 8% (10/121) of women 1 to 25 months after 50 Gy to the para-aortic nodes for metastatic cervix cancer (12). The lesions were all ulcers in or near the pylorus; only two required surgical intervention. In addition, 1 of 52 men who received 40 to 50 Gy of para-aortic nodal RT for testicular tumors developed gastric outlet obstruction secondary to a pyloric ulcer 3 months later.

The effect of adding chemotherapy to RT on late toxicity is uncertain. Cohen *et al.* reported only 1 Grade 3 GI toxicity in 104 patients treated to 59.4 Gy to a pancreatic tumor with 2-cm margin; half of the patients also received 5-FU and mitomycin-C (13). However, median overall survival was <9 months and thus was possibly not long enough for some late toxicity to appear. Talamonti *et al.* observed an unacceptable rate of gastric and duodenal ulcers from RT to the pancreatic tumor plus a 2-cm margin with weekly concurrent gemcitabine ( $50 \text{ mg/m}^2$  per week) and protracted intravenous 5-fluorouracil (5-FU;  $200 \text{ mg/m}^2$  per day) (14). Others have reported no difference between toxicity observed with RT plus 5-FU vs. RT plus gemcitabine alone ( $600 \text{ mg/m}^2$  weekly  $\times 6$ ) (15), which was the regimen used in a Eastern Cooperative Oncology Group (ECOG) study (16). Using a higher dose of weekly gemcitabine ( $1,000 \text{ mg/m}^2 \times 3$ ) concurrent with 36 Gy in 15 fractions for unresectable pancreas cancer, Murphy *et al.* reported an 8% incidence of upper GI bleeding as a late complication. Patients with the larger PTVs (>260 cc) were at higher risk of severe acute or late toxicity than were patients with smaller PTVs (17).

Thus, for the stomach, a dose on the order of 50 Gy has been associated with a 2% to 6% risk of clinical severe late injury, generally concordant with the Emami *et al.* whole organ TD5/5 estimate. The effect of stomach volume is not well characterized.

#### *Acute RT-induced toxicity to the small bowel*

A literature review for small-bowel complications (diarrhea, obstruction or constriction, fistula or perforation, ulceration) yielded six studies with quantitative dose–volume analyses (Table 1). In each study, either all or a majority of patients received concurrent chemotherapy, and thus each modality's independent contribution on toxicity is unknown. The major observations are shown in the table (see Mathematical/Biological Models section for further discussion of the threshold model).

Concurrent chemotherapy adds to RT-induced acute small-bowel toxicity. In a Gynecologic Oncology Group study, cervix cancer patients who received 45 Gy pelvic RT alone experienced a 5% (9/186) rate of Grade 3 to 4 GI toxicity vs. 14% (26/183) from RT plus weekly cisplatin ( $40 \text{ mg/m}^2$ ) (24). Macdonald *et al.* observed a 33% (89/273) rate of Grade  $\geq 3$  acute toxicity (nausea, vomiting, and diarrhea) from an initial cycle of 5FU ( $350 \text{ mg/m}^2/\text{day}$  for 5 days) + leucovorin followed by 5FU + leucovorin con-

current with 45 Gy postoperative RT for carcinoma of the stomach or gastroesophageal junction (25). This higher rate is possibly caused by a larger volume of small bowel in the field; the incidence of Grade 3 events in the group that received no adjuvant therapy was not reported. In the EORTC study comparing preoperative RT (45 Gy) vs. the same plus two cycles of 5-FU, diarrhea of Grade  $\geq 2$  occurred in 17% of patients after RT alone and in 38% of patients after chemotherapy + RT ( $p < 0.001$ ) (26). However, for rectal cancer acute effects on large bowel are difficult to distinguish from effects on small bowel.

#### *Late RT-induced toxicity to the small bowel*

Mak *et al.* reviewed 224 rectal cancer patients treated with a median dose of 54 Gy (34–66 Gy) at 1.8 to 2 Gy/fraction; 29 developed small-bowel obstructions 0 to 69 months (median, 7 months) later (27). The small-bowel obstruction rate was 30% in patients treated with fields extending to L1 or L2 vs. 9% with pelvis-only fields. Small-bowel obstruction was higher in the presence of postsurgical adhesions before RT and in the absence of reperitonealization at the time of initial surgery ( $p < 0.05$ ).

Hamilton *et al.* observed a 5% rate of duodenal ulceration in 142 patients treated for Stage I teratoma (28). The RT dose was primarily 40 Gy in 20 fractions (range, 30–51 Gy). Detailed dose–volume analysis was not reported.

The Uppsala University rectal cancer study compared preoperative pelvic RT, 25.5 Gy delivered in five fractions, vs. 60 Gy in 7 to 8 weeks of split-course postoperative RT, with a reduced field for the last 10 Gy (29). Some patients did not have RT. At a minimum follow-up of 5 years, a surgical or radiographic diagnosis of small-bowel obstruction was made in 5% of patients (14/255) after preoperative RT, 11% (14/127) after postoperative RT, and 6% (5/82) after surgery alone.

The Swedish and Dutch randomized rectal trials evaluated preoperative pelvic RT (25 Gy in 5-Gy fractions in 1 week) followed by surgery (30–32). The Swedish trial involved larger treatment fields (superior border, L4) than the Dutch trial (sacral promontory). In the Dutch trial, RT increased rates of fecal incontinence, need for pad wearing, bleeding, and dissatisfaction with bowel function. However, bowel obstruction rates were the same (11%) with or without preoperative RT (30). Long-term follow-up of the Swedish trial patients, by contrast, showed that preoperative RT increased the risk of small-bowel obstruction (14-year actuarial risk 14% vs. 6% in controls,  $p < 0.001$ ) (33).

Bujko *et al.* noted that short-course preoperative RT (25 Gy in 5 fractions in 1 week) and concurrent preoperative RT/chemotherapy (50.4 Gy in 28 fractions with concurrent 5-FU + leucovorin) were associated with a 5% and 1% rate of Grade  $\geq 3$  late GI toxicity (ileus, fistula, or anastomotic stenosis), respectively (median follow-up, 48 months) (34). In the Phase III German Rectal Cancer Study Group (35), pre- vs. postoperative pelvic RT (50.4 Gy in 28 fractions) were associated with a 9% vs. 15% rate of long term GI toxicity ( $p = 0.07$ ). This difference was primarily from chronic

Table 1. Quantitative analyses of acute small bowel toxicity

Authors, Reference, No. of patients	Primary cancer	Prescription dose (Gy)	Observed predictor of toxicity
Baglan <i>et al.</i> (18) (N = 40)	Rectal	45–50	Threshold volume at given doses
Roeske <i>et al.</i> (19) (N = 50)	Cervix	45	Absolute small bowel volume (peritoneal space) receiving 45 Gy
Tho <i>et al.</i> (20) (N = 41)	Rectal	45	Absolute small bowel volume receiving 5–40 Gy
Huang <i>et al.</i> (21) (N = 80)*	Cervix, endometrial	39.6–45	Absolute small bowel volume: > 16 Gy (prior surgery) >40 Gy (no prior surgery)
Robertson <i>et al.</i> (22) (N = 96)	Rectal	45–50	Baglan threshold model doses (see Fig. 1)
Gunnlaugsson <i>et al.</i> (23) (N = 28)	Rectal	50	Absolute small bowel volume >15 Gy

\* All studies were retrospective except Huang *et al.*, which was prospective. In all cases the fractionation scheme involved 1.8 to 2.0 Gy per day prescription dose. Most of the studies used concurrent 5-fluorouracil (5FU)-based chemotherapy except for cisplatin alone in the Roeske *et al.* study, 5FU + cisplatin in Huang *et al.*, and 5FU + oxaliplatin in Gunnlaugsson *et al.* In the Huang *et al.* study, 30 patients did not receive chemotherapy.

diarrhea; the rate of small-bowel obstruction requiring reoperation was small and not statistically significantly different between groups (2% vs 1%,  $p = 0.70$ ).

Thus, in modern series, after doses on the order of 50 Gy, late small-bowel obstruction or perforation rates of 2% to 9% have been observed after partial organ irradiation, concordant with the Emami *et al.* TD5/5 estimate. A dose of 25 Gy in five fractions of preoperative RT is associated with late toxicity within that same range.

## 5. FACTORS AFFECTING RISK

The effect of concurrent chemotherapy to increase acute toxicity is discussed above. Prior abdominal surgery, generally causing some scar tissue in the peritoneal cavity, can predispose a patient to small-bowel obstruction from RT. In the EORTC Hodgkin's disease trials, the late gastrointestinal complication rate was 2.7% without prior abdominal surgery and 11.5% after prior laparotomy (11).

## 6. MATHEMATICAL/BIOLOGICAL MODELS

Pan *et al.* reported gastric bleeds after hyperfractionated RT in 12 of 92 patients with liver tumors (36). Median time to bleeds was 3.5 months (range, 1–8 months). Mean dose to the stomach averaged 14 Gy (range, 0.1–68). The minimum dose to the 1 cc receiving the highest dose averaged 47 Gy (range, 0.30–93). Using the Lyman-Kutcher-Burman (LKB) model, the parameters TD50(1),  $m$ , and  $n$  were estimated to be 59 Gy, 0.30, and 0.09, respectively, consistent with a dose threshold for bleeding without a large volume effect. Multivariate analysis demonstrated that in addition to NTCP, the maximum dose to stomach and presence of cirrhosis were significantly associated with gastric bleed. Cirrhotic and noncirrhotic patients had an estimated 5% risk of bleeding if the maximum stomach dose was at least 6.8 Gy or 47.9 Gy, respectively.

Baglan *et al.* generated a threshold-type model of acute small-bowel toxicity in an analysis of patients treated for rectal cancer (18). A significant association between Grade 3 acute toxicity and absolute volume of small bowel irradiated was found at each dose level, analyzed in 5-Gy bins. Baglan *et al.* identified V15 as an especially important parameter: for

patients without Grade 3 toxicity, the mean V15 was 127 cc, whereas for patients who had Grade 3 toxicity the mean V15 was 319 cc ( $p < 0.001$ ). Other patient-related factors were statistically insignificant, including the sequence of RT and surgery. The model was later validated by Robertson *et al.* in a second cohort of patients (22).

In essence, the Baglan–Robertson model predicts a low risk (~10%) of Grade  $\geq 3$  acute small-bowel toxicity for patients whose absolute volumes of small bowel receiving 5 to 40 Gy (V5–V40) are below the curve shown in Fig. 1. Patients whose V5 to V40 values are above the curve have a higher (~40% risk) of Grade  $\geq 3$  toxicity.

Quantitatively concordant with the Baglan–Robertson model are two of the studies in Table 1. Gunnlaugsson *et al.* observed a point threshold effect whereby patients with an absolute V15 < 150 cc experienced a low risk (1/9) of Grade  $\geq 2$  acute toxicity vs. a higher risk (10/19) for V15  $\geq 150$  cc (23). The V15 cutoff in the Baglan–Robertson model was 120 cc. Likewise, results from Tho *et al.* support the Baglan–Robertson model: among 41 patients studied, the absolute small-bowel volumes determined at 5-Gy dose intervals (V5–V40 and  $V > 42.75$ ) correlated strongly with diarrhea severity at every dose level ( $p < 0.03$ ), with the strongest correlation at low doses (20). All other patient-related factors in the analysis were statistically insignificant.

Huang *et al.* evaluated small-bowel volumes at 10% intervals of the prescribed dose and observed volume dependence for toxicity largely consistent with the Baglan–Robertson model (21). Among patients without prior abdominal surgery, the mean V16 for those with acute Grade 2 to 3 toxicity was 489 cc, vs. 281 cc for those without toxicity ( $p = 0.001$ ). Likewise, for patients with prior surgery, the mean V40 was higher in those with Grade 2 to 3 toxicity vs. without (132 cc vs. 56 cc,  $p = 0.027$ ).

Quantitatively but not qualitatively different from the Baglan–Robertson model are the observations of Roeske *et al.*, who derived a similar volume threshold-based risk model (19). The Roeske *et al.* curve, however, contained y-axis (absolute volume) values several times greater than those of the Baglan–Robertson model for each dose level along the x-axis. The discrepancy is explained by the methods of delineating small bowel: Roeske *et al.* outlined the entire potential

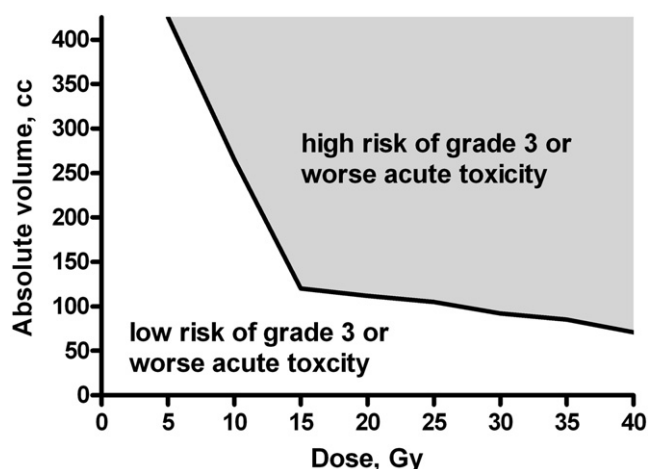


Fig. 1. Graphic representation of the Baglan–Robertson threshold model for risk of acute small bowel toxicity. Here, “low risk” implies  $\sim 10\%$  and “high risk”  $\sim 40\%$ . Note that the y-axis represents the absolute volume of individual bowel loops and not the peritoneal space.

space of small-bowel location, whereas Baglan and Robertson outlined only actual bowel loops. The Roeske volume constraints indicate that peritoneal cavity volume (small-bowel surrogate) above the prescription dose (45–50 Gy) should be held to  $<195$  cc.

Chen *et al.* assessed acute small-bowel toxicity in two cohorts of post-hysterectomy cervix cancer patients receiving adjuvant pelvic RT plus concurrent cisplatin ( $50 \text{ mg/m}^2$  weekly  $\times 6$ ) (37). The first 35 patients received conventional four-field box RT, and the next 33 patients received IMRT, in all cases to 50.4 Gy in 1.8-Gy/fractions. Acute GI toxicity was reduced with IMRT, which halved the small-bowel volume receiving 35 Gy, a result concordant with the threshold model concept.

All of the previously mentioned work pertains to predictions of acute toxicity. Letschert *et al.* related dose–volume parameters to late small-bowel complications (38). In 111 patients who received pelvic and/or para-aortic RT to a dose of 45 to 50 Gy over 5 weeks, the incidence of late toxicity was related to the volume of bowel within the field. The lowest risk group (three-field pelvic RT, estimated 165 cc of small bowel) had a 6% incidence of severe late toxicity, whereas the highest risk group (opposed anterior and posterior treatment fields, estimated 790 cc) had a 37% risk. The authors modeled complication risk as a power law function of volume that predicted isotoxicity for each doubling of the volume of bowel in the field if the RT dose was reduced by 17%.

## 7. SPECIAL SITUATIONS

Most published clinical data involve conventionally fractionated treatment with daily prescription doses to the tumor of approximately 2 Gy or less. Current interest in stereotactic body radiation therapy (SBRT) raises questions about the extent to which observations based on low dose per fraction

are applicable to SBRT, where the daily dose to the tumor is on the order of  $\geq 10$  Gy.

Hoyer *et al.* reported toxicities in 64 patients treated with SBRT to liver metastases (45 Gy in three fractions over 5–8 days) (39). With a median follow-up of 4.3 years, one colonic perforation and two duodenal ulcerations were noted. In all three cases, portions of the bowel received a total dose of  $\geq 30$  Gy in three fractions. Koong *et al.* treated 16 patients with locally advanced pancreatic cancer using concurrent 5-FU and RT to 45 Gy in 1.8 Gy fractions, followed by a single-fraction 25-Gy SBRT boost (40). Two patients (12.5%) developed duodenal ulcers 4 to 6 months later. Schellenberg *et al.* later reported on 16 patients receiving SBRT (25-Gy single fraction) alone between Cycles 1 and 2 of gemcitabine for pancreas cancer (41). The volume of small bowel receiving  $>12.5$  Gy was  $<30$  cc and  $>30$  cc for patients without and with late toxicity, respectively ( $p = 0.13$ ). A more recent analysis of a larger cohort, from the same institution, of 77 patients treated with 25 Gy single fraction SBRT (16 had 45 Gy external-beam RT also) included the constraints applied (42). For the stomach,  $<4\%$  of volume could receive  $>22.5$  Gy, and the 50% isodose line should not reach the nonadjacent luminal wall. For the small bowel (duodenum),  $<5\%$  received  $>22.5$  Gy, and  $<50\%$  received  $>12.5$  Gy, again not allowing the 50% isodose line to reach the opposite luminal wall. These constraints were associated with a 9% (7/77) crude rate of late stomach or duodenal toxicity.

Hoyer *et al.* observed a higher rate of late toxicity after SBRT (45 Gy in three fractions) for pancreatic cancer: 4 of 22 patients experienced severe mucositis or ulceration of the stomach or duodenum, and 1 of 22 had a nonfatal stomach perforation (43). A dose–volume effect likely explains the observations of these investigators to a large extent; in the Hoyer *et al.* study, the median volume receiving  $\geq 30$  Gy was 136 cc, notably higher than in the Schellenberg *et al.* trial.

After single-fraction high-dose-rate brachytherapy for liver cancers, Streitparth *et al.* found a threshold dose to the 1 ml receiving the highest dose (D1 ml) of 11 Gy for general gastric toxicity and 15.5 Gy for ulceration. Among patients with D1 ml  $> 15.5$  Gy, 5 of 13 patients experienced gastric ulceration, versus none for D1 ml  $< 15.5$  Gy (44).

## 8. RECOMMENDED DOSE/VOLUME LIMITS

Literature on RT-induced stomach toxicity is relatively sparse, with insufficient data to arrive at firm dose–volume constraints for partial volume irradiation. Doses of RT on the order of 45 Gy to the whole stomach are associated with late effects (primarily ulceration) in approximately 5% to 7% of patients. Emerging data suggest that the maximum point dose might be an important predictor of toxicity, but corroborating data are needed to confirm this hypothesis. For SBRT, the volume of stomach receiving  $>22.5$  Gy should be minimized and ideally constrained to  $<4\%$  of the organ volume, or approximately 5 cc, with maximum point dose  $<30$  Gy for three-fraction SBRT.

The absolute volume of small bowel receiving  $\geq 15$  Gy should be held to  $<120$  cc when possible to minimize severe acute toxicity, if delineating the contours of bowel loops themselves. Alternatively, if the entire volume of peritoneal space in which the small bowel can move is delineated, the volume receiving  $>45$  Gy should be  $<195$  cc when possible. Such a limit likely also reduces late toxicity risk, although this correlation is not established. The volume of small bowel receiving higher doses should also be minimized. For SBRT, the small-bowel volume receiving  $>12.5$  Gy in a single fraction should ideally be kept to  $<30$  cc with avoidance of circumferential coverage above that dose; for a three- to five-fraction regimen, the maximum point dose should be  $<30$  Gy.

## 9. FUTURE TOXICITY STUDIES

The body of literature relating RT dose to risk of stomach/small-bowel toxicity is small compared with the amount of data published on RT effects in some other organs. The widespread use of computed tomography-based treatment plan-

ning should allow expansion of this literature. In addition, the impact of systemic agents on RT-induced stomach and small-bowel toxicity needs to be understood more completely. Characterizing the molecular events of RT-induced stomach and small-bowel injury might reveal opportunities for injury mitigation by modulation of key signaling pathways.

## 10. TOXICITY SCORING

Acute and late RT-induced stomach and small-bowel injury scoring should measure nausea, diarrhea, obstruction, bleeding/ulceration, weight loss, and fistulae. The Common Terminology Criteria for Adverse Events v3.0 (CTC AE v3.0) provides a framework to capture data regarding the timing and severity of symptoms. Patient-reported outcomes should also be used when possible. General nutrition surrogates such as weight or albumin might also serve as markers of RT-induced GI toxicity.

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