13

Critical Normal Tissue and Radiation Injury: The Stomach

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1. Introduction

There is limited detailed information regarding morbidity and toxicity following radiation treatment in gastric cancer. The curative effectivity of external radiotherapy necessitates exposure of normal tissues with significant radiation doses, and hence must be associated with an accepted rate of side effects. Based on the time of first treatment, complications can range from the acute side effects of external beam radiation therapy which resolve shortly after treatment to those that develop 6 months to 2 years after completion radiotherapy.

2. An outline of anatomy and normal histology of the stomach

2.1 Anatomy

Anatomically stomach is divided into 4 regions: the cardiac region is surrounded by esophageal sphincter. The fundus lies against the diaphragm.Body (corpus) ensue from fundus and pylorus (pyloric antrum): ends at the pyloric sphincter which is a thickening of the muscle walls. (figure 1 et 2)

2.2 Types of cells present in the stomach

Mucous secreting cells (goblet cells) line the luminal surface of the stomach and gastric pits and gastric glands which produce mucus and bicarbonate. Mucous neck cells are present in the neck of the gland andproduce mucin. Parietal cells (oxyntic cells) are distributed throughout the length of the gland, but numerous in the middle portion. Large, rounded cells with eosinophilic cytoplasm and centrally located nucleus. Chief cells (peptic or zymogenic cells) produce gastric acid. They are clustered at the base of the gland and identified by basally located nuclei and strongly basophilic granular cytoplasm. They produce pepsinogen, which digests protein.

2.3 Normal histological features

The gastric mucosa consists of surface epithelium, gastric pits and gastric glands. The gastric glands extend from the muscular mucosae to extend into the stomach lumen via gastric

pits.The foveolar cells lining the surface and gastric pits are identical throughout the stomach. Glands differ in different regions of the stomach. Gastric pits occupy approximately 25% of the mucosa. Pits lie parallel to one another. These are separated by the lamina propria. There is more lamina propria separating the pits than between the glands. In normal gastric biopsy, degree of pit and glandular separation should be same throughout the biopsy. Cardia is a small area of predominantly mucus secreting glands surrounding the entrance of the esophagus. Glands are less coiled than in the antralglands.The pits are shorter than the antropyloric pits.Fundus and body are a major histological region consisting of straight, tubular glands. Strands of muscularis mucosae extend between the glands from the base. The glands secrete gastric juices as well as protective mucus. In pylorusbranched glands open into deep irregular shaped pits and are composed of mucus secreting cells. Mucus secreted by pyloric glands lubricate and protect entrance to the duodenum.Scattered 'G' cells (endocrine cells), secrete gastrin. Gastric mucosa forms a barrier todiffusion of gastric acid from the gastric lumen.The fundus is best seen by inverting the gastroscope to see the dome-shaped upper portion of the stomach.When the patient is lying on the left side, the gastric juice is seen to the left in the fundus, called "the mucous lake".

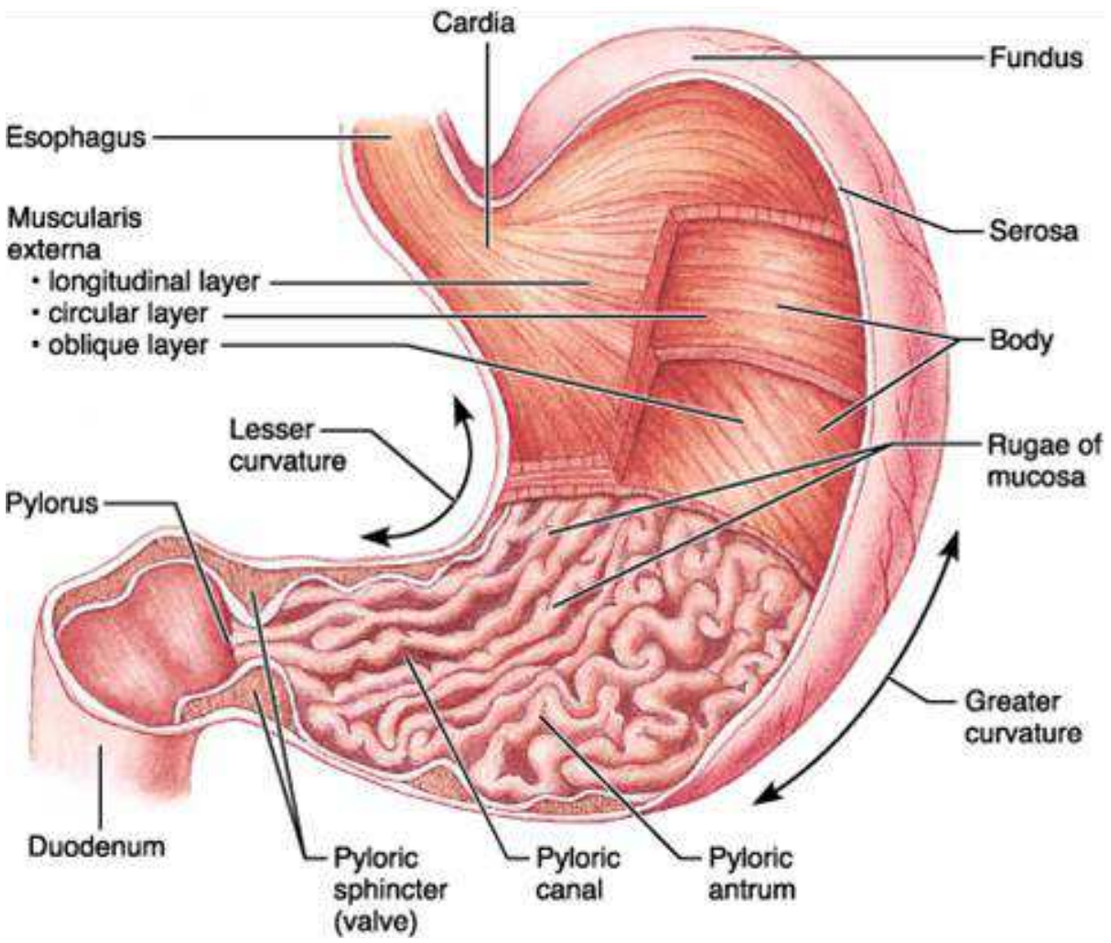

Fig. 1. The anatomy of the human stomach

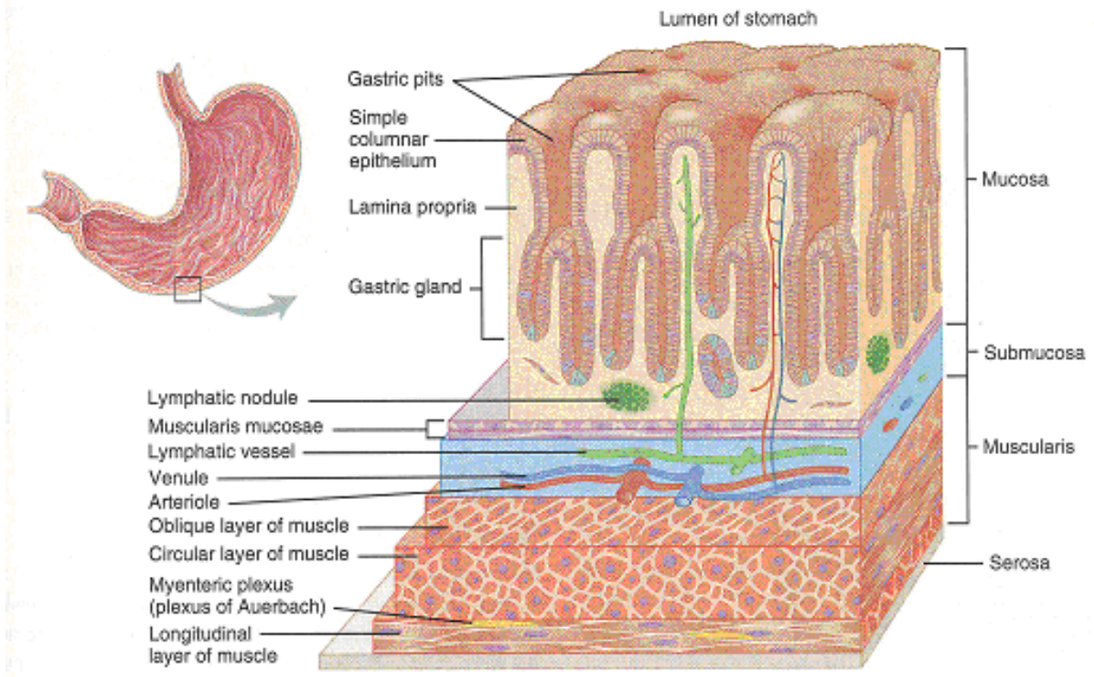

Fig. 2. Histology of the stomach. a three-dimensional view of layers of the stomach

3. Critical normal tissue

Early reactions per definition occur within 90 days after onset of the radiation exposure. They are based on impairment of cell production in turnover tissues, which in face of ongoing cell loss results in hypoplasia and eventually a complete loss of functional cells. The latent time is largely independent of dose and is defined by tissue biology (turn-over time). Usually, complete healing of early reactions is observed. Late radiation effects can occur after symptom-free latent times of months to many years, with an inverse dependance of latency on dose. Late normal tissue changes are progressive and usually irreversible. They are based on a complex interaction of damage to various cell populations (organ parenchyma, connective tissue, capillaries), with a contribution from macrophages. Late effects are sensitive for a reduction in dose rate (recovery effects). A number of biologically based strategies for protection of normal tissues or for amelioration of radiation effects was and still is tested in experimental systems, yet, only a small fraction of these approaches has so far been introduced into clinical studies. Published data suggest that the risk of moderately severe (>or=Grade 3) radiation-induced acute small-bowel, pulmonary or others organs 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. One advantage of most of the methods is that they may be effective even if the treatment starts way after the end of radiation exposure. For a clinical exploitation, availability of early indicators for the progression of subclinical damage in the individual patient would be desirable. Moreover, there is need to further investigate the molecular pathogenesis of normal tissue effects in more detail, in order to optimise biology based preventive strategies, as well as to identify the precise mechanisms of already tested approaches (e.g. stem cells).

3.1 Radiation tolerance (radiation gastritis)

Any discussion about the use of radiation therapy in the treatment of any cancer with critical normal tissue than stomach must prefaced by a description of the radiotolerance of stomach. It is commonly held that there is a low risk of gastritis or ulcer if the whole stomach receives less than 45Gy with a classic fractionation (1.8Gy or 2 Gy once a day 5 times per week).In the rat after irradiation with single doses, three distinct gastric disorders were observed which occurred at different latency times. Acute death 2–3 weeks after irradiation was caused by ulcerative gastritis and occurred in all animals given 28.5 Gy without diet, in 17% of the animals given 28.5 Gy plus diet, and in 13% of the animals given 23 Gy. Subacute to chronic fatal disorders 4 weeks to 7 months after irradiation were seen as stomach dilatation and gastroparesis, associated with the replacement of the normal gastric mucosa by a hyperkeratinized multilayered squamous epithelium(Breiter et al1989). These disorders occurred in 40–100% of the animals after doses between 16 Gy and 28.5 Gy (+diet). Late gastric obstruction exceeding 7 months after irradiation was seen in the rats because of profound changes in the gastric wall in 13–18% of the animals after doses between 23 Gy and 14 Gy. In animals surviving these three periods, an atrophic mucosa and intestinal metaplasia developed. From functional and morphohistological studies, it can be concluded that there are differences in the pathogenesis of the fatal radiation damage for each of these periods after irradiation. The most sensitive cells in fundus would be the parietal cells and chief cells. They are the first two to necrose. Glands are colonized by mucous neck cells and are an inflamatorylymphocitic reaction seat. Mucous gland metaplasia, the reversible replacement of differentiated cells, occurs in the setting of severe damage of the gastric glands, which then waste away (atrophic gastritis) and are progressively replaced by mucous glands.Acute gastric ulcers may develop and are rather linked to a mucosa desquamation. Vascular necrosis occurs second time and is responsible for late perforation(golgraber et al 1975, roswit,et al 1972))

Gastric acid is produced by cells lining the stomach, which are coupled to radiotherapy, radiation ionizing decrease earlier acid production but only with low dose radiotherapy. Stemcells of the gastric mucosa seems to be insensitive to radiotherapy. In one hour ,they repair 60% of ADN lesions and the stems cells doubling time is fast (about 43hours) (chen et al 1972). However, these in vitro data are not always correlated with clinical data on late effects of stomach radiotherapy. Clinically nauseas occur in the first hours after irradiation. Vomiting and anorexia are reported in clinical trial MALT lymphoma, lomboaortic radiotherapy or in preoperative gastric radiation (ajani et al 2004). Moderate (2–3 Gy of radiation) exposure is associated with nausea and vomiting beginning within 12–24 hours after exposure.

3.2 Acute and chronic side effects

3.2.1 Ulcer and gastritis

The late effects of radiation gastric therapy can include ulcer and gastritis (bush 1993, otsuka 2008). Ulcer is usually alone and in pyloric antrum. Microscopic appearance is telangectasia, fibrin deposit and numerous fibroblasts. Microscopic chronic gastritis appears with lympocytic cells mass,gastric gland are infrequent, not typical architecture, perivascular lymphocytic cells cluster, submucosal fibrosis dividing muscularis fibers, Intestinal metaplasia typically begins

in response to chronic mucosal injury in the stomach and may extend to the body. Gastric mucosa cells change to look like intestinal mucosa. (coia et al 1995).

Grigsby reported a series of 30 patients received 48Gy(1.2 Gy twice a day). One patient declared a toxicity grade 3. In a similar review of the literature of patients treated with 26Gy and a lomboaortic field (normal fractionation) in seminoma stage I, any patient presented late gastro intestinal toxicity (Grisgby et al 2001).

3.2.2 Previous gastric radiation and incidence of gastric cancer

In previous radiation therapy for benign gastric disease there are limited data to suggest that radiation delivered may be a risk factor for gastric cancer. Gastric radiation was used in the ulcer gastro-duodenal treatment. Doses ranging from 15Gy to 20 Gy in 10 fractions were used before prescribing the inhibitors of pump proton. In small series of patients Peters et al described patients with partial gastrectomy and radiotherapy had an increased incidence of gastric cancer. Grien and coll reported 1831 patients with ulcers disease who were treated with radiation therapy and compared them to a similar group of medically managed patient over an average of 22 years. Radiotherapy was linked to an increased relative risk for cancers of the stomach (rr=2.77 and 95% as was partial gastrectomy(rr=2.6). So if surgery was combined with radiation therapy the risk increased 10 fold (Griem et al 1994).

3.3 Gastric tolerance dose

3.3.1 Conventional fractionation

The most of clinical information come from trials about hodgkin lymphoma, MALT (mucosa associated lymphoid tissue) or postoperative radiation of the paraaortic and ipsilateral pelvic lymph nods in testiculars tumors, or uterine cervix carcinoma. Two trials are relevant and expose acute and late toxicity in radiation gastric adenocarcinoma treatment. Forty three patients received concurrent radiation 45Gy(1.8Gy/fraction) and chemotherapy (infusional fluorouracil and weekly paclitaxel). Resection was attempted 5 to 6 weeks after chemoradiotherapy was completed. Any ulcer but gastritis grade 3 in one patient were noticed (ajani et al 2004). Cosset et al reported the toxicity results of 2 trials and 516 patients were entered in two consecutive EORTC trials for supra-diaphragmatic Hodgkin's lymphoma received an sub-diaphragmatic irradiation and, 36 (7%) developed late radiation injuries of the gastrointestinal tract. Twenty-five patients presented with ulcers (stomach or duodenum), two with severe gastritis. Although there was a significant improvement of complication in previous laparotomy the complication rate was 2.7% without any previous abdominal surgery, it was 11.5% after laparotomy ($p < 0.001$). Fractionation was also found to be of importance in the occurrence of complications: three different weekly schedules were used -5 x 2 Gy, 4 x 2.5 Gy and 3 x 3.3 Gy; the GIT complication rates were 4, 9 and 22%, respectively (p less than 0.001). When combining laparotomy and fractionation, we found that the patients who were treated using 5 weekly fractions of 2 Gy without any prior laparotomy had a very low rate of late digestive complications (1%), whereas the patients who received 3 weekly fractions of 3.3 Gy after laparotomy presented a 39% complication rate. The other subgroups of patients were at an intermediate risk (from 5 to 13%) of late digestive injuries. The median time occurring gastric ulcer was 18 months(3-92 months). Authors illustrate the effect of the difference with linear quadratic equation often used to model biological response to radiation. For the acute effect if the ratio α/β =10, 40Gy(2 Gy

per fraction) is an equivalent to 41.7 Gy(2.5Gy per fraction) and 44.3Gy(3.3Gyper fraction). So a ratio α/β =2.5 40Gy(2 Gy per fraction) is an equivalent to 44.4 Gy(2.5Gy per fraction) and 51.8Gy (3.3Gy per fraction)(Cosset al 1988). Mohiuddin studied 81 patients with localized, unresectable carcinoma of the pancreas with a combination of intraoperative Iodine-125 implantation, external beam radiation 50-55Gy with standard fractionation, and peri-operative systemic chemotherapy and 22% of the patients developed gastric bleeding mainly antral bleeding(mohiuddin et al 1992). Grisby reported a series of 30 patients received 48Gy(1.2 Gy twice a day). one patient declared a toxicity grade 3(Grigsby et al 2001). In a similar review of the literature of patients treated with 26Gy and a lomboaortic field (normal fractionation) in seminoma stage I, any patient presented late gastro intestinal toxicity(classen et al 2004).Yang et al reported radiation toxicity in 153 Patients treated for an hepatocarcinoma. The median dose received was 38Gy into15 fractions and a median dose of 3Gy. Twenty percent of the patients received an oesogastric endoscopy. Six percent of the patients presented gastro-duodenal ulcer and 5% gastritis. Fifty percent of the gastric ulcer and 75% of duodenal ulcer were in the irradiated target volume. Gastric bleeding was significantly commonly for femal, but not in cirhosis, total dose, dose per fraction and this study doesn't identify an high risk group(yang et al 2005). In the paraaortic lymph node treatment, 121 patients received 50Gy normal dose per fraction, 5% presented gastro duodenal ulcer and 2 patients gastrectomy (Goldstein et al 1975).

3.3.2 Hypofractionation of radiation

In general, rates of gastric-specific toxicity are inconsistently reported in the literature, often in combination with other GI toxicities. Additionally, other side effects such as anorexia, nausea, and vomiting are often included in gastrointestinal toxicity profiles. Other authors have also reported GI toxicity with hypofractionated regimens. Hoyer, et al conducted, Phase-II study on stereotactic radiotherapyof locally advanced pancreatic carcinoma, conducted a Phase II trial in which 22 patients with locally advanced pancreatic adenocarcinoma received 45 Gy split into three fractions. These investigators reported significantly greater acute GI toxicity than in our previous pancreatic cancer SBRT studies. The greater toxicity observed in the Hoyer study may be attributed in part to the significantly larger treatment volumes reported in this cohort of patients. Five patients (23%) experienced severe mucositis of the stomach or duodenum, including one who developed a gastric perforation. In each of these patients, part of the stomach or duodenum received at least 67% of the prescribed dose (30Gy over three fractions)(Hoyer et al 2005).Guidelines and different trials phase I- II propose to respect Dose volume histograms (DVHs) and to analyze V0.5 (volume of gastric in cm^3 receiving 30 Gy), and the maximum dose to 0.5cm^3 of stomach (D_{max} ≤30Gy)(Murphy et al 2009, lee et al 2009)

Streitparth reported gastric mucosa acute tolerance to high dose rate brachytherapy. Study treated 33 patients and liver segment tumor II and III(near stomach). In all patients a minimum dose applied to 1 ml of the gastric wall ($D_{1\ ml}$) ranged from 6.3 to 34.2 Gy; median, 14.3 Gy. Toxicity was present in 18 patients (55%). Nausea was present in 16 patients (69%), emesis in 9 (27%), cramping in 13 (39%), weight loss in 12 (36%), gastritis in 4 (12%), and ulceration in 5 patients (15%). they found a threshold dose $D_{1\ ml}$ of 11 Gy for general gastric toxicity and 15.5 Gy for gastric ulceration verified by an univariate analysis (p = 0.01).Authors conclude for a single fraction, small volume irradiation we found in the upper abdomen a threshold dose $D_{1\ ml}$ of 15.5 Gy for the clinical endpoint ulceration of the gastric

mucosa the tolerance dose of gastric mucosa after EBT applied as a single fraction dose can be estimated at 15.7 Gy, converted by using the linear-quadratic model with an assumed α/β of 12 Gy for gastric tissue for a TD50/5 of 70 Gy (probability of 50% during the next 5 years after irradiation to one third of the total gastric volume) (Streitparth et al 2006) these data are in adequacy with Emami who assessed perforation gastric risk for 60Gy and one third volume of gastric treated, 5% rate severe complication at 5 years was 60Gy.(Emami et al 1991.)

3.4 Guidelines to minimizing toxicity

There are several means to reduce normal tissue toxicity when combining radiotherapy and chemotherapy. Generally radiotherapy fields should cover clinically evident disease only and not attempt to cover areas where subclinical carcinoma is likely to present. But in gastric cancer and postoperative radiation or in trial with perioperative radiotherapy fields and clinical target volume cover all stomach organ. In the current state of the medical knowledge, there remains an uncertainty about dose and stomach tolerance and especially the ratio dose/volume and dose/time. Scientific Studies evaluating the dose and critical stomach organ tolerance are difficult to compare. It seems not necessary to delineate stomach and it is important to verify any hot point more than 35Gy. The ICRU "hot spot" (i.e. the dose outside of the PTV with a volume of at least 1.8 cc) should not exceed the prescription dose by more than 7%.(matzinger et al 2009)

Thirty five Gy is probably the threshold beyond the ulcer risk increase. Fifty four Gy maximal dose may be administred in a small volume with a classical fractionation.In SBRT Guidelines propose to respect Dose volume histograms (DVHs) and to analyze V0.5 (volume of gastric in cm^3 receiving 30 Gy), and the maximum dose to $0.5cm^3$ of stomach ($D_{max} \leq 30Gy$)(Murphy et al 2009).

4. Conclusion

Stomach is a critical normal tissue that need to be considered in the radiation treatment but toxicities are rare and it seems not necessary to delineate stomach. But in the current state of knowledge there is still uncertainty about the stomach dose tolerance and especially the ratio dose volume and dose time. Acute toxicities, vomiting, nausea occur precociously. Stomach tolerance dose if the totality is irradiated is 45Gy and classical fractionation35Gy is the threshold beyond which the ulcer risk appear and it is possible to prescribe 54 Gy in a reduce volume.

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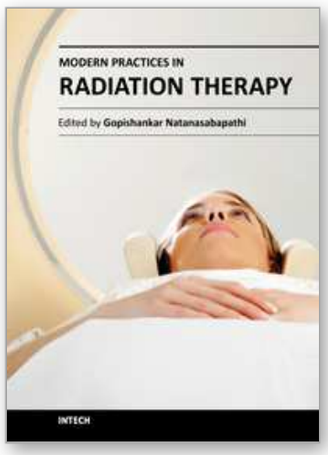

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Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. It is an enormous global health encumbrance, growing at an alarming pace. Global statistics show that in 2030 alone, about 21.4 million new cancer cases and 13.2 million cancer deaths are expected to occur, simply due to the growth, aging of the population, adoption of new lifestyles and behaviors. Amongst the several modes of treatment for cancer available, Radiation treatment has a major impact due to technological advancement in recent times. This book discusses the pros and cons of this treatment modality. This book "Modern Practices in Radiation Therapy" has collaged topics contributed by top notch professionals and researchers all around the world.

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