Carcinoma of the gastric stump: risks and pathogenesis

Gastric carcinoma occurring five or more years after gastric surgery for benign disease is now widely recognised as a distinct clinical entity – gastric stump carcinoma. The earlier appearance of cancer questions the true nature of the original preoperative disease and it is, therefore, discounted. Historically, carcinoma of the gastric stump is most closely associated with simple gastroenterostomy and Billroth II gastrectomy, but this may simply reflect that these were the most popular surgical treatments for peptic ulcer disease. Stump cancer can occur with similar frequency after the less common Billroth I gastrectomy and with truncal vagotomy and drainage procedures; cases of this complication after highly selective vagotomy are now being reported.

Gastric surgery and gastric cancer

Controversy surrounds the relation between gastric surgery and gastric cancer: is gastric surgery a causative factor in the carcinogenic process or is the association purely coincidental? The most carefully controlled data on this subject relate to animal experiments with and without administration of initiating carcinogens. With few exceptions these data show that operations which promote duodenogastric bile reflux increase the susceptibility of the stomach to neoplastic change. Conversely, the oral administration of bile acids with initiating carcinogens enhances tumour yield in the non-operated stomach. Thus, experimentally at least, gastric surgery seems to promote gastric carcinogenesis by mechanisms which involve bile reflux. Human data are inevitably much less consistent and reliable epidemiological studies suggest that achlorhydria and atrophic gastritis are factors predisposing to gastric cancer.

Achlorhydria is promoted by most types of gastric surgery; and atrophic gastritis, increased in peptic ulcer disease, is further accelerated by surgery for this condition. More specific data from case-control studies are difficult to interpret since they are retrospective and usually include no more than a few hundred postgastrectomy subjects yielding less than 50 gastric stump carcinomas. Incomplete data, and uncontrolled variables such as the nature of the preoperative peptic ulcer disease, age at operation, type of operation, and length of postoperative course, further limit their value. Only in postmortem investigations can the presence or absence of gastric stump carcinoma be unequivocally defined. Even in such studies the incomplete matching of study and control groups for important environmental and lifestyle factors may confound the observed differences. Despite these limitations recent publications of studies of large cohorts of postgastrectomy subjects (2633–4466 cases) monitored for several decades suggest that in humans, as in animals, gastric surgery does predispose to gastric cancer with increased risk beginning 15–20 years postoperatively and rising steadily thereafter. So far the available data are not substantial enough to withstand more critical analysis to determine the true influence of such factors as preoperative ulcer type, type of operation, and age at operation.

N-nitroso compounds

What are the likely mechanisms for the development of gastric stump carcinogenesis? Increasingly, N-nitroso compounds are recognised as a group of potent carcinogens possibly responsible for a variety of human tumours including gastric carcinoma. In animals these agents display both organ and species specificity and are capable of tumour production when given in minute, environmentally relevant dosage. In experimental gastric carcinogenesis only the N-nitroso compounds are consistently active by oral administration. Such compounds as N-methyl-N-nitroso-N-acyetylurea, N-methyl-N-nitrosourea, and N-methyl-N-nitro-N-nitrosoguanidine induce in dogs and hamsters, as well as rats, gastric adenocarcinoma in association with atrophic gastritis and intestinal metaplasia, thereby closely mimicking the histological features of human disease. In humans administration of foodstuffs epidemiologically associated with high gastric cancer risk – that is, smoked and pickled fish, meat, and vegetables – show that many contain the precursors of nitrosation and trace quantities of N-nitroso compounds themselves; low risk fresh fruit and vegetables are rich in the vitamins C and E, micronutrients known to inhibit nitrosation in vitro and in vivo. The N-nitroso compound hypothesis of gastric carcinogenesis is most plausible and incorporates virtually all known risk factors. It suggests that in the high risk achlorhydric stomach high intragastric pH promotes the overgrowth of bacteria which reduces dietary nitrate and nitrite and then converts this nitrite, in the presence of ingested proteinaceous amines and amides, into carcinogenic N-nitroso compounds. While high intragastric pH encourages bacterial proliferation and nitrite generation, there is little evidence of enhanced nitrosation. Technical problems hamper the accurate determination of N-nitroso compounds in human gastric juice and as yet no universally accepted method exists for their detection in complex biological media. Consequently, data on intragastric nitrosation show notable inconsistencies. Nevertheless, to date, most studies have not shown increased concentrations of N-nitroso compounds at high intragastric pH. Indeed, the less contentious N-nitrosoproline test of
endogenous nitrosation (indirectly measuring urinary yields of a non-carcinogenic N-nitroso compound after the human ingestion of harmless precursors) suggests that intragastric synthesis is maximal at pH 2–0–2.5.27 This pH maximum indicates that endogenous nitrosation reactions are largely governed by simple chemical kinetics; the role of bacteria in the genesis of the apparent low levels of N-nitroso compounds at neutral pH remains unknown.

High intragastric pH may be unimportant alone and could represent one manifestation of an extensively diseased mucosa, incapable of secreting acid and other essential functions. Defects in the mucosal barrier might facilitate the penetration of luminal carcinogens leading to increased alkylation of nuclear DNA. Reduced intracellular synthesis of DNA repair proteins such as O6-methylguanine transferase28 would leave chromosomal damage uncorrected, while increased cellular replication, a feature of atrophic gastritis, might promote the expression of such abnormalities as increasing degrees of epithelial dysplasia culminating in neoplasia.29

**Bile reflux**

Bile reflux is almost invariable after gastric surgery and commonly occurs to a less extent in the intact stomach. The mechanisms by which it exerts an influence on gastric carcinogenesis are uncertain. Refluxed material may contain initiating carcinogens and although such agents have not yet been identified, nitrosated derivatives of taurocholic and glycocholic bile acids have been synthesised in vitro and these produce gastric adenocarcinoma in the rat.30 Alternatively, bile reflux may play a promotional part by increasing permeability to initiating carcinogens or more specifically because of the particular characteristics of certain of its constituents. Experimentally, bile acids, lysolecinithin, and trypsin all digest gastric mucus to increase the backflow of hydrogen ions. Exposure of gastric mucosal cells to hydrogen ions results in atrophic gastritis.10,32

Thus, directly by the degradation of mucus and indirectly by causing atrophy to the mucosal cells, bile reflux may facilitate the transmucosal flow of large intraluminal molecules. Bacterial deconjugation of refluxed bile acids at high intragastric pH may generate co-carcinogens, for unconjugated lithocholic and deoxycholic acids can enhance experimental colorectal carcinogenesis.33 Indeed, these agents have been found in human gastric juice after gastrectomy.34 Low pH will render bile reflux physiologically inactive by inhibiting pancreatic enzymes and precipitating bile acids; it will also prevent the bacterial deconjugation of bile acids but might facilitate their nitrosation.

**Outlook for stump cancer**

Are all longstanding postoperative stomachs at increased risk of stump cancer or is risk restricted to a subgroup with a particular intragastric environment? Gastric surgery does not invariably result in severe end stage atrophic gastritis with achlorhydia; even after many years gastric histology may be normal and the ability to secrete acid retained.35

If gastric surgery predisposes to gastric stump cancer with an increased risk two to fourfold after 20 years what are the implications for clinical practice? Some would advocate screening programmes based on gastroscopy with multiple biopsy in an attempt to diagnose early asymptomatic disease amenable to total gastrectomy. The rationale for this is the poor prognosis of symptomatic disease. Furthermore, there is evidence that prolonged survival is possible if the disease can be excised surgically.36 This approach is probably impractical because endoscopic screening is very expensive with only the prospect of low detection rates; poor patient tracing and low patient compliance are inherent difficulties.37 These practical problems have been shown in the few screening programmes so far undertaken.38 The prevalence of stump cancer may be increasing. In the first 30 years after Billroth’s description of the operation in 1882 only 55 cases were reported, now the number is well over 2000.39 Some of this increase is due to improved awareness and interest in the controversy concerning the aetiology of stump cancer.

As peptic ulcer disease has become less common and symptoms milder40 and because of the recent drug developments elective surgical treatment is now rare. Emergency surgery for bleeding peptic ulcer is still common but endoscopic treatments may soon be effective.41 As most patients requiring emergency surgery are either elderly or suffer from some serious systemic disease, they are unlikely to survive long enough to develop gastric stump carcinoma. The population at risk of gastric stump carcinoma will therefore diminish significantly. In addition, there has been a well documented and persistent downward trend in the world wide incidence of gastric cancer. Environmental changes largely involving improved dietary habits are the likely explanation. Whatever the mechanisms, it seems likely that the operated and intact stomach will benefit from this reduced exposure to extraneous carcinogens, thus further reducing the risk of stump cancer. There is every prospect, therefore, that in the next 20–30 years gastric stump carcinoma will become a rare phenomenon.

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