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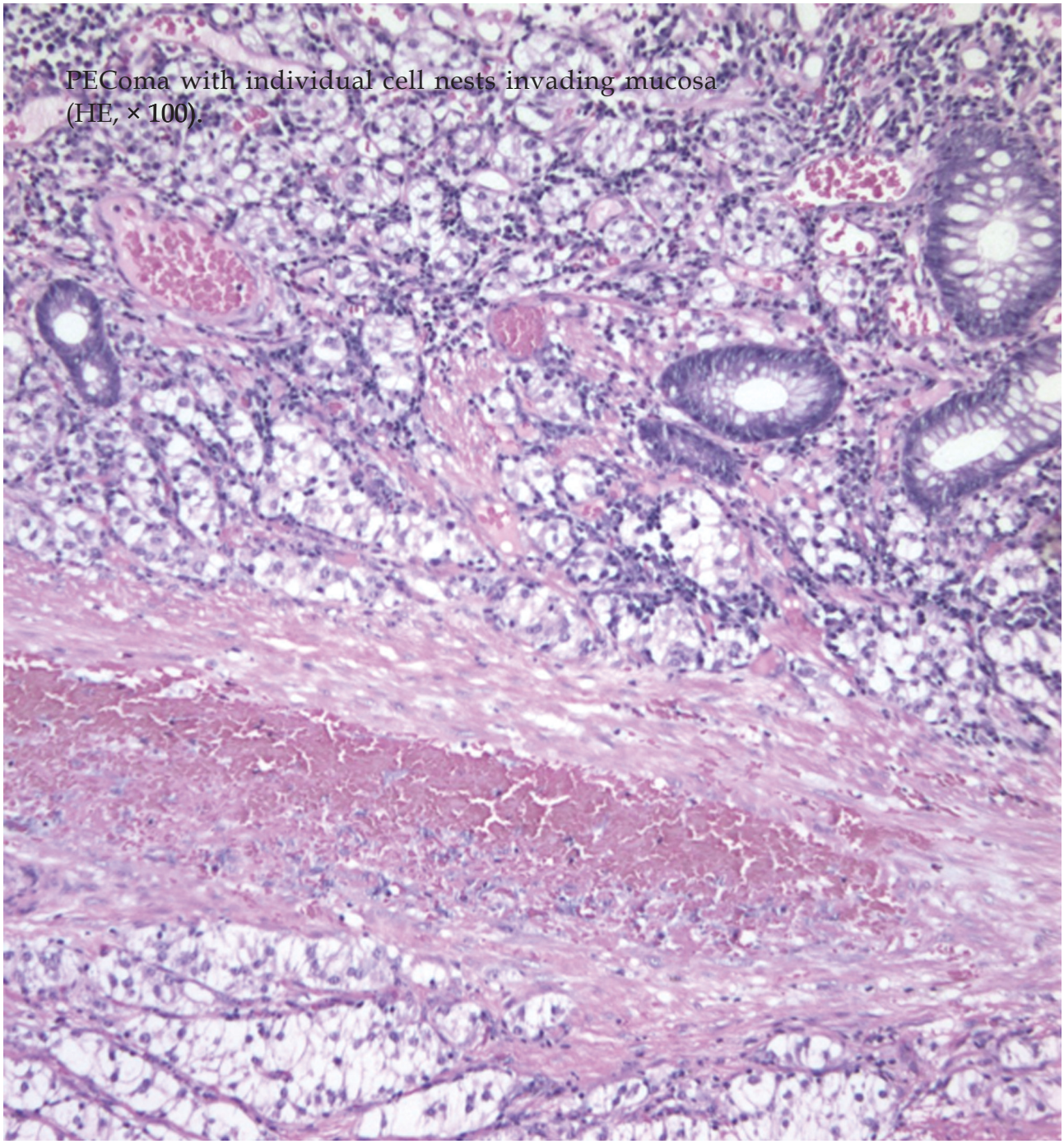

PEComa with individual cell nests invading mucosa (HE, × 100).

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EDITORIAL

Anti-carcinogenic properties of curcumin on colorectal cancer

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Abstract

Curcumin has been used in traditional Indian medicine for many centuries for its anti-inflammatory and anti-carcinogenic properties. There has been some promising research concerning curcumin as a safe therapeutic agent for many cancers, colorectal cancer being among them. This has been shown through research in cell cultures, animal models, and humans. At this time, it appears that curcumin's anti-carcinogenic properties are most likely due to its effects on multiple molecular targets, such as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1). NF-κB and AP-1 are both major transcription factors that regulate inflammation and thus affect cell proliferation, differentiation and even apoptosis. Curcumin has also been shown to affect a variety of other key players involved in carcinogenesis, such as cyclooxygenase-2, matrix metallopeptidases 2 and 9 and tumor necrosis factor α induced vascular cell adhesion molecule, just to name a few. Although many molecular targets are involved, curcumin has been well tolerated in many studies: doses up to 8 g a day have been confirmed to be safe for humans. In this brief review, we will examine the current studies and literature and touch upon many molecular pathways affected by curcumin, and demonstrate the exciting possibility of curcumin as a chemopreventive agent for colorectal cancer.

Key words: Chemopreventive; Anti-inflammatory; Anti-carcinogenic; Curcumin; Turmeric; Cancer; Colorectal cancer

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INTRODUCTION

Colorectal cancer is the third leading cause of cancer death in the United States[1]. A special need for non-toxic agents which are easy and effective to use for such cancer prevention and treatment is in demand. Epidemiologic findings may suggest a therapeutic possibility. Turmeric (and its active component curcumin) may be such an agent.

In India, traditional medicine uses turmeric for biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis[2]. It is pharmacologically safe even when consumed up to 100 mg per day in the Indian diet[3]. The incidence of colon cancer worldwide may vary 20-fold, with a higher prevalence in areas such as North America, Europe, Australia and New Zealand. A lower incidence is seen in countries such as India and less developed areas such as South America and Africa. Epidemiology suggests factors related to socioeconomic

and dietary conditions may be important to colorectal cancer development. Significant risk factors include lower fiber intake, high fat diet and low calcium micronutrient intake.

Genetic predisposition to polyposis and cancer is also well established in literature[4]. Colorectal cancer is patterned into sporadic, inherited (10%) and familial (25%) categories. Germline mutations are seen in the two most common forms of inherited colon cancer: familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer.

Curative therapy for colon cancer is largely the province of surgery. Adjunctive chemotherapy and radiotherapy may be used depending on the course of the disease[5]. Exploitation of the over-expression of cyclooxygenase-2 (COX-2) in sporadic colon cancers (90%) and 40% of colon adenomas has shown promise for it as an avenue for chemoprevention of colon cancer. Non-steroidal anti-inflammatory drugs (NSAIDS), such as sulindac, and COX-2 specific inhibitors, such as Celebrex (celecoxib), have shown great utility as a chemopreventive treatment for patients with the FAP genotype. Increased risk of myocardial infarction with COX-2 inhibitors, which led to the removal of valdecoxib and rofecoxib, and the increased risk of gastrointestinal bleeding and renal failure with NSAIDS (sulindac) make their recommendation problematic[6].

The response of suppressors of COX-2 for prevention of polyp development and cancer production in FAP does show the utility of control of deregulated pathways and, if not for the side effects, COX-2 inhibitors would be strongly recommended as a cancer/polyp chemopreventive agent. Thus agents that inhibit cellular pathways which create or promote carcinogenesis without toxicity are needed. Curcumin is a strong chemopreventive candidate with these properties (Figure 1)[6].

Turmeric, a spice common to India and its surrounding regions, is derived from the rhizome of Curcuma Longa. The use of turmeric as a medicinal compound dates back to around 2000 B.C. when it was used as an anti-inflammatory agent. Fractions of turmeric known as curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) are considered active compounds and possess a yellowish orange color[7]. Curcumin finds potential usefulness as an anti-inflammatory, anti-mutagenic, and anti-cancer molecule[8]. It also functions as an anti-oxidant and is capable of inducing apoptosis[9,10]. A wide variety of effects of curcumin are mediated by its capability to act as a free radical scavenger, to alter gene expression of various stress protein and genes involved in angiogenesis, and to inhibit activity of many important transcription factors such as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1)[11-15]. Its abilities are often seen to be concentration dependent. At 10 μm, it has an antioxidant effect and at 50 μm it induces apoptosis, possibly in conjunction with generation of superoxide radicals[16]. Oral intake of turmeric at 4-8 g per day in humans can generate plasma levels of as little as 0.41-1.75 μmol/L. When considering its elicited biological effects by regular oral consumption, the concentration of curcumin is very important. In light of low systemic bioavailability, the role of biotransformed moieties, tetrahexahydro-curcumin, has received interest as to their biologic importance.

The anti-oxidant activity of curcumin can arise either from the OH group or from the CH_2 group of the β-diketone (heptadiene-dione) moiety and it has been shown that the phenolic OH groups play a major role in the biological activity of curcumin[7,17]. Most of curcumin's cellular effects are an outcome of its redox characteristics; the phenolic OH groups seem to be the most important moiety in curcumin. Replacement of this group inhibits or eliminates the lipid peroxidation inhibitory and free radical scavenging properties of curcumin[18,19].

Curcumin, in addition to demonstrating anti-tumor action, has been also shown to be an effective chemopreventive agent. Its action in tumors of colon, stomach and skin involve inhibition of cyclooxygenase, phospholipase A2 and phospholipase-Cr1[20,21].

POTENTIAL ROLE OF CURCUMIN IN CARCINOGENESIS

Carcinogenesis is a complex process but may be largely considered to be comprised of three phases: initiation, promotion, and progression[22]. These closely related steps: going from a normal cell to a transformed initiated cell (initiation); from initiated to pre-neoplastic cell (promotion); and from pre-neoplastic to neoplastic (progression); may lend themselves to curcumin intervention.

There is suggestive evidence that inflammation may have a role in the three phases of carcinogenesis[23]. Cancer initiation has been produced by oxidative stress and chronic inflammation[24]. Inflammation acts a key regulator in promotion of these initiated cells, possibly by providing them with proliferating signals and by preventing apoptosis[25]. The role of inflammation in tumor induction and subsequent malignant progression has been investigated[26]. Inflammatory response produces cytokines which act as growth and/or angiogenic factors leading transformed cells to proliferate and undergo promotion. Leukocytes produce cytokines, angiogenic factors as well as matrix-degrading proteases that allow the tumor cells to proliferate, invade, and metastasize. Tumor-infiltrating lymphocytes secrete matrix-degrading proteinases like matrix metallopeptidase 9 (MMP-9), thus promoting neoplastic proliferation, angiogenesis, and invasion[26]. These details demonstrate the role of inflammation in all three stages of carcinogenesis. Substantial evidence for the role of inflammation in cancer may be seen by the frequent up regulation of inflammatory mediators like NF-κB. The pathways activated by NF-κB up regulators are implicated not only in tumor growth and progression but also in cancer cell development of resistance to anti-cancer drugs, radiation and death cytokines. NF-κB is an excellent target for anti-cancer therapy[27]. The effect of curcumin on carcinogenesis is felt to be through inhibition of NF-κB as well as other molecular targets (Figure 2).

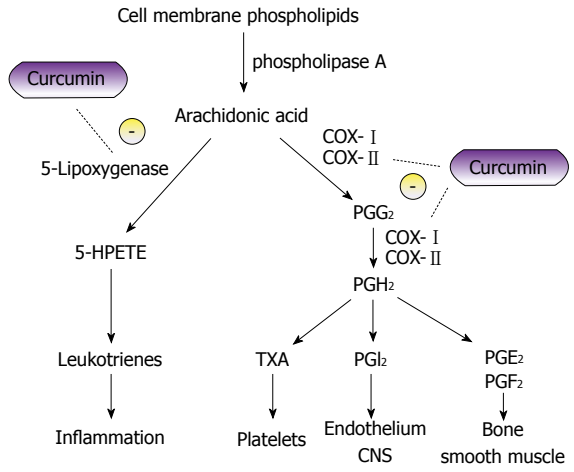

Figure 1 Diagram showing curcumin and its potential inhibitory effects on the metabolic pathway of arachidonic acid. The anti-inflammatory properties of curcumin can be attributed to its effects on many molecular targets, 5-lipoxygenase and cyclooxygenase to name a few. Curcumin has been found to inhibit 5-lipoxygenase *in-vitro* in a concentration dependent manner in mouse epidermal cells[6]. The proposed mechanism of cyclooxygenase (COX) inhibition is believed to be due to the inhibition of Nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) activation[53].

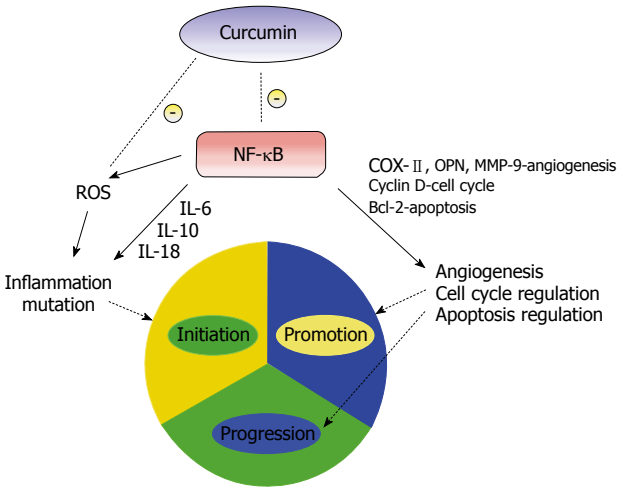

Figure 2 A simplified illustration of curcumin and its effects on the three stages of carcinogenesis. NF-κB has been the subject of research for the development of anti-cancer therapeutic agents due to its effects on multiple stages of carcinogenesis. Curcumin has been shown to prevent phosphorylation and degradation of inhibitor κ B α, thereby blocking NF-κB activation[30]. NF-κB, through multiple pathways, can promote inflammation, angiogenesis and disrupt cell cycle and apoptosis regulation, thus promoting carcinogenesis.

Tumor initiation is modified by curcumin in several ways. Many of these seem to involve the blockade or inhibition of NF-κB.

EFFECTS ON TUMOR INITIATION BY CURCUMIN

Inflammation may initiate carcinogenesis through the production of reactive oxygen species (ROS) and reactive nitrogen species by activated neutrophils and macrophages that leads to cancer causing mutations[28]. Curcumin has demonstrated significant reduction of levels of inducible nitric oxide synthesis (iNOS). Curcumin inhibits the induction of nitric oxide synthase and is a potent scavenger of free radicals like nitric oxide[29]. NF-κB has been implicated in the induction of iNOS which produces oxidative stress, one of the causes of tumor initiation. Curcumin prevents phosphorylation and degradation of inhibitor κ B α, thereby blocking NF-κB activation which down regulates iNOS gene transcription[30].

Deregulatory imbalances between adaptive and innate immunity results in chronic inflammation which is associated with epithelial tumorigenesis, the prominent mechanism being NF-κB activation[31]. Curcumin was found to inhibit cell proliferation and cytokine production by inhibiting NF-κB target genes involved in this mitogen induction of T-cell proliferation, interleukin IL-2 production and nitric oxide generation[30]. Reduction induced over expression of cytokines, such as IL-10, IL-6, and IL-18, is accompanied by NF-κB induction which is controlled by and inhibited by curcumin[32].

Curcumin has been demonstrated to increase expression of conjugation enzymes (phase Ⅱ). These have been shown to suppress ROS-mediated NF-κB, AP-1 and mitogen-activated protein kinases (MAPK) activation[33]. These enzymes, such as sulfotransferase and glutathione-s-transferase, conjugate toxic metabolites (through phase I enzymatic action) and then excrete them[33]. Curcumin modulates cytochrome p450 function and has been demonstrated to reduce aflatoxin B1-DNA adduct formation, an inhibitory step important in chemical carcinogenesis[34]. In various cancer models, curcumin was seen to further counteract ROS by increasing ornithine decarboxylase, glutathione, antioxidant enzymes and phase Ⅱ metabolizing enzymes[35]. Heme oxygenase-1 (HO-1) has been seen to counteract oxidative stress, modulate apoptosis and inhibit cancer cell proliferation. Curcumin induces HO-1 expression by signaling through nuclear factor (erythroid-derived 2)-related factor 2 (NRF-2) and NF-κB and thereby has the potential to reduce oxidative stress[36-40]. NRF-2 is a transcription factor that regulates the expression of conjugatory enzymes like glutathione-s-transferase *via* an anti-oxidant response element (ARG)[41]. Curcumin prevents initiation of tumors either by curtailing the pro-inflammatory pathway or by inducing phase Ⅱ enzymes[42].

TUMOR PROLIFERATION AND PROGRESSION SUPPRESSION BY CURCUMIN

Evidence suggests NF-κB has an important role in cancer initiation, promotion and progression. NF-κB binds to DNA and results in transcription of genes contributory to tumorigenesis: inflammation, anti-apoptosis and positive regulators of cell proliferation and angiogenesis[42]. NF-κB activation occurs primary *via* inhibitor κ B kinase (IKK)-mediated phosphorylation of inhibitory molecules[43]. Curcumin blocks NF-κB signaling and inhibits IKK activation[44]. Suppression is also noted on cell survival and

cell proliferation genes, including Bcl-2, cyclin D1, IL-6, COX-2 and MMP[44,45]. Curcumin also induces apoptosis by caspase activation of a poly (ADP-ribose) polymerase (PARP) cleavage[41,44]. Regulation of NF-κB by curcumin is associated with activation of caspase 3 and 9, decreasing Bcl-X (L) messenger RNA (mRNA) and increasing Bcl-X (S) and c-IAP-2 mRNA[45]. COX-2 is the inducible form of cyclooxygenase that catalyzes the role limiting step in prostaglandin synthesis from arachidonic acid and plays an important role in cancer and tumor promotion[46,47]. Over-expression of COX-2 leads to malignant cell proliferation and invasion and the effect is reversed by non-steroidal anti-inflammatory agents, elucidating the importance of COX-2 inhibitors in cancer chemotherapy[48]. It has been suggested that COX-2 induction is mediated by NF-κB intracellular signaling pathway[49]. Curcumin has also been noted to decrease proliferation of various cancer cells, especially in the colon by down-regulating COX-2[45,50,51]. Curcumin inhibits COX-2 but not COX-1 in colon cancer cells, demonstrating its selectivity[52]. It has been shown to inhibit COX-2 expression by repressing degradation of the inhibitory unit inhibitor κ B α and hindering the nuclear translocation of the functionally active subunit of NF-κB, thereby blocking improper NF-κB activation[53].

Curcumin has been found to reduce the invasion and subsequent metastasis of cancer cells. Curcumin suppresses MMP expression which is believed to play a major role in mediating neovascularization and is increased during tumor progression. MMPs play an important role in endothelial cell migration and tube formation. Two determinants of neovascularization that help in forming new capillaries from preexisting blood vessels are MMP-2 and MMP-9. These two MMPs are known to be involved in tumor angiogenesis mainly through their matrix-degrading capacity[54]. Curcumin down regulates MMP-9 expression by inhibiting NF-κB and AP-1 binding to the DNA promoter region[55]. Adhesion molecules, such as vascular cell adhesion molecules (VCAM), are implicated in cancer progression and they are elevated in patients with advance disease[56].Curcumin has been noted to cause significant inhibition of tumor necrosis factor α induced VCAM-1 expression, related to the activation of the MAPK NF-κB pathway[57]. Curcumin has been shown to reduce cell migration and invasion induced by osteopontin, an extracellular matrix protein, through the NF-κB pathway[58]. Curcumin may inhibit cancer cell growth through down regulation of IL-1 and IL-8 induced receptor internalization[59]. Curcumin controls cancer progression by either blocking tumor growth or inhibiting its invasive and aggressive potential. Most of the effects in either case are exerted by curcumin-induced NF-κB inhibition.

Certain molecular targets of curcumin's chemoprotective action are β-catenin, β-catenin/T cell factor (TCF), and lymphoid enhance factor (LEF) which are often disrupted in many cancer cells, especially colorectal carcinoma[60-62]. Dysregulated β-catenin (TCF) is implicated in cancer progression and poor prognosis. β-catenin in the cytoplasmic pool is phosphorylated by the axin adenomatous polyposis coli-glycogen synthase kinase 3β complex and subjected to degradation by the ubiquitin proteasome pathway[63]. Non-degraded β-catenin either enters the nucleus to transactivate the TCF/LEF transcription factors, leading to the up regulation of many genes responsible for cell proliferation, or binds to the E-cadherin adhesion complex. Reduction or loss of E-cadherin and/or increased localization of β-catenin in the nucleus is associated with invasive metastatic cancer progression and poor prognosis[64,65]. Curcumin has been found to decrease nuclear β-catenin and TCF4 and hence inhibit β-catenin /TCF signaling in various cell cancer lines[66]. Curcumin induced G2/M phase arrest in the cell cycle and apoptosis in colon cancer cells by impairing Wnt signaling and decreasing transactivation of β-catenin /TCF/LEF, subsequently alternating tumor progression[67]. The anti-tumor effect of curcumin was evidenced by its ability to decrease intestinal tumors in an animal model of FAP by reducing the expression of the oncoprotein β-catenin[68]. Some human β-catenin /TCF target genes, including cyclin D, MMP7, OPN, IL-8 and matrilysin, play a role in tumor promotion and progression[69]. NF-κB repression and decreased β-catenin signaling are some of the mechanisms by which curcumin suppresses the promotion and progression of cancer.

CURCUMIN CLINICAL TRIALS

Every clinical trial with curcumin has shown it to be safe with minimal adverse effect. Doses of up to 8000 mg per day were well tolerated.

Sharman and colleagues assessed the pharmacodynamic and pharmacokinetic properties of curcumin in 15 Caucasian patients with a history of colorectal cancer[70]. One patient had visible disease at the time of the study and the rest had complete surgical resection. Side effects were minimal, transient and not always determined to be due to curcumin. The one patient with local colonic disease saw a decline in a cancer biomarker, carcinoembryonic antigen, from 310 ± 15 to 175 ± 9 after 2 mo of treatment (440 mg/d). Computed tomography scan revealed that disease of the colon stabilized but metastasis was noted in the liver. This was felt due to probable low systemic bioavailability of curcumin though serum levels were not measured. Safety and tolerability of curcumin doses up to 2.2 g for 4 mo were documented.

A phase I clinical trial assessed tolerability of curcumin in 25 subjects from Taiwan with high risk or premalignant lesions[71]. In this study, curcumin was provided as 500 mg capsules for 3 mo. Twenty four of the twenty five subjects finished the study. Higher doses produced higher systemic levels. Subjects who consumed 2000 mg or less had curcumin levels barely detectable in serum and no detectable levels in the urine. Histological improvements independent of dosage were observed in precancerous lesion in 7 of the

25 subjects. Frank malignancies were observed in 2 of the 25 subjects during the 3 mo treatment regimen. This study showed the possible activity of chemoprevention, safety and tolerability in doses up to 8000 mg per day, warranting further studies.

A second phase I clinical study by Sharma *et al*[72] assessed curcumin biomarkers for systemic activity. This was investigated in 15 patients with histologically proven adenocarcinoma of the colon and rectum. Two of the patients had disease seemingly limited to the colon and thirteen beyond the colon. Patients received between 450-3600 mg curcumin per day with water after a 2 h fast in the morning as a single dose. Side effects were mild and some elevation of alkaline phosphatase and lactate dehydrogenase were noted. Patients consuming 3.6 g of curcumin saw a 46% decrease in Prostaglandin E2 (PGE2) levels (P = 0.028). Mean plasma levels of 11.1 ± 0.6 mmol/L were shown at the 1 h point in 3 patients consuming 3.6 g of curcumin. The levels were 1/40 of that noted in the previous study. The previous study used a synthetic version of curcumin while this study used a natural curcumin with the presence of other curcumanoid properties[71,72]. A question of ethnically related nucleotide polymorphism in the metabolizing enzyme UGT1A1 gene which might produce altered metabolism should be considered[73]. No partial responses were seen and no reduction in tumor markers was observed. Safety and tolerability of curcumin was seen up to daily dosage of 8000 mg.

A phase I study was based on evaluating the presence of curcumin metabolites in hepatic tissue and portal blood on 12 patients. Dosages ranged from 450-3600 mg of curcumin capsules which were taken for 7 d before surgery. Only 3 of 12 patients receiving 3600 mg of curcumin had detectable curcumin metabolites. Curcumin, curcumin sulfate and curcumin glucuronide were not present in bile or liver tissues in any patient. Low oral availability was noted in this study but the possibility of an oral agent to treat distant metastases of the gastrointestinal tract was advanced.

Garcea *et al*[74] studied curcumin levels in the colorectum and the pharmacodynamics of curcumin in 12 patients with confirmed colorectal cancer. The staging of patients was noted; 2 patients with Duke A, 3 patients were Duke B, and 7 patients were Duke C. Patients were assigned to 450 , 1800 or 3600 mg of curcumin per day for 7 d prior to surgery. Detectable curcumin levels were seen in the serum of only one patient (who was taking 3600 mg per day). Every patient had detectable curcumin levels in normal and malignant colorectal tissue ranging from 7 nmol/g to 20 nmol/g of tissue. Curcumin levels were highest in the normal tissue of the cecum and the ascending colon as opposed to the transverse, splenic flexure and the descending colon, which suggests a local effect. COX-2 levels were undetectable in normal tissue but detectable in malignant colorectal tissue. Curcumin was not found to modulate the expression of Cox-2 in malignant tissues. It appears from this study that doses of 3600 mg of curcumin are safe and sufficient to see pharmacodynamic changes in the gastrointestinal tract.

Colonic polyps are considered to be a precursor to cancer. The effect of curcumin has been studied on humans and animals (mice) with FAP coli.

The CS7B1/6J Min/+ mouse is an established model for the study of FAP coli[75]. A study where 0.2% and 0.5% of curcumin in the diet reduced adenoma multiplicity by 39% and 40% compared to control. Concentration in the small intestine mucosa was noted to be between 39 nmol/g and 240 nmol/g of tissue. Curcumin disappeared from the tissues and plasma within 2-8 h after dosing. A suggested dosage for humans was estimated by extrapolation to be 1.6 g per day. Tumorigenesis was noted in the small bowels of the animal model.

A human study of 5 patients with familial adenomatous polyps was performed using 480 mg of curcumin and 20 mg quercetin three times a day[76]. Four patients had a retained rectum and one had an ileoanal anastomosis. This study spanned 6 mo. All five patients had a decrease in number and size of polyps from their baseline. A mean decrease in polyp number by 60.4% ($P < 0.05$) and size by 50.9% ($P < 0.05$) was noted. No adverse effects were noted to any patient and no related laboratory abnormalities were seen. This is the first human demonstration of the reduction in size and number of ileal and rectal polyps in patients with FAP by a curcumin containing agent. The lack of toxicity coupled with the benefits demonstrated makes larger studies compelling.

CONCLUSION

The preponderance of colon cancer is a subject of paramount importance. A need has been demonstrated for compounds that target multiple molecular and cellular pathways which may be important to chemoprevention and/or chemotherapy. Curcumin has demonstrated these chemopreventive properties in cell cultures, animal models and human investigations. Human trials have concluded that curcumin is safe and poses minimal adverse effects. Doses up to 8000 mg per day were well tolerated. Effectiveness in altering pathologic changes was demonstrated. Further studies and possible developments are necessary to fully confirm cardiovascular safety due to suppression of COX-2, albeit the mode of suppression is more difficult than COX-2 inhibitors such as celecoxib, valdecoxib, and rofecoxib. Further studies related to the relevance of bioavailability and curcumin effect on carcinogenesis are important. The development of standardized criteria for preparations of curcumin is critical for further in depth studies. There needs to be further investigation of the role of nucleotide polymorphism and altered metabolism of curcumin (i.e. VGT enzymes) and its impact on carcinogenesis.

Curcumin chemotherapy and chemoprevention of colon cancer presents many exciting possibilities. Many things need to be evaluated, investigated, and developed but the prospects for curcumin as a therapeutic agent are indeed promising.

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GUIDELINES FOR CLINICAL PRACTICE

Circulating galectin-3 in the bloodstream: An emerging promoter of cancer metastasis

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Abstract

Increased concentrations of free circulating galectin-3 are commonly seen in the blood circulation of patients with many types of cancers including colorectal cancer. Recent studies have shown that changes in circulating galectin-3 levels in cancer patients may contribute significantly to the metastatic spread of disseminating cancer cells by enhancing their ability to adhere to blood vessel endothelium and by helping their avoidance of immune surveillance. Thus, targeting the galectin-3 actions in the circulation may hold significant promise for future development of novel therapeutic agents to prevent metastasis and reduce cancer-associated fatality.

Key words: Circulating galectin-3; Cancer cell adhesion; Cancer dissemination metastasis

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INTRODUCTION

Galectin-3 is a galactoside-binding, small molecular weight (about 30 kDa) protein that is expressed in many types of human cells, in particular epithelial and immune cells. As a multi-functional protein with multiple cellular localizations, galectin-3 is over-expressed and abnormally localized in many types of human cancers and has attracted significant interest in cancer research over the past decades[1,2].

CELL-ASSOCIATED GALECTIN-3

Many earlier investigations were focused on the expression and roles of the cell-associated form of galectin-3. Galectin-3 is synthesized in the cytoplasm as a cytosolic protein but can be transported to multiple subcellular localizations in the cell nucleus, to the cell surface or can be secreted to the outside of cells. Cytoplasmic galectin-3 functions as an apoptosis inhibitor by suppressing mitochondrial depolarization and preventing the release of cytochrome C[3], while nuclear galectin-3 acts as a mRNA splicing promoter[4], and in contrast to cytoplasmic galectin-3, has pro-apoptotic activity[5]. Loss of galectin-3 nuclear localization and its accumulation in the cytoplasm is commonly seen in many types of human cancers, including colorectal[6,7], prostate[8] and tongue carcinoma[9]. Change in galectin-3 localization from the nuclei to the cytoplasm closely correlates with tumour progression. *In vitro* studies have shown that accumulation of galectin-3 in the cytoplasm by stable galectin-3 gene transfection increases cancer cell invasion and promotes tumour angiogenesis[5].

Cell surface-associated extracellular galectin-3 interacts with basement matrix glycans (e.g. laminin and fibronectin) and promotes tumour cell release from the primary tumour sites by increasing tumour cell adhesion and invasion[2]. Over expression of the cell surface-associated galectin-3 in epithelial cancer cells increases the interaction of cancer cells with galactoside-terminated glycans expressed on the surface of adjacent cells and promotes cancer cell homotypic aggregation and heterotypic adhesion to endothelium in cancer cell haematogenous dissemination[10,11]. The cell surface-associated galectin-3 has also been shown to be required in stabilization of epithelial-endothelial interaction networks during cancer cell extravasation[12]. Suppression of galectin-3 expression in melanoma cells reduces tumour cell invasiveness and capacity to form tube-like structures on collagen[13], while suppression of galectin-3 expression in metastatic human colon[14] and breast[9] cancer cells before inoculation of the cells into nude mice results in significant reduction of tumour growth and metastasis.

CIRCULATING GALECTIN-3 IN THE BLOODSTREAM

Galectin-3 is also found in the bloodstream. While little is known of a physiological role for free galectin-3 in the circulation of healthy people, recent investigations have shown that the concentrations of circulating galectin-3 is significantly increased in the bloodstream of cancer patients. For example, up to 5-fold increase of galectin-3 concentration was reported in the sera of patients with colorectal cancer[15]. Compared to healthy people, galectin-3 concentration was also significantly higher in the serum of patients with breast, lung[15], head and neck[16] cancers and melanoma[17]. Furthermore, patients with metastatic disease have higher concentrations of circulating galectin-3 than those with localized tumours. The source of increased serum galectin-3 in cancer patients remains unknown but has been speculated to be generated by the tumour cells as well as the peri-tumoral inflammatory and stromal cells[15].

Recently, it has been revealed that introduction of recombinant galectin-3 at pathologically-relevant circulating galectin-3 concentrations induces a significant increase of cancer (such as colon and breast cancer and melanoma) cell adhesion to both macro- and micro-vascular endothelial cells *in vitro* under static as well as fluid flow conditions[18]. These effects of galectin-3 are thought to be related to the binding of galectin-3 to the Thomson-Friedenreich carbohydrate (galactose β1, 3N-acetylgalactosamine-, TF) antigen expressed by the transmembrane mucin protein MUC1[19].

The TF antigen is the core 1 structure of O-linked mucin type glycans. Unsubstituted TF antigen does not appear in normal epithelial cells but is found in over 90% of all types of human cancer cells studied[20]. The increased expression of TF antigen is one of the most common glycosylation alterations in human cancer. The transmembrane mucin protein MUC1 is a large and heavily glycosylated (up to 50% of the molecular weight) protein that is over-expressed (up to 10-fold) and is aberrantly glycosylated in most epithelial cancer cells[21]. It is one of the major cell surface glycoproteins that carry the unsubstituted TF antigen in gastric and colorectal adenocarcinomas[22,23]. The increased occurrence of TF antigen and the increased expression of MUC1 are each independently associated with high metastatic potential and poor prognosis in several types of human cancers, including colorectal and breast cancers[24,25].

Earlier investigations have shown that MUC1 protrudes over 10 times higher from the cell surface than the typical cell surface adhesion molecules[26] and promotes tumour cell release from the primary tumour sites by inhibiting E-Cadherin-mediated cell-cell and integrin-mediated cancer-matrix interactions[27,28]. It has recently been shown that the huge size and length of MUC1 form a protective shield around the cell surface and prevent adhesion of cancer cells to endothelial cells[18]. Binding of galectin-3 to cancer-associated MUC1 breaks up the protective shield of MUC1 by causing MUC1 cell surface polarization and the subsequent exposure of the cell adhesion molecules, including CD44 and ligand(s) to endothelial-associated E-selectin, which results in adhesion of the cancer cells to endothelial cells. As is the increased expression of MUC1 by cancer cells, the increased expression of the galectin-3-ligand TF antigen by cancer-associated MUC1 and increased circulation of galectin-3 are all common features in cancer. It is most likely that an increased interaction between circulating galectin-3 and cancer-associated MUC1 in the bloodstream of cancer patients enhances disseminating cancer cell adhesion to the blood vessel endothelium, which then promotes cancer cell haematogenous spread to remote metastasis sites. This is supported by the *in vivo* experimental metastasis assays that showed pre-treatment of the MUC1 positively-, but not negatively-, transfected human melanoma cells with recombinant galectin-3 before inoculation of the cells into immune deficient mice causes significant reduction of metastasis-associated animal survival[18].

Free circulating galectin-3 may also be involved in the regulation of T cell activity and may play a role in the inhibition of anti-tumour immunity[29]. T cells play a critical role in cancer immune surveillance for the control and destruction of tumour cells[30]. Cell surface binding of soluble galectin-3 has been shown to activate tumour-reactive T cells to produce immunosuppressive cytokines (e.g. IFNγ) and to induce T cell apoptosis. Interestingly, these effects of galectin-3 are seen to occur only in tumour-experienced but not naïve T cells, indicating that initial T cell receptor activation may induce changes in cell surface glycosylation in antigen-experienced T cells that make such T cells more sensitive to galectin-3 binding and activation. The concentrations of soluble galectin-3 for T cell activation and apoptosis induction in these studies usually occur at ⩾ 25 μg/mL, which are much higher than

the concentrations of the circulating galectin-3 in cancer patients. However, cell surface binding of galectin-3 often induces clustering of the cell surface receptors[19,31,32]. There is evidence that clustering of galectin-3 receptors could enhance the galectin-3 binding affinity by as much as 10000-fold[33]. Thus, it is possible that a higher galectin-3 concentration could be achieved at a local galectin-3 binding site/microenvironment in the circulation that would allow galectin-3 to drive tumour-reactive T cell activation and apoptosis and, therefore, help the avoidance of tumour cell destruction by immune surveillance.

CONCLUSION

Recent investigations have demonstrated that increased levels of free circulating galectin-3 in the blood circulation of cancer patients may play an important role in promoting disseminating cancer cell survival and haematogenous spread to remote tumour sites. This implies that targeting the actions of circulating galectin-3 in the blood circulation may have significant implications for the development of novel therapeutic agents to prevent metastasis and reduce cancer-associated high fatality.

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GUIDELINES FOR CLINICAL PRACTICE

Gastric low-grade mucosal-associated lymphoid tissue-lymphoma: *Helicobacter pylori* and beyond

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Abstract

The stomach is the most frequently involved site for extranodal lymphomas, accounting for nearly two-thirds of all gastrointestinal cases. It is widely accepted that gastric B-cell, low-grade mucosal-associated lymphoid tissue (MALT)-lymphoma is caused by *Helicobacter pylori* (*H. pylori*) infection. MALT-lymphomas may engender different clinical and endoscopic patterns. Often, diagnosis is confirmed in patients with only vague dyspeptic symptoms and without macroscopic lesions on gastric mucosa. *H. pylori* eradication leads to lymphoma remission in a large number of patients when treatment occurs at an early stage (Ⅰ-Ⅱ$_1$). Neoplasia confined to the submucosa, localized in the antral region of the stomach, and without *API2-MALT1* translocation, shows a high probability of remission following *H. pylori* eradication. When both bacterial infection and lymphoma recur, further eradication therapy is generally effective. Radiotherapy, chemotherapy and, in selected cases, surgery are the available therapeutic options with a high success rate for those patients who fail to achieve remission, while data on immunotherapy with monoclonal antibodies (rituximab) are still scarce. The 5-year survival rate is higher than 90%, but careful, long-term follow-up is required in these patients since lymphoma recurrence has been reported in some cases.

Key words: Mucosal-associated lymphoid tissue; Therapy; *Helicobacter pylori*; Gastric lymphoma; Predictive factors; Endoscopy; Clinical presentation

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INTRODUCTION

Extranodal lymphomas account for 24%-29% of all the lymphomas in the USA and Taiwan, 36%-41% in Israel and the Netherlands, and 48% in Italy[1]. The gastrointestinal tract is the most frequent site of extranodal lymphoma, and the stomach is involved in up to two-thirds of these cases, accounting for 30%-45% of all extranodal lymphoma[2]. Although primary gastric lymphoma remains a rare disease, representing nearly 2%-8% of all tumors of the stomach, there is evidence that its incidence has been increasing in previous decades, similarly to lymphomas of the central nervous system and skin[1]. In particular, a study performed in a Japanese tertiary center found that gastric lymphoma

was diagnosed in 15 patients in the period 1963-1967 and in 70 patients in the period 1998-2002, with percentages increasing from 32% and 26% in periods 1963-1982 and 1983-1992, respectively, to 43% in the period 1993-2002, clearly showing an increasing trend[3]. Moreover, there are some geographic areas, such as north-eastern Italy, where the frequency of primary gastric lymphoma is particularly high, with an incidence as high as 13.2 cases per 100000 per year, which is significantly higher than that of other European countries[4]. In 1991, the first study documenting the presence of *Helicobacter pylori* (*H. pylori*) infection in virtually all study cases of primary, low-grade, B-cell mucosal-associated lymphoid tissue (MALT)-lymphoma of the stomach was reported[5]. Two years later, the first study reporting complete histological remission of gastric MALT-lymphoma in 5 of 6 patients following *H. pylori* eradication was published[6], starting a new era in the management of patients with low-grade lymphoma of the stomach.

HOW DOES GASTRIC LYMPHOMA ARISE?

Although some aspects still remain unclear, the pathogenetic cascade of gastric lymphoma has been revealed. Structured lymphatic tissue; i.e. lymphatic follicles, is lacking in normal gastric mucosa. Indeed, through the alimentary tract, lymphatic tissue is exclusively present in tonsils and Peyer's patches. However, following inflammatory processes, lymphatic follicles may appear on gastric mucosa, configuring the so-called MALT, as described by Wright in 1983[7]. Ten years later, Genta *et al*[8] clearly showed that the main cause of MALT onset on gastric mucosa was *H. pylori*-related gastritis. In fact, when an adequate biopsy sampling (8-11 specimens) was performed, it was possible to document the presence of lymphatic follicles (from 1 to 20) in all infected patients, while none of the uninfected patients showed MALT. In addition, the study found that 1 year following *H. pylori* eradication, the number of lymphatic follicles was significantly reduced (from 6.6 to 2.2)[8]. The presence of MALT in gastric mucosa could virtually be considered as a typical sign of *H. pylori* infection and, consequently, each infected patient is potentially at risk of developing gastric MALT-lymphoma during a life-long infection. However, based on the high prevalence of *H. pylori* infection in the general population, on the one hand, and the low incidence of gastric lymphoma, on the other, it is arguable that some particular conditions are needed for the neoplasia to develop. In an experimental study that involved co-culturing lymphocytes isolated from 3 gastric MALT-lymphoma and various inactivated *H. pylori* strains, a proliferation of B cells that also expressed IL-2 receptors was observed and a simultaneous IL-2 production by T cells in supernatant was detected[9]. Of note, only 1 of the 13 different *H. pylori* strains tested was able to stimulate B lymphocyte proliferation, and the involved bacterial strain was different among the 3 studied lymphoma patients. Moreover, T cell removal from the culture markedly reduced *H. pylori*-induced proliferation of B cells, suggesting an interaction between bacteria and T helper lymphocytes[9]. In addition, no B cell proliferation was observed when incubating gastric lymphoma cells with either *E. coli* or *C. jejuni*, suggesting a specific role for *H. pylori*. Moreover, *H. pylori* were unable to stimulate B cells of either thyroid- or salivary-derived lymphoma[9]. The latter observation is particularly worthy of attention, since lymphoma onset following a chronic inflammatory process on either thyroid (autoimmune thyroiditis) or salivary glands (Sjögren syndrome) has been clearly recognized[10,11].

On the other hand, certain genetic predispositions to gastric lymphoma onset have been highlighted. Noteworthy, a significantly higher prevalence of both HLA-DQA1*0103 and HLA-DQB1*0601 alleles and of DQA1*0103-DQB1*0601 haplotypes has been observed in MALT lymphoma patients as compared to controls with or without *H. pylori*-infection[12]. In addition, the R702W mutation in the NOD2/CARD15 gene was significantly associated with gastric lymphoma, and those subjects with the rare allele T had an increased risk (OR = 2.4, 95% CI: 1.2-4.6) to develop lymphoma compared to controls[13]. Similarly, the TNF-857 T allele was found in 15.1% of patients with low-grade lymphoma and 9.1% of controls (OR = 1.8, 95% CI: 1.1-2.8)[14]. The rare allele G of Toll-like receptor 4 (TLR4 Asp299Gly) appeared to be one putative factor in the genetic susceptibility to gastric lymphoma[15]. On the contrary, homozygous haplotypes for the rare allele G of SNP3 (rs12969413) of the *MALT1* gene significantly protected patients from high- but not from low-grade gastric lymphoma[16].

In summary, these observations clearly demonstrate that only some *H. pylori* strains in some predisposed patients determine lymphoma development in the stomach, according to a strain-host-organ specific process[17].

WHAT IS THE CLINICAL-ENDOSCOPIC LYMPHOMA PRESENTATION?

H. pylori infection induces a B-cell, low-grade, gastric MALT-lymphoma, typically CD19+, CD20+, usually CD5-, always CD10- and CD23-, with a clinically indolent progression[18]. Indeed, the neoplasia remains confined in the gastric mucosa for a long-time, so that its real tumoral nature has been questioned in the past when it was interpreted as "pseudo-lymphoma"[19]. Successive studies documented the monoclonal feature of B cells and the presence of a number of genetic alterations in these cells, such as trisomy 3, *API2-MALT1* translocation, *p53* mutation, and *p16* deletion[18,19]. Moreover, neoplastic B cells show aggressive behaviour causing the so-called lymphoepithelial lesions, which are a pathognomonic sign of lymphoma, by invading and destroying gastric glands. In addition, lymphoma cells are able to invade the entire gastric wall, from the mucosa to the serosa, and have the potential of metastasizing in both lymph nodes and other organs, particularly the bone marrow, lungs and liver[18-20].

Table 1 Endoscopic presentation of primary gastric MALT-lymphoma

Type	Main endoscopic presentation
Ulcerative	Single or multiple ulcerations or multiple erosions
Exophytic	Tumor-like appearance with an irregular or polypoid mass
Hypertrophic	Large or giant folds; nodular pattern
Mixed	A combination of more than one pattern
Petechial haemorrhage	Presence of several mucosal petechial haemorrhages
Normal/ hyperaemic	Normal appearing mucosa/hyperaemic changes

MALT: Mucosal-associated lymphoid tissue.

Therefore, the tumoral nature of MALT-lymphoma of the stomach has been definitely demonstrated. From a clinical point of view, gastric MALT lymphoma occurs over a wide age range, with a median of 57 years[18,21]. Although the sex ratio incidence is essentially equal, neoplasia appears to be slightly more prevalent in males (male:female = 1.27:1)[21]. Frequently, only vague dyspeptic symptoms are present, and B symptoms are extremely rare in MALT-lymphoma of the stomach, so that the diagnosis is often incidental[19]. In other cases, neoplasia may present as a complication of the gastric lesion, such as gastrointestinal bleeding or perforation. Persistent vomiting and weight loss are other possible presenting symptoms. Similarly, at endoscopic observation, MALT-lymphoma may present with different macroscopic features, from a normal appearing gastric mucosa to an ulcerative or vegetant mass, clearly suggesting a malignancy.

In a recent systematic review, clinical and endoscopic presentation of gastric lymphoma has been assessed considering data from 2000 patients[21]. By classifying the presenting symptoms as "alarm" (anaemia and/or melaena and/or haematemesis, persistent vomiting, weight loss) or "not alarm" (epigastric and/or abdominal pain, dyspepsia and/or bloating, heartburn), according to the current international guidelines[22,23], we found that alarm symptoms were present in only 42.1% of low-grade lymphoma patients[21]. The relatively low prevalence of alarm symptoms seems to be different from that observed in gastric or oesophageal cancer patients, in whom these symptoms are present in 56%-62% of cases[24]. Despite the indolent behaviour of low-grade gastric lymphoma, we computed that neoplasia was diagnosed in an advanced stage (Ⅲ-Ⅳ) in as many as 9.4% of the cases[21]. Such an observation presumably depends on the absence of alarm symptoms in the majority of cases, prompting both patients and physicians to undertake an upper endoscopy.

As for the presenting endoscopic feature, we have recently proposed a modified classification (Table 1)[21], updating the classification previously proposed by Ahmad *et al*[25] Using this updated classification, the neoplasia appeared as an ulcerative type in 52.1%, hypertrophic in 23.5%, normal/hyperaemic in 12.7%, exophytic in 9.7%, and as petechial pattern in 1% of cases among 1055 low-grade MALT-lymphoma patients[21]. Of note, these data showed that, in nearly 15% of cases, such a neoplasia may be detected on normal appearing mucosa or in the presence of solely petechial haemorrhages; that is, endoscopic features suggesting a benign condition.

Table 2 Gastric lymphoma staging

Ann Arbor	TNM	Description
Ⅰ	T1-T4 N0 M0	Confined within the gastric wall
Ⅱ1	T1-T4 N1 M0	Perigastric lymph nodes
Ⅱ2	T1-T4 N2 M0	Regional lymph nodes
Ⅲ	T1-T4 N3 M0	Lymph nodes on both sides of the diaphragm
Ⅳ	T1-T4 N0-3 M1	Visceral metastasis or second extranodal site

HOW TO TREAT LOW-GRADE GASTRIC LYMPHOMA?

The discovery of the etiologic role of *H. pylori* infection in gastric low-grade, B-cell MALT-lymphoma has radically changed the therapeutic approach for such neoplasia. Moreover, recent studies suggest that this infection plays a relevant role even in high-grade, large B cell lymphoma of the stomach, although data are still limited[26]. Current international guidelines suggest *H. pylori* eradication as first-line therapy in all low-grade gastric lymphoma patients when neoplasia is diagnosed at an early stage[22,23,27], according to the modified Ann Arbor classification (Table 2). Therefore, a comprehensive staging procedure, with a complete physical examination including Waldeyer's ring, routine laboratory tests, chests radiograph, endoscopic ultrasonography, computed tomography of the abdomen and pelvis, as well as bone marrow biopsy is mandatory in all gastric lymphoma patients. Indeed, bone involvement (stage Ⅳ) has been reported in up to 15% of cases, requiring oncologic therapy[19,28]. In a very large, pooled data analysis on patients with gastric lymphoma and *H. pylori,* it has been found that after first-line eradication therapy, the infection was cured in 91% of cases, with the success rate being higher following dual therapy as compared to the 7-day or 14-day triple therapies[29]. After second-line therapy, the eradication rate was 80.8%, being higher following triple rather than quadruple therapy. Further therapies (from three to five attempts) cured the infection in 75% of patients, so that *H. pylori* infection was ultimately cured in 99.8% of cases[29]. Another study found that lymphoma remission was achieved in 77.5% of 1408 patients with low-grade lymphoma at an early stage (Ⅰ-Ⅱ1) following successful bacterial eradication with a median time of 5 mo[30]. Interestingly, different predictive factors for lymphoma remission were identified, including neoplasia stage, depth of infiltration in the gastric wall, localization in the stomach, patient ethnicity, and presence of the *API2-MALT1* translocation. Indeed, neoplasia remission was higher in stage Ⅰ than in stage Ⅱ1 (78.4% *vs* 55.6%; P = 0.0003), as well as when it was confined to the submucosa as compared to a deeper invasion (82.2% *vs* 54.5%; P = 0.0001), when it was localized to the distal rather than in the proximal stomach (91.8% *vs* 75.7%; P = 0.0037), and in

Asian rather than in Western patients (84.1% *vs* 73.8%; $P = 0.0001$)[30]. Moreover, the remission rate was higher among patients without the *API2-MALT1* translocation (78% *vs* 22.2%; $P = 0.0001$)[30], a mutation which impairs the control of cell apoptosis, disconnecting the proliferation process by the bacterial antigenic stimulus[18]. Several long-term follow-up trials showed that the overall 5-year survival (OS) and disease-free survival (DFS) rates were as high as 90% and 75%, respectively, when lymphoma was treated in an early stage[31]. In a multicenter, Italian study, we calculated an OS of 94.7% and a DFS of 74.6% based on 60 patients with a mean follow-up of 65 mo[28].

HOW TO TREAT NOT RESPONDING LYMPHOMA PATIENTS?

Although specific guidelines on the management of lymphoma patients who failed to achieve neoplasia remission following *H. pylori* eradication are lacking, the European Society of Medical Oncology recommend the use of conventional anti-neoplastic therapeutic approaches[32]. In detail, either chemotherapy or radiotherapy is suggested as first-line oncologic treatment, while surgery should be reserved for selected cases. Recently, the possible role of immunotherapy with rituximab, which is an anti-CD20 monoclonal antibody, has been investigated, but data are still limited[33]. Considering the results of 27 trials enrolling 280 patients with early stage neoplasia who failed to respond to *H. pylori* eradication therapy, it has been found that lymphoma remission was achieved overall in 92.8% of patients treated with an oncologic therapy[34]. In particular, the remission rate following radiotherapy was higher than that of chemotherapy (97.8% *vs* 85.9%; $P = 0.01$), and was similar to that of surgery. However, radiotherapy preserves the stomach and its functions, without the possible long-term complications of gastric surgery, which include cancer risk on the remnant stomach. On the contrary, data on rituximab monotherapy seem to be less encouraging, with the lymphoma remission rate being achieved in only 59.3% of 27 treated patients[34]. Overall, these data suggest that it is possible to successfully treat more than 90% of patients who fail lymphoma remission following *H. pylori* eradication.

HOW TO PERFORM THE FOLLOW-UP?

Since neoplasia recurrence is possible even years following a complete histological remission, patients with gastric lymphoma need long-term follow-up. In an analysis of results from 994 patients, 7.2% experienced lymphoma relapse during 3253 patient-years of follow-up, with a yearly recurrence rate of 2.2%[30]. Lymphoma relapse in these patients may occur either following *H. pylori* reinfection or without infection recurrence. A systematic review found a bacterial reinfection in 18 (2.7%) of 676 gastric lymphoma patients at long-term follow-up, with an estimated yearly reinfection rate of 0.7%[29]. Therefore, a scheduled histological follow-up is mandatory in these patients in order to promptly detect either a bacterial recurrence or lymphoma relapse.

Based on both the possible multifocal involvement of the gastric mucosa and the absence of clear endoscopic lesions in some patients, lymphoma remission should be regarded as achieved only when consecutive controls have been negative. In particular, following *H. pylori* therapy, as well as an anti-neoplastic therapy, at least 2 consecutive (at 1 and 3 mo) negative endoscopic and histological controls are recommended to correctly establish neoplasia remission[32]. When remission is achieved, further endoscopic controls, with biopsy mapping on all the gastric sites, should be performed every 6 mo for the first 2 years and every 12 mo for the successive 5 years (Table 2), even though there are no clear recommendations for the end of follow up[32]. In some patients, minimal lymphoma residuals may persist at histological assessment without macroscopic lesions detectable at endoscopy. It has been suggested that these patients may be safely managed with a "watch and wait" strategy based on scheduled follow-up. Indeed, a recent study enrolling 107 stage I lymphoma patients with a median follow-up of 42.2 mo found that histological residuals regressed in 32% cases without any further therapy, remained stable in 67%, progressed in 4%, while one patient developed high-grade lymphoma[35]. The possibility of onset of a high-grade neoplasia has been also determined in a pooled-data analysis where 0.05% of patients who were initially cured for low-grade lymphoma developed a high-grade neoplasia at long-term follow-up[30]. Another possible consequence following successful remission of gastric lymphoma is represented by the onset of a second neoplasia[28,36]. Indeed, a study found that as many as 9 of 10 deaths were due to a cancer development within 3 years following lymphoma remission[37]. In particular, an increased incidence of gastric cancer has been observed in these patients[31,38]. These observations suggest that patients with gastric lymphoma require an extensive follow up, not only for possible lymphoma recurrence in the stomach, but also for an increased neoplastic risk, which seems only in part to be related to the use of chemotherapy[19,39].

CONCLUSION

The stomach is the most frequently involved site for extranodal lymphoma. Among gastric lymphomas, the onset of a low-grade, B-cell neoplasia is strictly linked to *H. pylori* infection, according to a strain-host organ-specific process[9]. A definitive role for *H. pylori* in high-grade transformed MALT lymphoma has been also recently highlighted[26], and remission of low-grade lymphoma with antibiotic therapy has been anecdotally reported in some patients with undetectable *H. pylori* infection[40]. Primary gastric lymphoma shows an overall good prognosis when diagnosed and treated at an early stage; that is, when it is confined to the gastric wall or local lymph nodes. Indeed, *H. pylori* eradication leads to lymphoma remission in nearly 80% of stage I patients and in more than half

of the cases when neoplasia is treated in stage Ⅱ1. When neoplastic lesions are confined within the sub-mucosa, localized in the antral region of the stomach, or the *AP12-MALT1* translocation is lacking in the tumoral B cells, lymphoma remission is highly probable following *H. pylori* eradication[30]. In those patients with lymphoma persistence despite bacterial cure, anti-neoplastic therapy is needed, and radiotherapy seems to be the most effective treatment[34]. Immunotherapy with monoclonal antibodies is an emerging therapeutic strategy and its role, particularly as a concomitant therapy, deserves to be evaluated in future trials. It has been recommended that surgery should be reserved for select cases, since equally effective and stomach-conserving therapies are available[32]. When lymphoma remission has been opportunely verified, a scheduled long-term endoscopic, histological follow up is needed in all gastric lymphoma patients. Finally, the higher probability of a second neoplasia in these patients requires careful clinical control.

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GUIDELINES FOR CLINICAL PRACTICE

Early postoperative feeding in resectional gastrointestinal surgical cancer patients

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Abstract

Malnutrition is present in the majority of patients presenting for surgical management of gastrointestinal malignancies, due to the effects of the tumour and preoperative anti-neoplastic treatments. The traditional practice of fasting patients until the resumption of bowel function threatens to further contribute to the malnutrition experienced by these patients. Furthermore, the rationale behind this traditional practice has been rendered obsolete through developments in anaesthetic agents and changes to postoperative analgesia practices. Conversely, there is a growing body of literature that consistently demonstrates that providing oral or tube feeding proximal to the anastomosis within 24 h postoperatively, is not only safe, but might be associated with significant benefits to the postoperative course. Early post operative feeding should therefore be adopted as a standard of care in oncology patients undergoing gastrointestinal resections.

Key words: Early feeding; Surgery; Meta-analysis; Randomised controlled trials

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INTRODUCTION

Malnutrition is a common finding in patients presenting for surgical management of gastrointestinal malignancies, with an estimated prevalence in this group of 40% to 80%[1]. A complex mix of factors, such as tumour location, tumour type, stage of disease, and preoperative radiation and/or chemotherapy treatments, might predispose patients to malnutrition. Nausea, vomiting, reduced appetite, early satiety, taste changes, diarrhoea, pain, mucositis, physical obstruction, and malabsorption could result in weight loss, which in turn is a strong prognostic indicator of poor outcome in terms of survival and response to treatment. Similarly, cancer cachexia is frequently observed in patients with solid tumours of the gastrointestinal tract, and it is estimated that the physical

Table 1 Randomised controlled trials investigating early feeding published since 2005

Study	Year	Types of Gastrointestinal Surgery	*n* (Trad/Early)	Early feeding protocol	Outcomes
Lucha *et al*[4]	2005	Open colorectal surgery	25/26	Regular diet from 8 hr following surgery	No difference in post operative complications between groups (1 d *vs* 1 d) or LOS 6.6 d *vs* 6.3 d
Zhou *et al*[5]	2006	Excision and anastomosis for colorectal tumour	155/161	Liquid fibreless diet D1-3 post *op*	Statistically significant benefits of early feeding Flatus 3.0 ± 0.9 d *vs* 3.6 ± 1.2 d, $P = 0.000$ Stool 4.1 ± 1.1 d *vs* 4.8 ± 1.4 d, $P = 0.000$ LOS 8.4 ± 3.4 d *vs* 9.6 ± 5.0 d, $P = 0.016$ Reduced complications with early feeding Reduced febrile illness: 3 *vs* 15, $P = 0.042$ Pulmonary infection: 1 *vs* 7, $P = 0.034$ Pharyngolaryngitis: 5 *vs* 36, $P = 0.000$ No differences in wound complications 4 *vs* 3, $P = 1.0$ No differences in anastomotic leakage 2 *vs* 4, $P = 0.441$
Han-Geurts *et al*[6]	2007	Open colorectal surgery	50/46	Regular diet from D1 post *op*	No statistically significant differences in outcomes between groups in any in-hospital complication, including mortality. No statistically significant differences between return of bowel function and length of hospital stay between groups
Lassen *et al*[7]	2008	Hepatic, pancreatic, oesophageal, gastric resections, bilioenteric and gastroenteric bypass procedures, unspecified procedures in which traditional NBM management would be indicated	227/220	Early oral feeding provided with ordinary hospital diet from D1 post *op* NB control group received enteral nutrition *via* a jejunostomy tube from D1 post *op*	No differences between number of patients major complications between groups (33% in jejunum fed *vs* 28% early oral, $P = 0.26$); less overall complications in early oral feeding group (100 *vs* 165, $P = 0.012$) No differences in mortality between groups within the trial period (8.4% early jejunum feeding *vs* 5.9% early oral, $P = 0.36$) Increased likelihood of intra-abdominal abscesses in gastrectomy patients with early jejunum feeding *vs* early oral intake (6 *vs* 0, $P = 0.012$) Shorter duration to passage of flatus early oral feeding group (2.6 *vs* 3.0 d, $P = 0.01$); no difference for duration to first bowel motion (4.3 *vs* 4.0 d, $P = 0.112$) Longer length of stay with jejunum fed patients (16.7 *vs* 13.5 d, $P = 0.046$)

wasting of both fat and lean body tissue associated with this syndrome is implicated in approximately 30% to 50% of all cancer deaths[1].

EDITORIAL

Traditional perioperative care following resectional surgery for gastrointestinal cancer involves, among other things, withholding of nutritional provision postoperatively until resumption of bowel function, as evidenced by passage of flatus or first postoperative bowel motion, which in some cases might not occur for close to a week after surgery. Reasons purported for this practice include reducing the risk of postoperative abdominal distension, nausea/vomiting and subsequent concerns regarding anastomotic breakdown, wound dehiscence, and pulmonary aspiration. Moreover, when dietary intervention is recommenced, fluids of limited nutritional value such as water, tea, lemonade, consommé soups and jelly are traditionally provided for the first several days until tolerance is thought to be established[2]. This could result in a patient receiving little or no nutrition within the first week post surgery, further contributing to the nutritional deficit incurred during the perioperative period and exacerbating the weight loss and malnutrition experienced by this already nutritionally vulnerable patient group[2].

However, in the last 30 years, many studies have challenged this traditional approach to postoperative nutritional care by investigating the safety, feasibility, and benefits of providing nutrition within 24 h following gastrointestinal surgery. Since the first randomised controlled trial investigating this topic in 1979[3], there have been no less than 30 randomised controlled trials investigating this topic in some form, the majority of which have been conducted in patients receiving surgical oncology management. The results of these studies have collectively failed to support the traditional postoperative management principles, and many demonstrate clear benefits associated with early feeding in terms of nutritional, biochemical, anthropometric, financial, and clinical outcomes. In particular, despite long held concerns that early feeding would increase the likelihood of anastomotic dehiscence, this finding was not significantly associated with the early provision of nutrition in any individual study that reported on this outcome (Table 1)[4-7]

Table 2 Comparison of outcomes and characteristics of published meta-analyses on early feeding

	Lewis, Egger, Sylvester & Thomas *BMJ* 2001[8]	Andersen, Lewis & Thomas *Cochrane Database Syst Rev* 2006[9]	Lewis, Andersen & Thomas *J Gastrointest Surg* 2009[10]
Inclusion criteria	Elective gastrointestinal surgery RCTs Enteral feeding within 24 h post *op vs* NBM/traditional management Included unpublished data	RCTs (un/published) Colorectal surgery Early feeding (within 24 h) *vs* NBM Malignant/benign disease incl. IBD Studies solely in paediatric population RCTs with no blinding If reported on outcomes including adverse outcomes, mortality	RCTs (unpublished/published) Colorectal surgery Early feeding (within 24 h) *vs* NBM Malignant/benign disease including inflammatory bowel diseases Studies solely in paediatric population RCTs with no blinding If reported on outcomes including adverse outcomes, mortality
Exclusion criteria	Not stated	PN Non-RCTs Unpublished abstracts with no correspondence data	PN Non-RCTs Unpublished abstracts with no correspondence data
Number of patients	929	1173	1173
Number of included studies	11	13	13
Publication dates	1979-1998	1979-2004	1979-2004
Gastrointestinal surgery types included	Colonic, ileal or colonic resection; oesophago-gastrectomy, gastrectomy, ileoanal J pouch, reanastomosis; esophagectomy, pancreatoduoden-ectomy; unspecified laparotomy	Colonic, ileal or colonic resection; oesophago-gastrectomy, gastrectomy, ileoanal J pouch, reanastomosis; esophagectomy, pancreatoduodenec-tomy; unspecified laparotomy	Colonic, ileal or colonic resection; oesophago-gastrectomy, gastrectomy, ileoanal J pouch, reanastomosis; esophagectomy, pancreatoduodenectomy; unspecified laparotomy
Outcomes			
Wound infections	RR 0.71 (0.44-1.17) χ^2 value not reported, $P = 0.074$	RR 0.77 (0.48-1.22) $P = 0.3$ (FEM) $\chi^2 = 10.30$ $P = 0.26$	RR 0.78 (0.38, 1.68) (REM) RR 0.77 (0.48-1.22) $P = 0.3$ (FEM) $\chi^2 = 10.30$ $P = 0.26$
Intra-abdominal abscesses	RR 0.87 (0.31-2.42) χ^2 value not reported, $P = 0.84$	RR 0.87 (0.31–2.42) $P = 0.8$ $\chi^2 = 1.45$ $P = 0.84$	RR 0.94 (0.32, 2.77) (REM) RR 0.87 (0.31–2.42) $P = 0.8$ (FEM) $\chi^2 = 1.45$ $P = 0.84$
Pneumonia	RR 0.73 (0.33–1.59) χ^2 value not reported, $P = 0.85$	RR 0.76 (0.36-1.58) $P = 0.5$ $\chi^2 = 3.73$ $P = 0.81$	RR 0.71 (0.32, 1.59) (REM) RR 0.76 (0.36-1.58) $P = 0.5$ (FEM) $\chi^2 = 3.73$ $P = 0.81$
Any infection	RR 0.72 (0.54-0.98) $P = 0.036$ $\chi^2 = 10.7$, $P = 0.22$	Not assessed	Not assessed
Mortality	RR 0.48 (0.18-1.29) $P = 0.15$ χ^2 value not reported, $P = 0.99$	RR 0.41 (0.18-0.93) $P = 0.03$ $\chi^2 = 0.6$ $P = 0.99$	RR 0.42 (0.18, 0.96) (REM) RR 0.41 (0.18-0.93) $P = 0.03$ (FEM) $\chi^2 = 0.6$ $P = 0.99$
Anastomotic dehiscence	RR 0.53 (0.26-1.08) $P = 0.08$ $\chi^2 = 2.1$, $P = 0.96$ NB-little evidence that data from proximal *vs* distal feeding results differed $P = 0.42$	RR 0.69 (0.39-1.32) $P = 0.3$ $\chi^2 = 4.89$ $P = 0.77$	RR 0.62 (0.30, 1.28) (REM) RR 0.69 (0.39-1.32) $P = 0.3$ (FEM) $\chi^2 = 4.89$, $P = 0.77$ for FEM. No χ^2 reported for REM
Length of hospital stay	-0.84 d (-0.36-1.33) $P = 0.001$ $\chi^2 = 16.2$, $P = 0.094$	-0.60 d (-0.66, -0.54) $\chi^2 = 18.86$ $P = 0.06$	-0.89 d (-1.58, -0.20) (REM) -0.60 d (-0.66, -0.54) (FEM) $\chi^2 = 18.86$ $P = 0.06$
Vomiting	RR 1.27 (1.01-1.61) $P = 0.045$ χ^2 value not reported, $P = 0.52$ NB-non-significant increase in N&V with early feeding where NGs were not placed at time of surgery RR 1.21 (0.73-1.99) $P = 0.46$	RR 1.27, (1.01-1.61) $P = 0.04$ $\chi^2 = 4.21$ $P = 0.52$	RR 1.23 (0.97, 1.55) (REM) RR 1.27 (1.01-1.61) (FEM) $\chi^2 = 4.21$ $P = 0.52$

95% Confidence intervals in closed brackets. RCT: Randomised controlled trial; PN: Parenteral nutrition; NBM: Nil by mouth; RR: Relative risk ratio; FEM: Fixed effects model (of meta-analysis); REM: Random effects model (of meta-analysis); N&V: Nausea and vomiting.

or by any of the meta-analyses examining this topic (Table 2)[8-10]. Furthermore, a recent study has also demonstrated the safety of early oral feeding within 24 h of receiving major upper gastrointestinal surgery such as gastrectomy and Whipple's procedures[7].

Withholding nutrition from patients until the resolution of the transient postoperative ileus has been employed as the standard postoperative management for well over

100 years[11], and is thought to have developed in response to the high rates of postoperative emesis experienced by patients anaesthetised with traditional agents, such as ether and chloroform[12]. From this origin, a cautious reintroduction of diet following operative procedures has been adopted, irrespective of the site of surgery, and particularly so if it has involved the gastrointestinal tract[12]. A textbook on surgical after-treatment from 1915 recommends "feed(ing) the patient as soon as possible, but at the same time to avoid distension" for patients undergoing abdominal surgery, for which a clear fluid diet (consisting of water, tea and sparkling wine) is promoted in the first few days post surgery, followed by boiled fish or eggs after "a day or two"[13]. The addition of other elements such as dairy and "farinaceous" (starchy) foods are recommended to be "cautiously added" after a few days on the light protein diet allowing the "gradual return made to a full mixed diet"[13]. Similar concepts were promoted into the 1930's with dietary intake being limited to milk diluted with limewater on the third or fourth postoperative day, once flatus had been passed[12]. By the 1940's a more rapid progression through the dietary stages were appearing in surgical texts; however, little in terms of dietary composition or reasoning behind the provision of this had changed. A textbook from 1940 advises to avoid oral nutrition within the first 24 h post surgery so as not to "interfere with" the anticipated paralytic ileus resulting from physical manipulation of the bowel, and to commence milk and water orally after 1 d, then solids 48 h thereafter[14]. Another source makes the recommendation of "giving water in the first 12 h, then liquids for the next 24 h, and thereafter a light diet until the bowels have moved" following abdominal and thoracic surgery[15]. Even within the last 20 years these recommendations have been largely adhered to and promoted[16].

Despite a growing number of studies that challenge the benefit of this long held surgical tradition, clinicians in many cases have been slow to adopt these practices. Perhaps this is best illustrated through the example of "Fast-Track" perioperative programs, which incorporate early feeding, among other strategies, in a structured program in an attempt to hasten postoperative recovery[17]. These programs have demonstrated compelling results in support of a structured, multi-modal approach-particularly in colorectal surgery[18]; However, the widespread implementation of these practices has been disappointingly low[19,20].

Based on this information, several points should be made clear. Firstly, patients undergoing resectional surgery for gastrointestinal malignancies frequently present with malnutrition symptoms, weight loss, and/or cachexia, and do not have the reserves to withstand extended periods of fasting without risking further nutritional compromise that will adversely affect their postoperative course and overall prognosis. Secondly, the evidence supporting the ongoing practice of withholding nutrition postoperatively is lacking: oral nutrition has been shown to be safe even after major upper gastrointestinal surgery. Furthermore, it appears to confer significant benefits to the postoperative course, especially when incorporated into a multi-modal perioperative program. Thirdly, the rationale for which traditional postoperative nutritional management was introduced has essentially been rendered obsolete with the availability of modern anaesthetic agents and changes to post-operative analgesic management. In this day and age of evidence-based practice, there can be little justification for the continuation of the outdated and detrimental practice of withholding much needed nutrition to oncology patients during their postoperative course. Early feeding appears to have much to offer both to the patients and the institutions in which they are being treated, and given the overwhelming evidence supporting its safety, early feeding can, and should, be adopted with confidence as part of standard postoperative care.

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REVIEW

Appendiceal neuroendocrine tumors: Recent insights and clinical implications

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Abstract

New insights emerged last decade that enriched our knowledge regarding the biological behavior of appendiceal neuroendocrine tumors (NETs), which range from totally benign tumors less than 1cm to goblet cell carcinomas which behave similarly to colorectal adenocarcinoma. The clinical implication of that knowledge reflected to surgical strategies which also vary from simple appendicectomy to radical abdominal procedures based on specific clinical and histological characteristics. Since the diagnosis is usually established post-appendicectomy, current recommendations focus on the early detection of: (1) the subgroup of patients who require further therapy; (2) the recurrence based on the chromogranin a plasma levels; and (3) other malignancies which are commonly developed in patients with appendiceal NETs.

Key words: Appendiceal carcinoids; Neuroendocrine tumors; Goblet cell carcinoma; Right hemicolectomy

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INTRODUCTION

In 1907, Oberndorfer[1] first introduced the term "carcinoid" to describe "little carcinomas" of the small intestine which were thought (by him at that time) to be probably benign.

However, the continuous knowledge which was added by studying these tumors for nearly a century strengthen the notion that the above term was inaccurate or inadequate to describe several parameters of this heterogeneous group of gastrointestinal tumors (including the appendiceal one). Thus, the term "carcinoid" was replaced by the term "gastroenteropancreatic neuroendocrine tumors, GEP-NETs"[2]. The term "appendiceal NET" will be used hereafter.

According to the current WHO classification[3], appendiceal NETs are classified as: (1a) Well differentiated NETs with benign biological behaviour or (1b) Well differentiated NETs with uncertain malignant potential; (2) Well differentiated neuroendocrine carcinoma (with low malignant potential); and (3) Mixed exocrine-neuroendocrine carcinoma. Goblet cell carcinoma (synonyms: adenocarcinoid, mucous adenocarcinoid) belongs to the last category.

BENIGN AND MALIGNANT APPENDICEAL NETs

Epidemiology

Although appendiceal NETs constitute an unusual and sporadic entity, it accounts for more than 50% of all primary tumors of the appendix[4].

Benign appendiceal NETs represent the second commonest neuroendocrine neoplasms of the gastrointestinal tract (small bowel NETs being the commonest) and their histological diagnosis is established, usually incidentally, in 0.3%-0.9% of patients undergoing appendicectomy. This means that the probability of a surgeon coming across an appendiceal NET is once for every 100 to 300 appendectomies performed by him. The annual incidence is about 2-3 newly diagnosed cases per million of general population although post-mortem studies increase the incidence to 170 cases per 100 000. The mean age of patients at the time of diagnosis is at end of the second decade of life with an increased incidence among females[5-8]. The last finding probably reflects the increased use of diagnostic laparoscopy among females for atypical lower abdominal pain and the concomitant laparoscopic appendectomies performed[9].

Malignant appendiceal NETs represent the third commonest (after small bowel and rectum) malignant neuroendocrine neoplasms of the gastrointestinal tract with an annual incidence of 0.63 cases per million of the general population and the mean age of the patients at time of the diagnosis in the 5th decade of life[8].

Clinical presentation

Normally, appendiceal NETs remain asymptomatic. Although accurate preoperative diagnosis using abdominal computed tomography (CT)[10] or ultrasound[11] scans has been reported, the total number of the enrolled patients is extremely small (only case reports have been published) and thus is not suitable for definite conclusions. Therefore, for the vast majority of cases, the diagnosis of appendiceal NETs is established incidentally postoperatively in the specimens of appendectomies which had been performed due to either acute appendicitis or recurrent, chronic, dull, nonspecific lower right quadrant abdominal pain[6,12]. Carcinoid syndrome is very uncommon (< 1%).

Diagnosis

Since most appendiceal NETs are diagnosed postoperatively, any effort to be diagnosed preoperatively is practically unrealistic so the diagnostic work-up should focus on the early detection of recurrence in patients who have already had surgery.

The use of plasma chromogranin-A levels as a tumor marker contributes to the differential diagnosis from goblet cell carcinoma, the early detection of recurrence and the long term follow-up of metastatic disease. All patients should be investigated 6 and 12 mo postoperatively and then annually while the follow-up should be lifelong[13].

Especially for tumors > 2 cm, a CT scan and somatostatin receptor scintigraphy (SRS) is recommended at 6 mo and 12 mo postoperatively and then annually. Colonoscopy is advised for the early detection of synchronously present or metachronously developed large bowel tumors[13].

Biological behavior

Approximately 80% of appendiceal NETs have a maximum diameter of < 1 cm, 15% have a diameter 1-2 cm and only 5% have a diameter greater than 2 cm[14]. Tumor size greater than 2 cm strongly correlates both to metastatic potential[15] and to an unfavourable 5 years survival rate[16].

Approximately 70%-75% of the tumors are located in the apex, 15%-20% in the body and 5%-10% in the base of the organ[14]. Although there is not enough evidence to support the theory that the location of the tumor correlates to the overall survival, cecum invasion or positive resection margins should be considered for planned future therapeutic strategies[17].

A multifocal pattern of the disease along the appendix has not been described yet. However, the coexistence of appendiceal NET with small bowel or rectal NETs[15], colorectal cancer[18], Crohn's disease[19] and synchronous or metachronous development of malignancies outside the gastrointestinal tract[15] are well documented.

The possibility of lymph node metastases from appendiceal NETs with vascular invasion is estimated as high as 30%[7] but only 1% for tumors with appendiceal mesentery invasion[20]. However, the prognostic significance of appendiceal mesentery invasion remains controversial since its relationship to distant metastases development has been reported as between 0[20] and 4.1%[15]. To date, there have been no reports correlating lymph node metastases to appendiceal serosa invasion.

The rate of cellular proliferation (as it expressed by the Ki-67) does not seem to be of prognostic value.

Table 1 Classification and staging of appendiceal NETs according to the TNM system

Stage	T	N	M
I	T1	N0	M0
II	T1	N1	M0
	T2	N0	M0
III	T2	N1	M0
	T3	Any N	M0
IV	Any T	Any N	M1

NETs: Neuroendocrine tumors; T1: Tumor < 2 cm; T2: Tumor ⩾ 2 cm but < 3 cm; T3: Tumor ⩾ 3 cm; N0: No lymph node metastases; N1: Regional lymph node metastases; M0: No metastases; M1: Distant metastases.

Classification and staging

Based on the analysis of the published report from the SEER database between 1977-2004, it is suggested that the first proposed TNM classification and staging systems for appendiceal NETs (which was based on the report from the SEER database between 1973-1999)[21] should be modified[22] according to Table 1.

Treatment

Current guidelines[13,22,23] propose simple appendectomy as adequate and curative for the treatment of appendiceal NETs < 1 cm, while for tumors 1-2 cm, a simple appendectomy followed by periodic postoperative follow-up for 5 years is recommended.

Right hemicolectomy (within 3 mo from the appen-

dicectomy) should be reserved for patients in whom at least one of the following criteria is present: tumor size > 2 cm, location of the tumor at the base of the appendix, infiltration of the cecum, positive surgical resection margins, appendiceal mesentery invasion, metastatically infiltrated mesoappendiceal lymph node, presence of undifferentiated or low differentiated cells or presence of goblet cells.

Serosal, vascular, lymphatic or perineural invasion alone does not constitute inclusion criteria for right hemicolectomy.

GOBLET CELL CARCINOMA

Epidemiology

Goblet cell carcinomas (GCC) constitute less than 5% of all primary appendiceal tumors[24] and, similar to the appendiceal NETs, their diagnosis is established usually incidentally in 0.3%-0.9% of patients undergoing appendicectomy. Its annual incidence is 0.05 new cases per 100000 of general population[23] with an equal distribution between the sexes and the mean age of the patients at the time of diagnosis in the 6th decade of life, nearly 20 years later than the mean age of the diagnosis of malignant appendiceal NETs and almost 10 years earlier than the mean age of the diagnosis of the appendiceal adenocarcinoma[25].

Histology

GCC is derived from undifferentiated stem cells which are completely different from the endocrine cells in the mucosal stroma. The degree of integration of the goblet cells versus APUD cells varies from pure GCC to pure carcinoid tumor. GCC cells have two type of granules which are mainly acid mucinous, are not mixed and can be recognized by different histochemical staining[26].

In their recent study, Tang *et al*[27] tried to answer the long-standing question: "Should GCCs be classified as NETs or as *de novo* mucous adenocarcinomas of the appendix?" Based on histological findings, they proposed classification of GCCs in: (1) Typical GCC (type A); (2) adenocarcinoma ex GCC, signet ring cell type (Type B); and (3) adenocarcinoma ex GCC, poorly differentiated carcinoma type (Type C).

On one hand, GCCs are developed in epithelium without dysplasia and this development is not related to the adenoma-carcinoma sequence of carcinogenesis. The immuno-phenotype of typical GCCs is different from the immuno-phenotype of adenocarcinoma and genetic alterations of neuroendocrine origin, completely different from the genetic alterations which lead to adenocarcinoma formation, are responsible for that[28]. Moreover, both NETs and GCCs of the appendix express chromogranin-A[29].

On the other hand, the positive expression of p53 range from 0% in type A GCC to 100% in type C GCC, findings suggestive that for the transformation to the adenocarcinoma phenotype in type C, the immunohistochemical expression of Cytokeratins (CK) 7 and 20 in appendiceal NETs and GCCs disclosed that GCCs express CKs similarly to colonic adenocarcinomas, while NETs do not[30]. Immunohistochemical expression of Math1 and HD5 is observed in GCCs but not in NETs[31] while the biological behavior of GCCs is identical to adenocarcinomas but not to NETs.

Based on the above findings, it is proposed that GCCs should constitute a distinct histological and clinical entity different from the appendiceal NETs, while the classification which is proposed by Wang *et al*[32] seems to comply to the biological behavior of the tumors and with the prognosis of the patients.

Clinical presentation

In the majority of cases, the disease remains asymptomatic. Acute appendicitis (due to luminal obstruction by the tumor) is the main symptom followed by atypical abdominal pain and abdominal mass. Unusual symptoms are intussusception, gastrointestinal bleeding, bowel obstruction, anemia and miscellaneous urinary manifestations[26].

In 11% of cases the disease is already metastatic at the time of diagnosis, mainly to the ovaries and peritoneum[23]. However, studies[33] propose that the ovarian metastases should be considered as secondary to adenocarcinoma rather than to appendiceal GCC, further supporting the proposed by Tang *et al* classification.

Diagnosis

In fact, most appendiceal GCCs are diagnosed postoperatively so any effort for accurate preoperative diagnosis is unrealistic. The diagnostic work-up should focus on the early detection of recurrence in patients who have already had surgery.

Magnetic resonance imaging is more sensitive than CT and CT more sensitive than SRS in the early detection of pulmonary, hepatic and peritoneal metastases[34]. Plasma chromogranin-A levels have no diagnostic value while the periodic measurement of tumor markers related to the mucinous characteristics of the tumor such as CEA, CA 19-9 and CA 125 is recommended[23]. Lifelong screening for synchronous or metachronous malignancies is also recommended[13].

Treatment

Right hemicolectomy (usually performed after the initial appendectomy) is recommended as the treatment of choice after the histological confirmation of GCC independent of the size of the primary tumor[13]. In female patients with GCC of the appendix, regardless of age, bilateral salpingo-oophorectomy is also advocated. In cases with advanced peritoneal dissemination, cytoreductive surgery with adjuvant intraperitoneal chemotherapy may offer prolonged survival[35]. Adjuvant chemotherapy is usually not effective although it can be used in patients with obvious spread of the disease[36]. Chemotherapeutic protocols are the same as those used in the treatment of colorectal adenocarcinoma.

CONCLUSION

Based on new insights that emerged last decade, the biological behavior of appendiceal NETs ranges from totally

Table 2 Recommended surgical strategies for appendiceal NETs based on specific clinical and histological characteristics

Indications	Type of operation
Tumor size < 1 cm	Appendicectomy
Tumor size 1-2 cm	Appendicectomy + Regular F/Up for 5 years
Tumor size > 2 cm	Right hemicolectomy
Location of the tumor at the base of the appendix	Right hemicolectomy
Infiltration of the cecum	Right hemicolectomy
Positive surgical resection margins	Right hemicolectomy
Appendiceal mesentery invasion	Right hemicolectomy
Metastatically infiltrated mesoappendiceal lymph node	Right hemicolectomy
Presence of undifferentiated or low differentiated cells	Right hemicolectomy
Presence of goblet cells	
Goblet cell carcinoma in males	Right hemicolectomy
Goblet cell carcinoma in females (regardless of age)	Right hemicolectomy + Bilateral salpingo-oophorectomy
Peritoneal dissemination from goblet cell carcinoma	Cytoreductive surgery + Adjuvant intraperitoneal chemotherapy

benign tumors less than 1 cm to goblet cell carcinomas which behave similarly to colorectal adenocarcinoma. Depending on specific clinical and histological characteristics, surgical strategies also vary from simple appendicectomy to radical abdominal procedures (Table 2). Since, in the vast majority of cases, the diagnosis is usually established post-appendicectomy, it is crucial for clinicians to identify the subgroup of patients who require further therapy, to detect early the recurrence based on the chromogranin A plasma levels and to detect early other malignancies which are commonly developed in patients with appendiceal NETs.

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BRIEF ARTICLE

Computed tomography overestimation of esophageal tumor length: Implications for radiotherapy planning

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Abstract

AIM: To assess the relationship between preoperative computed tomography (CT) and postoperative pathological measurements of esophageal tumor length and the prognostic significance of CT tumor length data.

METHODS: A retrospective study was carried out in 56 patients who underwent curative esophagogastrectomy. Tumor lengths were measured on the immediate preoperative CT and on the post-operative resection specimens. Inter- and intra-observer variations in CT measurements were assessed. Survival data were collected.

RESULTS: There was a weak correlation between CT and pathological tumor length (r = 0.30, P = 0.025). CT lengths were longer than pathological lengths in 68% (38/56) of patients with a mean difference of 1.67 cm (95% CI: 1.18-2.97). The mean difference in measurements by two radiologists was 0.39 cm (95% CI: -0.59-1.44). The mean difference between repeat CT measured tumor length (intra-observer variation) were 0.04 cm (95% CI: -0.59-0.66) and 0.47 cm (95% CI: -0.53-1.47). When stratified, patients not receiving neoadjuvant chemotherapy showed a strong correlation between CT and pathological tumor length (r = 0.69, P = 0.0014, n = 37) than patients that did (r = 0.13, P = 0.43, n = 19). Median survival with CT tumor length > 5.6 cm was poorer than with smaller tumors, but the difference was not statistically significant.

CONCLUSION: Esophageal tumor length assessed using CT does not reflect pathological tumor extent and should not be the only modality used for management decisions, particularly for planning radiotherapy.

Key words: Computed tomography; Esophageal cancer; Radiotherapy

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INTRODUCTION

Tumor length is a recognised independent adverse prognostic factor following surgery or radiotherapy in patients with esophageal cancer[1-3]. In a study by Griffiths *et al*[2], patients with pathological tumor length > 3.5 cm had a poorer prognosis than those with shorter tumors following esophagogastrectomy for cancer. Tumor dimensions, including length, are included in the United Kingdom Royal College of Pathologist's minimum dataset for the histopathological reporting of the disease[4]. As such, its accurate measurement preoperatively would provide essential information for treatment planning and prognosis.

Contrast enhanced computed tomography (CT) is an important aspect of staging patients with esophageal cancer[5-8]. However, published studies on the relationship between tumor lengths reported on the preoperative CT scan and the corresponding length on the postoperative pathological specimen are inconsistent. Using pathological length as the gold standard and discounting length differences of 1 cm or less, Drudi *et al*[9] reported 32% concordance between the two measurement types and CT was found to under-estimate tumor length. However, Quint *et al*[10] reported CT generally overestimated tumor length by 1.5-7.5 cm. This finding was echoed by Gao *et al*[11] in which 34 patients with middle and distal third esophageal squamous cell carcinoma were found to have longer tumor length on the preoperative CT scans with a mean CT length of 4.48 cm *vs* mean pathological length of 3.82 cm.

The extent of gross esophageal tumor impacts on the surgeon's choice of operative approach. Also, delineation of gross tumor volume (GTV) for radiotherapy is reliant on a CT scan performed for the purposes of radiotherapy planning, supplemented by information obtained from clinical staging procedures. The clinical target volume (CTV) will encompass the GTV and additional tissue based on pathological extent of subclinical disease from resected surgical series[11]. It is, therefore, essential to ascertain as accurately as possible the gross tumor extent and staging by CT, barium imaging, endoscopy and endoscopic ultrasound (EUS).

The aims of this work were to compare the level of agreement between pathological and CT length of resected esophageal adenocarcinoma and evaluate the implication of any inter- and intra-observer variation in CT measurement. We also assessed any association between tumor length and other clinico-pathological factors and the degree of contrast distension of the stomach or esophagus. In principle, good visceral distension by contrast agent should help delineate tumor dimensions but whether this plays a role in optimising the accuracy of CT measurement of tumor length is not clear. The study also investigated the prognostic value of tumor length measured preoperatively using CT.

MATERIALS AND METHODS

The study was retrospective and involved 56 patients who underwent esophagogastrectomy for cancer between September 1999 and June 2007 at the University Hospital of South Manchester, UK. There were eight females (14%) and 48 males (86%), and the median age was 65 years (range 36-82 years). Sixty-six percent (37/56) of the patients underwent neoadjuvant chemotherapy. In these cases, the post chemotherapy/pre-surgery scan was used. All tumors were adenocarcinomas of the distal third of the esophagus. Ethical approval for the study was obtained from the South Manchester Research Ethics Committee.

Radiology methods

All 56 patients underwent intravenous and oral contrast enhanced preoperative staging CT scans of the thorax and upper abdomen. The subjects were scanned at several referring hospitals using a variety of scanners. Different oral contrast preparations were utilised: Gastrografin™ based solution in 55 patients and water based, negative oral contrast in one patient. Slice thickness ranged from 4-10 mm. The CT carried out closest to the time of tumor resection was reviewed in each case. The mean time from the date of scanning to surgery was 37 d (range 1-149 d). All images were reviewed on hard copy axial images.

The slices judged to be tumor free superior and inferior to the cancer were identified, allowing a judgement of the cranio-caudal extent of the tumor. The maximal esophageal wall thickness, maximal esophageal diameter, esophageal distension, gastric distension and presence of hiatus hernia were all recorded.

The cranio-caudal tumor lengths in the immediate preoperative contrast enhanced axial CT images were estimated independently by two radiologists. A senior trainee radiologist assessed the scans of 56 patients and a specialist consultant radiologist assessed 42 of the 56 patients. The CT tumor lengths of a cohort of the patients were subsequently re-estimated independently by both radiologists. This allowed evaluation of inter- and intra-observer variation.

Pathology methods

During the study period, all esophagogastrectomy specimens from the operating theatres were immersed in formalin and sent to the Department of Histopathology for analysis. On receipt of the specimen, the pathologists inked the circumferential resection margin (CRM). The esophagus was subsequently opened along its longitudinal axis from proximal to distal extending along the greater curvature of the stomach. The opened specimen was then fixed in formalin for at least 24 h.

Information on whether the specimens were pinned or unpinned was not available. The histopathological tumor details of all the patients in the study were obtained from the computed pathology records. Macroscopic parameters were recorded as detailed in the United Kingdom Royal College of Pathologists minimum dataset for the histopathological reporting of esophageal cancer[4].

Table 1 Summary of clinicopathological factors and relationship with CT tumor length

Variable	*n*	*P*
Mean tumor length (range) (cm)		
4.2 (0-11.5)		
Median age (range) years (yr)		
65 (36-82)	56	0.12[1]
Gender		
Male	48	0.92[2]
Female	8	
Neoadjuvant chemotherapy[3]		
No	19	0.64[4]
Yes	37	
Tumor type		
Adenocarcinoma	56	
Tumor morphology		
Polypoidal	14	0.07[4]
Stenosing	15	
Ulcerating	27	
Differentiation		
Well	4	0.36[1]
Moderate	32	
Poor	20	
T-stage		
T1	8	0.18[1]
T2	13	
T3	34	
T4	1	
N-stage		
N_0	19	0.12[2]
N_1	37	
M-stage		
M_0	54	
M_{1a}	2	
Resection category		
R_0	47	0.22[2]
R_1	9	

CT: Computed tomography; R_0: Both macroscopic and microscopic clearance of the longitudinal resection margins; R_1: Microscopic evidence of tumor at the longitudinal resection margins; [1]Spearman's; [2]Mann-Whitney; [3]CT scans were carried out following neo-adjuvant chemotherapy; [4]ANOVA.

Table 2 Radiological parameters and relationship with CT tumor length

Variable	*n*	*P*
Mean tumor length (range)/(cm)		
5.9 (0-15)	56	
Mean maximum esophageal thickness (range)/(cm)		
3.1 (1.7-4.7)	56	0.011
Mean slice thickness (range)/(mm)		
5.5 (4-10)	56	0.25
Presence of hiatus hernia		
Yes	9	0.76[2]
No	47	
Degree of esophageal distension		
Good	16	0.83[1]
Moderate	16	
Poor	24	
Degree of gastric distension		
Good	23	0.74[1]
Moderate	22	
Poor	11	

[1]Spearman's; [2]Mann-Whitney.

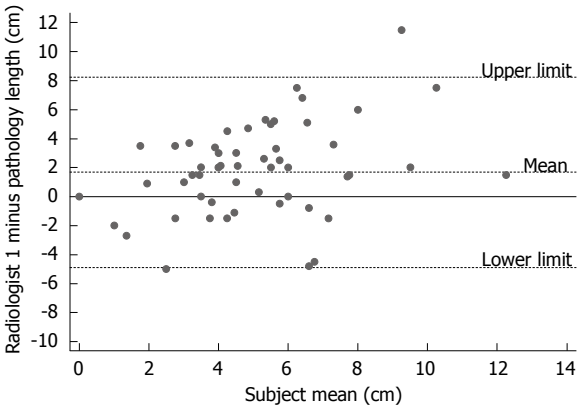

Figure 1 Bland-Altman plot showing the relationship between computed tomography (CT) and pathology measurements of esophageal tumor lengths. The difference between the two measurements was plotted against their mean. The majority of the points fall above and below the zero line showing a weak agreement.

Statistical analysis

Statistical analysis was performed using SPSS® (SPSS, Chicago, Illinois, USA) Version 11.5 and Stata® (StataCorp, 4905 Lakeway Drive, College Station, TX 77845 USA) Version 9.2. One-way analysis of variance (ANOVA), the Mann-Whitney or Spearman's tests were used to assess factors associated with tumor length. Agreement between pathological and CT lengths for each radiologist and inter- and intra-observer variation was assessed using the Bland-Altman plot[12]. Survival was defined as the time from the date of surgery until death or most recent follow up appointment and was analysed using log rank test. A $P \leqslant 0.05$ was considered to be statistically significant.

RESULTS

Tables 1 and 2 summarise the clinico-pathological and radiological details of the 56 patients. No significant associations were found between CT or pathology measurements of tumor length and patients' age, gender, tumor morphology, differentiation, overall histological stage, resection category (complete microscopic clearance *vs* microscopic evidence of tumor cells at the resection margins), presence of hiatus hernia, slice thickness and the degree of the gastro-esophageal contrast distension. However there was a significant correlation between maximal esophageal thickness and tumor length on the CT scan ($P = 0.01$).

There was a weak positive correlation between CT and pathology measurements of esophageal tumor lengths ($r = 0.30$, $P = 0.02$, $n = 56$). However, the Bland-Altman plots in Figure 1 illustrate the generally poor level of agreement between CT measurements of esophageal tumor lengths and their corresponding pathological lengths. In the Bland-Altman plot, the difference between the two measurements is plotted against their mean-the best estimate of the true value. If there is good agreement between the methods, then the results would be close to zero. Pre-operative CT

Table 3 Two separate tumor lengths readings measured by two radiologists with the corresponding pathology lengths

Patient	Pathology	1st reading of Radiologist 1	2nd reading of Radiologist 1	1st reading of Radiologist 2	2nd reading of Radiologist 2
1	3.0	5.0	5.0	5.0	6.0
2	5.0	5.3	8.1	6.7	4.6
3	5.0	7.0	6.5	7.0	8.0
4	1.5	2.4	3.4	3.5	4.0
5	4.0	9.1	8.4	8.4	3.5
6	4.0	5.0	4.5	4.5	4.0
7	2.7	4.2	4.2	3.0	3.0
8	4.2	5.6	4.9	4.2	4.9
9	7.0	8.4	8.4	9.1	9.3
10	0	6.5	5.5	8.0	7.0
11	4.0	6.6	6.6	6.2	6.6
12	3.5	5.6	4.9	6.3	5.8
13	5.5	9.1	10.3	10.3	11.6
14	4.0	7.3	5.9	9.4	6.7

Measurements are in cm.

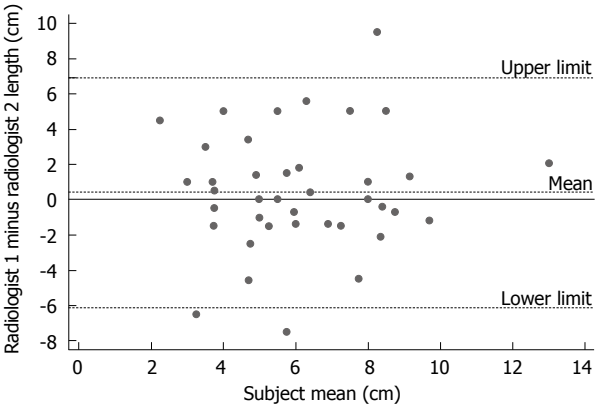

Figure 2 Bland-Altman plot for inter-observer variability of the radiologists. The limits of agreement between the radiologists range from -6.10-6.95 cm with a mean difference (95% CI) of 0.39 (-0.59 to 1.44); Indicating weak agreement between the independent measurements.

length was longer than post-operative pathology length in 68% (38/56) of the patients with an average tumor length difference of 1.67 cm (95% CI: 1.18-2.97). The difference in tumor length between CT and pathological measurements was statistically significant ($P < 0.0005$, $n = 56$, paired t-test). There was no relationship between the time from CT scan to surgery (median 37 d, range 1-149 d) and the difference in CT and pathological tumor length ($r = -0.16$, $P = 0.25$).

In order to address whether the poor agreement between CT and pathology measurements of tumor length was due to a poor reliability in obtaining CT data, a second radiologist measured tumor length in 42 of the patients. Qualitatively similar results were found to the first radiologist. There was a weak positive correlation between CT and pathological tumor length ($r = 0.20$, $P = 0.92$, $n = 42$). The average tumor length difference (CT minus pathology) was 1.52 cm (95% CI: 0.62-2.68), and CT length was longer in 69% (29/42) of the patients ($P = 0.006$, $n = 42$, paired t-test). Agreement between the two radiologists was summarised by calculating the mean difference between their measurements (Figure 2). This analysis shows a small inter-observer difference in

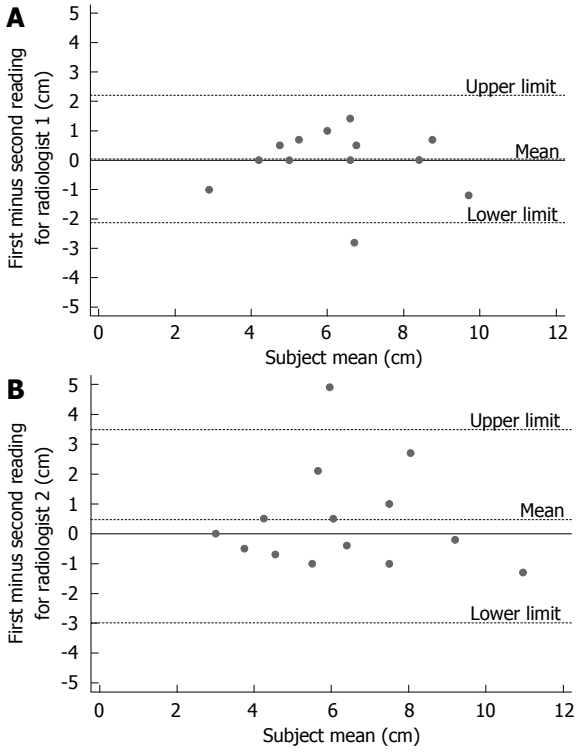

Figure 3 Bland-Altman plots of intra-observer agreement in CT measurements of esophageal tumor length. A: For radiologist 1, the limits of agreement range from -2.13 to 2.20 cm with a mean difference (95% CI) of 0.04 (-0.59 to 0.66); B: For radiologist 2, the limits of agreement range from -2.98-3.92 cm with a mean difference (95% CI) is 0.47 (-0.53-1.47).

measurements of tumor length with a mean difference in the measured tumor length between the two radiologists' being 0.39 cm (95% CI: -0.59-1.44). However, a large spread in the observations was observed, with radiologist 2 measuring one tumor 6 cm shorter and another tumor 7 cm longer than radiologist 1. As this lack of agreement between CT and pathology measurements can be attributed, at least in part, to variability in obtaining CT measurements, an assessment was made of intra-individual variability in measuring tumor length.

Table 3 summarises the two separate tumor length

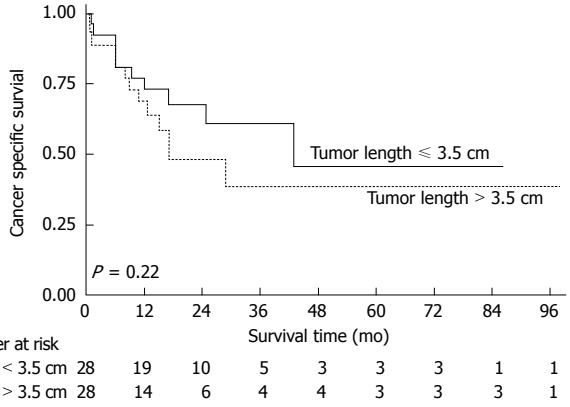

Figure 4 Kaplan-Meier plot of cancer-specific survival following surgery for 56 patients with esophageal cancer stratified according to tumor length measured using CT.

readings by the two radiologists with the corresponding pathological lengths and Figure 3 illustrates the Bland-Altman plot for intra-observer variation or repeatability. For radiologist 1 the mean difference between the two scores was 0.04 cm (95% CI: -0.59-0.66). For radiologist 2, the mean difference was 0.47 cm (95% CI: -0.53-1.47). The large 95% CIs for both radiologists suggests it is difficult to measure reliably preoperative esophageal tumor length using CT.

When patients were stratified into whether they underwent neoadjuvant chemotherapy ($n = 19$) or not ($n = 37$), a strong correlation was found between preoperative CT and postoperative pathological measurement of tumor length in the latter ($r = 0.69$, $P = 0.001$, $n = 37$) but not the former ($r = 0.13$, $P = 0.43$, $n = 19$). Bland-Altman analysis for inter-observer variability revealed a smaller mean tumor length difference between the two radiologists and relatively tighter 95% confidence intervals in the group with no neoadjuvant chemotherapy (0.27 cm; 95% CI: -1.05-1.59) than those who underwent preoperative chemotherapy (0.36 cm ; 95% CI: -136-2.08).

The median CT tumor length was 5.6 cm ($n = 56$). Despite the difficulty in obtaining repeatable CT measurements of tumor length, survival analysis revealed that the patients with tumor length ≤ 5.6 cm ($n = 28$) and > 5.6 cm ($n = 28$) had median survival times of 44 mo and 17 mo respectively. Although the survival difference was large it was not statistically significant (Figure 4).

DISCUSSION

In this study, we found no association between preoperative contrast enhanced CT defined tumor length and clinico-pathological factors. The preoperative cranio-caudal axial CT images of esophageal tumor lengths were longer than their corresponding pathological lengths following esophagogastrectomy in approximately two-thirds of the patients. In addition, results of CT measurement of tumor lengths estimated independently by the two radiologists showed marked inter- and intra-observer variability.

The proximal and distal resection margins of various tumor types have been reported to shrink significantly following formalin fixation. Some example are breast[13], colorectal[14], esophageal cancers[15] and cervical intra-epithelial neoplasia[16]. However, in all such cases, the proportion of size shrinkage attributable to the tumor itself is negligible[13-16]; and in the case of esophageal cancer, Siu *et al*[15] reported only 8% shrinkage in the formalin fixed specimen compared to tumor length *in-vivo*. This suggests that longitudinal tumor length measured in formalin fixed resected specimens is comparable to their non-fixed *in-situ* state.

The tendency for CT to overestimate esophageal tumor length compared to the corresponding pathological length was also reported by Gao *et al*[11]. They studied 34 patients with middle and distal third esophageal squamous cell carcinoma and found a statistically significant difference between the two measurement types (mean CT length of 4.48 cm *vs* mean pathological length of 3.82 cm, $P < 0.05$). This is in keeping with our finding of mean CT and pathological tumor lengths of 5.9 and 4.2 cm respectively. However, in a study of 22 patients, Drudi *et al*[9] found tumor length on the preoperative CT to be consistently shorter than the corresponding lengths on the resected specimens. The reasons for this finding were not discussed but may be related to observer error, scanning methodology or inadequate tumor delineation by contrast agent.

Although contrast CT was found to generally overestimate esophageal tumor length, the difference with pathological tumor length measurement was less marked in the cohort of patients who did not undergo neoadjuvant chemotherapy. In contrast, the correlation coefficient and inter-observer agreement were both weaker in the group of patients who had neoadjuvant chemotherapy. This finding illustrates the inherent unreliability of contrast CT in assessing tumor length particularly following preoperative chemotherapy.

A number of studies have highlighted the deficiencies of CT in assessing the extent of post chemotherapy esophageal tumor bulk regression. In these studies, the radiological response rates were significantly lower than the pathological response rate to chemotherapy resulting in an apparent upward tumor stage migration[17-20]. This in part is due to chemotherapy associated inflammatory and fibrotic changes[17].

Several factors might contribute to the differences in tumor lengths obtained using the two approaches. Such factors include the difficulty in distinguishing tumor from mural thickening resulting from peri-tumor fibrosis, edema and gastric folds at the gastro-esophageal junction by CT[17,21,22]. Other possible factors contributing to disparity between CT and pathological tumor lengths are sub-optimal coating of the mucosa by contrast agent[23], movement artefacts during the scanning process such as the respiratory or cardiac cycle[24,25] and difficulty in determining the macroscopic proximal and distal limits of the tumor radiologically. Some of these factors might also

contribute to the intra-observer variability in measuring tumor length using CT.

An important implication of this study is the selection of patients for appropriate treatment. Surgical data have shown that longer tumors are associated with increasing T-stage, nodal metastasis, worse overall TNM stage and increased tumor involvement of the resection margins[2]. In addition to selection for treatment and staging, CT is also routinely used as part of the radiotherapy planning process but protocols usually do not include the use of oral contrast medium. As larger radiation treatment volumes are associated with higher radiation doses to normal tissues such as the lungs[26-30] resulting in a higher incidence of treatment related morbidity and a poor therapeutic index, radiation therapy protocols usually exclude patients with longer tumor lengths (> 7-10 cm) from receiving radical radiotherapy. Since overestimation of *in vivo* tumor length has been commonly observed in our study, we would urge caution in excluding patients from radical radiotherapy treatment on the basis of CT findings alone. It is recommended that determination of treatment intent and target delineation of esophageal tumors during radiotherapy planning should be based on at least a further modality in addition to CT scanning as in the SCOPE (Study of Chemo-radiotherapy in Oesophageal cancer Plus or Minus Erbitux) clinical trial, currently recruiting in the UK. In the SCOPE study, where patients with a total tumor length greater than 10 cm are excluded from radical treatment, an endoscopic ultrasound (EUS) is required in addition to CT for determination of tumor length[31]. This stems from the observation that EUS more accurately measures esophageal tumor length and this imaging modality has been investigated in a number of studies[32,33].

Target definition during radiotherapy planning must be not only precise but also reliable and reproducible to avoid a geographical tumor miss and minimise the volume of normal tissue irradiated. Accurate target definition would also allow radiation dose-escalation studies to be carried out which may potentially improve clinical outcome. In a trans-Canada study in which 58 radiation oncologists were independently asked to determine the cranio-caudal length and CTV of esophageal tumors using CT images, Tai *et al*[34] found significant inter-observer variations in the target volume dimensions and also reported low longitudinal overlap of the CTV among the oncologists. They went on to show that specific training of oncologists could reduce the variations seen[35]. Our study echoes the implications of this finding in that imprecise target definition, as evidenced here by marked inter- and intra-observer variability of tumor length, may reduce the potential benefits of three-dimensional radiotherapy planning and high precision radiation dose delivery. A multidisciplinary approach in target delineation with close co-operation between the radiation oncologist and specialist gastro-intestinal CT radiologists may be helpful in this context.

Importantly, the use of positron emission tomography in combination with CT (PET-CT) in this setting could potentially ameliorate some of the limitations of CT alone, such as distinguishing a metabolically active tumor from peri-tumor edema, fibrosis and normal gastric rugal folds adjacent to subcardial tumors[36-38]. However, as PET acquisition is over several minutes, the tumor extent seen on PET images will include the tumor motion due to movement and patient breathing during the period, in contrast to helical or multi-detector CT scans, which are acquired in a few seconds. Methods such as gating of PET images may be helpful in this context.

Finally, survival analysis revealed that patients with CT tumor length ⩽ 5.6 cm had a median survival of 44 mo compared with 17 mo for those with tumor lengths > 5.6 cm (P = 0.22). This finding, albeit based on a small number of preoperative CT length measurements, concurs with published work indicating that patients with tumor length > 3.5 cm recorded from the postoperative pathological specimen have a worse prognosis[2]. The failure of our survival analysis to achieve statistical significance may be related to the small number of patients studied. However, the marked survival time difference between the two groups of patients (17 mo *vs* 44 mo) suggests that accurate measurement of tumor length on the preoperative CT scan in a bigger series could provide useful prognostic information. A sample size of approximately 100 in each arm would be required to have 80% power to detect a difference in survival using the log-rank test with a 50% and 70% survival after 12 mo (assuming a constant hazard ratio of 1.9 and a conventional significance level of 0.05).

The strength of this study lies in its relatively large number of patients compared with other series, the involvement of specialist radiologists to measure tumor length and establishing, in an objective way, intra- and inter-observer variability in the radiological reporting of esophageal tumor length. The two key limitations lie in its retrospective nature and the lack of softcopy review of scans performed on a variety of scanners in referring district general hospitals. Only axial images were reviewed and many were performed on single slice scanners (11 of 56 patients). Where scans were performed on multi-slice scanners, only hard copy axial images were available for review from the referring hospitals.

CONCLUSION

This study suggests that staging CT assessments generally overestimate macroscopic esophageal tumor length particularly when tumor length is assessed following neoadjuvant chemotherapy. CT measurements of tumor length can not, therefore, act as a surrogate for pathological measurement. The limitation of CT should be considered when it is used for staging, in the selection of treatment and in radiotherapy planning. In particular, inter- and intra-observer variability in CT reporting of esophageal tumor length may result in inappropriate radiotherapy target volume delineation if based on CT scan data alone. Consequently, decisions on whether patients should

have palliative or curative radiotherapy may need to be revised. The situation may be ameliorated by supporting information on tumor length provided by complementary modalities and close multidisciplinary collaboration between clinical oncologists, surgeons and radiologists with specialist interest in esophageal cancer.

COMMENTS

Background

Tumor length is a recognised predictor of survival in resected esophageal cancer. Studies have shown that patients with longer tumors in the resected specimens have a worse prognosis than those with shorter ones; and this is independent of advanced T-stage, lymph node metastasis and resection margin involvement with cancer cells. Consequently, accurate measurement of tumor length prior to surgery using standard imaging modalities such as computed tomography (CT) may potentially serve two purposes. First, it would provide additional prognostic information prior to surgery. Second, it would enable oncologists to more accurately calculate tumor target volumes for radiotherapy delivery. This study looked at the correlation between esophageal tumor length measured on the preoperative CT scan and the length on the postoperative pathological length (considered the gold standard).

Research frontiers

CT is widely used to stage esophageal cancer. It is also used by radiation oncologists to determine tumor dimensions including tumor length for radiotherapy planning. The research hot spot, therefore, is to investigate the accuracy of CT in determining tumor length and factors that influence the accuracy.

Innovations and breakthroughs

Previous studies correlating tumor length measured using CT (CT tumor length) and on resected specimen (pathological tumor length) did not evaluate inter- and intra-observer variability. In this study, CT tumor lengths were measured independently by two radiologists and each radiologist measured the same tumor on two different occasions. The key findings were: (1) CT measurements of tumor length are longer than those obtained from pathology specimens, even after allowing for an effect of formalin fixation; and (2) there is a weak correlation between measurements obtained by two radiologists and repeat measurements made by the same radiologist on the same CT image, i.e. inter- and intra-observer variability hampers accurate measurements of esophageal tumor length.

Applications

The study has a number of implications. First, the work highlights the need for a review of the indications for palliative radiotherapy. This study suggests that CT tends to over-estimate the true length of esophageal tumors. In some centres, if the CT tumor length is longer than 7-10 cm, patients are considered unsuitable for radiotherapy with curative intent. Such patients might be incorrectly managed with palliative intent. Second, the high inter- and intra-observer variations in measuring tumor length using CT suggest that in some cases tumor will be excluded from the radiotherapy field-reducing the probability of local control. Third, in most cases CT over-estimation of esophageal tumor length would lead to larger volumes irradiated than required, which would increase the risk of radiation injury to important adjacent organs such as the heart and the lungs.

Terminology

GTV or the gross tumor volume is the volume of tumor that can be seen on imaging (CT scan) or is visible (by endoscopy *etc.*) or can be felt. This is the demonstrable extent and location of the malignant growth. CTV or the clinical target volume is the gross tumor volume plus a margin allowing for microscopic spread of the disease.

Peer review

This is a retrospective study in which the authors investigated the correlation between CT and pathology measurements of esophageal tumor length. All tumors were adenocarcinoma of the distal third of the esophagus. In about two-thirds of the cases, the esophageal tumor lengths measured from CT images were longer than measurements made on the resected specimen. The study also found wide variations in measurements of tumor length made by two radiologists and the same radiologist on two separate occasions. The authors conclude by highlighting the potential implications of the findings for radiotherapy planning in the treatment of esophageal cancer.

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CASE REPORT

Perivascular epithelioid cell neoplasm of the colon

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Abstract

A 17-year-old female presented with rectal bleeding from an ulcerated sigmoid mass in 1994. Initial pathological evaluation revealed a rare clear cell neoplasm of the colon, possibly originating from kidneys, adrenals, lung or a gynecologic source as a metastatic lesion. Extensive imaging studies were negative, and over the next 15 years, she remained well with no recurrence. The original resected neoplasm was reviewed and reclassified as a perivascular epithelioid cell neoplasm (PEComa). Although the long-term natural history of PEComas requires definition, increased clinical and pathological awareness should lead to increased recognition of an apparently rare type of colonic neoplasm that likely occurs more often than is currently appreciated.

Key words: Perivascular epithelioid cell neoplasm; Carcinoid tumor; Colonic adenocarcinoma; Clear cell tumor

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INTRODUCTION

Clear cell tumors were historically described as benign and malignant neoplasms consisting of cells with clear cytoplasm characteristic of kidneys and adrenal glands[1]. Later, it was appreciated that these clear cell neoplasms might develop in a variety of other sites in addition to the kidneys, including tissues originating from the developing mullerian ductal system[2]: ovaries, extra-ovarian endometriosis, uterine cervix, upper vagina or lower genital tract. Detailed pathological descriptions of clear cell tumors in the lung were also reported (clear cell "sugar tumors")[3]. Finally, cytoplasmic clearing was detected in other neoplasms (e.g. myoepithelial neoplasia in major salivary glands, squamous cell carcinoma, chordomas), and focally in neoplastic epithelium of colorectal adenomas, likely reflecting cytoplasmic glycogen or lipid[4].

Clear cell tumor in the colon was initially reported in 1964 by Hellstrom and Fisher because the neoplastic clear cells resembled the physaliferous (clear) cells of chordomas[5]. Since then, these colonic tumors have been described, largely in males and usually on the left side of the colon[2]. In 1988, the Canadian experience in these clear cell tumors emphasized their rarity being limited to a single report of 4 cases accessed from the National Canadian Tumor Reference Centre in Ottawa[1]. Some cases have also appeared in the literature described as metastatic clear cell carcinomas with a focus from other organs, including renal or ovarian sites[6]. Rarely, concomitant renal and colonic clear cell carcinomas were also noted[7]. Due to the limited number of reported cases, however, the natural history and long-term prognosis of this colonic neoplasm has not been determined.

In 1992, Bonetti *et al*[8] analyzed the the shared pathological features of angiolipomas and clear cell "sugar" tumors of the lung: In 2002, the World Health Organization officially recognized this family of neoplasms

derived from these distinctive cells as perivascular epithelioid cell neoplasms (PEComas)[9]. The family included: adenomyoepithelioma (AML), lymphangioleiomyomatosis (LAM), clear cell sugar tumor of the lung, clear cell myomelanocytic tumor of the falciform ligament and generic PEComas in a variety of sites, including the uterus, soft tissue, and rarely the intestinal tract[10-15]. An association was also described between tuberous sclerosis, AML and LAM[16].

The present report describes the pathological and histochemical features of a clear cell neoplasm of the colon, later re-classified as a PEComa, and notes an entirely benign clinical course extending over more than a decade with detailed clinical and endoscopic monitoring after a localized colonic resection.

CASE REPORT

A 33-year-old female was referred in 2009 for colonoscopic evaluation because of a past history of a resected sigmoid neoplasm in 1994. Her colonoscopy was normal with a well-healed anastomosis. Because of her age, however, her clinical history and the pathology of her previously resected tumor were re-evaluated. In addition, as part of this review, added pathological studies on the original stored paraffin blocks were done.

Clinical background

At the age of 17 years, she presented with an emergent rectal bleeding event and a hemoglobin of 90 g/L. Endoscopic evaluation showed an ulcerated polypoid lesion in the sigmoid colon suggestive of a possible carcinoid tumor. No transfusions were given. A sigmoid resection was performed for a tumor estimated to have a diameter of 4-6 cm showing features of a "clear cell" tumor of the colon. Later clinical evaluation and blood tests were normal. In particular, there was no evidence for tuberous sclerosis or other disorders. Computed tomography scanning of her chest, abdomen and pelvis were done to exclude metastatic disease from other possible primary clear cell neoplasms (e.g. renal cell or adrenal cell carcinoma) and the scanning was normal. Subsequent colonoscopies in 1997, 2000, 2003 and 2006 showed a well-healed anastomosis, but no other findings.

Pathological studies

Pathological review confirmed an unusual clear cell tumor composed of discrete rounded collections of clear cells in a fine vascular stroma with centrally placed low-grade nuclei (Figures 1 and 2). The mitotic rate was low. The tumor was well delimited but was unencapsulated. Intramucosal invasion was present but there was no invasion of the muscularis propria. There were no nodal metastases. The tumor appeared to arise in the submucosa of the colon and extended to the mucosal surface with ulceration. Initial pathological differential diagnosis were: metastatic clear cell carcinoma of the kidney or adrenal gland; clear cell variant of a primary colorectal carcinoma or carcinoid tumor; a paraganglioma variant; a clear cell variant of a smooth muscle tumor or gastrointestinal stromal tumor.

Special studies

The previous paraffin blocks from the resected tumor were recovered, reviewed and added special studies were done. All neuroendocrine markers that were initially negative were repeated and were again negative. These included neuron-specific enolase, synaptophysin, chromogranin and CD-56. Initial electron microscopy was not repeated, however, this did not reveal evidence of melanosomes or intercellular junctions and a cell of origin could not be defined. Histochemical staining for neurosecretory granules was negative by argyrophil and Fontessa-Masson methods, and the cells were also negative for mucin (mucicarmine). The cells were negative using a multimolecular weight pan-keratin cocktail antibody and did not express cytokeratin-7 or cytokeratin-20. Cells did not express c-kit (CD-117), desmin, smooth muscle actin, muscle specific actin, CD-34 or vimentin. The tumor cells were negative for S-100, but were strongly positive for HMB-45 (Figure 3). Based on this re-evaluation of the original stored tissue blocks, the colonic neoplasm was re-classified as a PEComa of the colorectum, or PEComa.

DISCUSSION

PEComas are rare tumors characterized by myomelanocytic differentiation. To date, the precursor lesion or cell of origin has not been identified. Intestinal PEComas, and specifically, colonic PEComas have been rarely described in only a few case reports that detail the morphologic and immunohistochemical features[16-23]. The precise incidence of these neoplasms is not known, but some have estimated these to occur in less than 0.1% of colon neoplasms[4]. In part, this low rate currently reflects different factors that may result in increased recognition in the future. As in the present case, earlier evaluation of some clear cell tumors may not have been conclusive, or the pathological studies may not have permitted final classification. Likely, an increased awareness among gastroenterologists and pathologists will result in increased recognition in the intestinal tract as these are likely to occur more often than is currently recognized.

The biological behavior of the PEComa family is still not very well understood. Clinically benign, but concomitant nodal involvement with angiomyolipomas may have represented multifocal, rather than metastatic disease[6,7]. Histologic criteria indicative of malignancy in PEComas have not been proven, in part, because information on the long-term natural history of intestinal lesions has not been reported. It does appear, however, that non-gastrointestinal PEComas with definite evidence of malignant behavior are usually large (over 5 cm), contain areas of coagulative necrosis and also have a high mitotic rate. Other important criteria that have been suggested

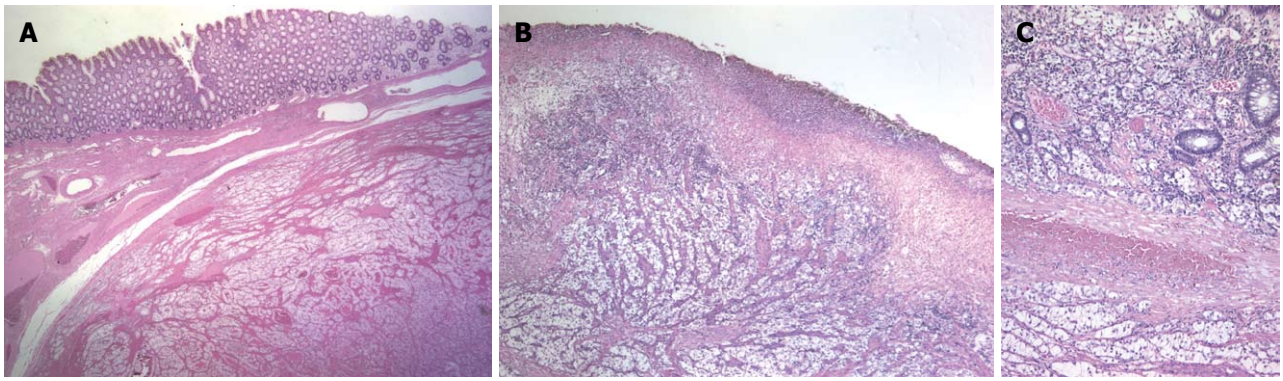

Figure 1 Perivascular epithelioid cell neoplasm (PEComa). A: PEComa in sigmoid colon site (HE, × 12.5); B: PEComa in sigmoid colon showing mucosal ulceration (HE, × 12.5); C: PEComa with individual cell nests invading mucosa (HE, × 100).

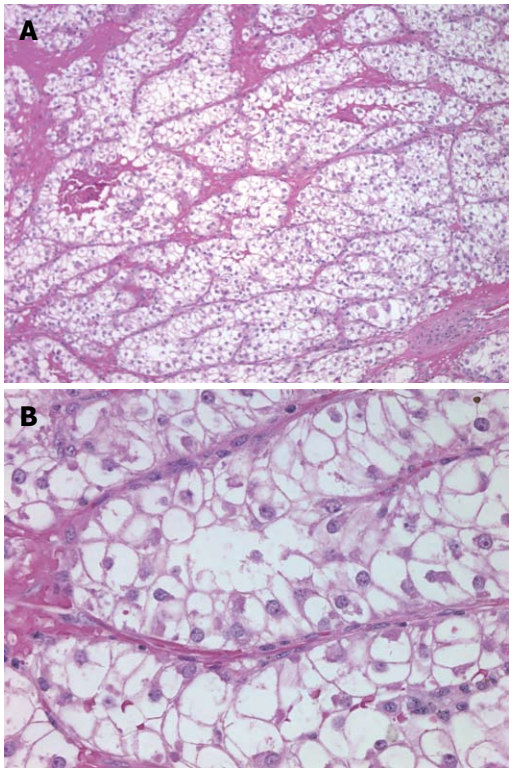

Figure 2 PEComa tumor body. A: PEComa tumor body with intervening delicate capillary network (HE, × 100); B: PEComa, tumor body (HE, × 400).

include: an infiltrative tumor border, high nuclear grade and cellularity, and vascular invasion. For intestinal lesions, the reported length of follow-up has been usually short (as with most case reports) and the outcome data are very limited. In a recent review[23], the longest duration of follow-up for a colonic PEComa was 24 mo. In the present case, the PEComa (initially defined as a clear cell tumor of the sigmoid colon) appeared to be completely resected. However, added imaging studies were performed to ensure that another primary site (e.g. kidney, lung) was not evident and further endoscopic follow-up has confirmed an entirely benign clinical course with no recurrence over a period of more than 15 years. Added histopathological studies with larger numbers of cases will be needed to further define the long- term natural history of this disorder.

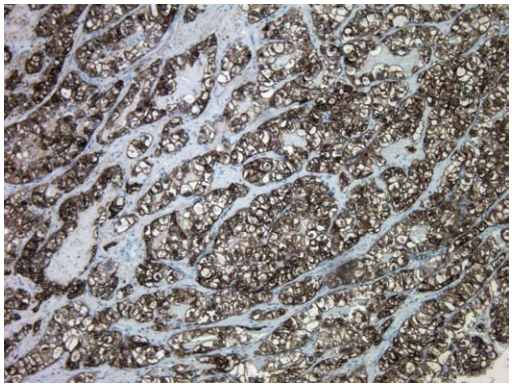

Figure 3 PEComa with HMB-45 antibody strongly stained cytoplasm of neoplastic cells (HMB-45, × 100).

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CASE REPORT

Isolated pancreatic metastasis of hepatocellular carcinoma after curative resection

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Abstract

Hepatocellular carcinoma (HCC) is a highly malignant tumor and extrahepatic metastasis is not rare. The most common organ of HCC metastasis is lung, followed by bone and adrenal gland. To the best of our knowledge, isolated pancreatic metastasis of HCC that developed after curative resection has not been described previously. We report a case of solitary pancreatic metastasis of HCC, which was found 28 mo after left hemihepatectomy for HCC. The lesion was successfully resected with the pancreas, and no other metastatic lesions have been found in follow-up.

Key words: Hepatocellular carcinoma; Pancreas; Metastasis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly malignant, generally fatal neoplasm arising from hepatocytes. HCC accounts for over 80% of all primary liver cancers, which rank fourth among the organ-specific causes of cancer-related deaths worldwide[1]. Extrahepatic metastases are not rare at diagnosis of HCC[2] and the most frequent sites of extrahepatic metastases are lung, abdominal lymph node and bone[3,4]. A review of the literature involving the surgical pathology of 355 solitary metastases to the pancreas identified 5 isolated pancreatic metastases from HCC[5]. Of these, 2 cases showed synchronous metastases and 3 cases were found at autopsy[6]. To the best of our knowledge, solitary pancreatic metastasis of HCC, which developed after curative resection, has never been described previously.

A variety of malignant tumors have been shown to metastasize to the pancreas[7-9]. At autopsy, pancreatic metastases are common and the primary carcinoma is usually located in the lung or in the gastrointestinal tract. In contrast, isolated pancreatic metastases at the time of diagnosis are rare and only account for only 2% to 3% of solid tumors of the pancreas[10]. Most do not present before the end stage of various primary neoplasms. At least 40% of these isolated metastases are derived from renal cell carcinomas while common primary sites for the remainder include lung cancer, breast cancer, colon cancer, melanoma and sarcomas[8,10,11].

A minority of these metastases are identified by imaging at the time of diagnosis of the primary tumor, while the majority are diagnosed at follow-up, either because of routine imaging or because of the development of symptoms[8]. In renal cell carcinoma, the mean interval between nephrectomy and the diagnosis of an isolated pancreatic metastasis is approximately 9 years. Unfortunately, pancreatic metastases are difficult to differentiate from primary pancreatic neoplasms. In particular, there are similar clinical presentations and similar features on radiological imaging. In this article, we report a case of isolated metastasis of an HCC to the pancreas 28 mo after curative resection of HCC.

CASE REPORT

A 46-year-old man with a history of surgical resection of hepatitis B associated HCC presented with a pancreatic mass that was identified with contrast enhanced dynamic computed tomography (CT) at follow-up. Two years and 4 mo previous to follow up, he was treated with an extended left hemihepatectomy for a 16.5 cm × 9 cm-sized solitary HCC compressing the intrahepatic duct. The pathology report disclosed a grade Ⅲ HCC with portal vein invasion, but the resection margin was free of tumor. No obvious bile duct invasion or intrahepatic micrometastasis was noted. The patient was diagnosed as T3N0M0 stage ⅢA disease by AJCC and modified UICC stage. The patient recovered well and subsequently had a 3 mo follow-up examination including liver dynamic CT and a serum α-fetoprotein test. Although series examinations revealed no definite intrahepatic recurrence, liver dynamic CT showed an irregular mass in the tail of the pancreas that was associated with dilatation of the distal pancreatic duct (Figure 1A). With a contrast-enhanced scan, the mass projected into the splenic vein (arrow, Figure 1B). Liver dynamic CT and 18F-FDG-positron emission tomography (PET) showed no recurrence of the primary HCC in the remnant. On FDG-PET, there was hypermetabolic activity in the pancreatic mass. Endosonography (EUS) revealed a rounded, well-defined mass (5 cm in diameter) in the tail of the pancreas (Figure 2). EUS-guided fine needle aspirations revealed a poorly differentiated carcinoma with histological features consistent with his previous HCC (Figure 3). The lesion was successfully resected, and no other metastatic lesions have been found in follow-up. Gross specimen study showed a mass in the tail of the pancreas, invading the splenic vein (Figure 4A). Microscopic examination revealed metastatic HCC in the pancreas (Figure 4B).

DISCUSSION

Differential diagnosis between a solitary pancreatic metastasis from a primary cancer and a double primary pancreatic cancer is difficult in almost all cases. The symptoms of metastases confined to the pancreas at the time of diagnosis are unspecific diagnostically, and imaging also rarely shows abnormalities seen only in primary neoplasms. This, together with the generally rare occurrence of solitary pancreatic metastases, explains why solitary pancreatic metastases are sometimes mistaken for primary tumors, particularly if there is a long interval from the resection of the underlying primary neoplasm. For differential diagnosis, solitary pancreatic metastases should be distinguished from primary neoplasms of the pancreas. Therefore, the diagnostic workup for tumors in the pancreas requires meticulous elaboration of the medical history.

The typical features of metastases from renal cell cancer detected by imaging studies (e.g. ultrasonography, CT, magnetic resonance imaging, and endoscopic ultrasonography) have been described repeatedly[12-15]. However, because these features are not confined to metastases from renal cell carcinoma, differentiation from other neo-

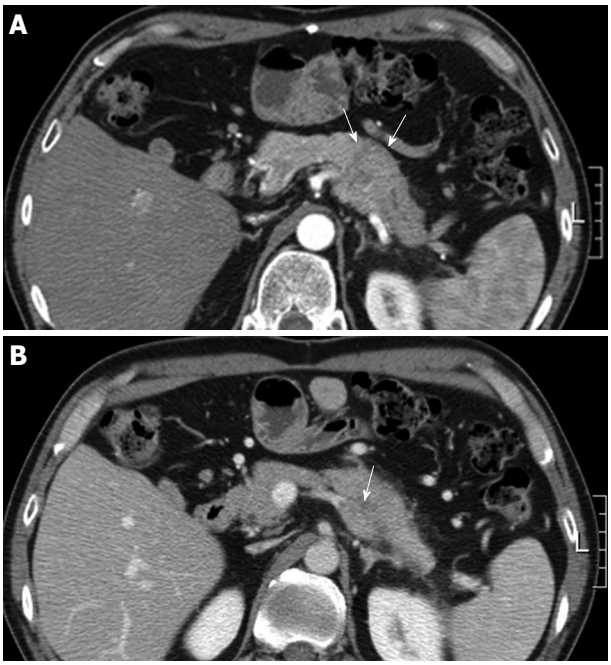

Figure 1 Abdominal computed tomography finding. A: Computed tomography showed an irregular mass in the tail of the pancreas that was associated with dilatation of the distal pancreatic duct (arrow); B: With a contrast-enhanced scan, the mass projected into the splenic vein (arrow).

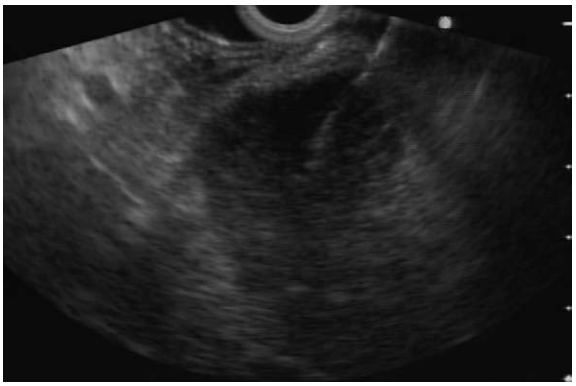

Figure 2 Linear endosonography (EUS) image revealing fine needle aspiration of a rounded, well-defined mass (5 cm in diameter) in tail of pancreas.

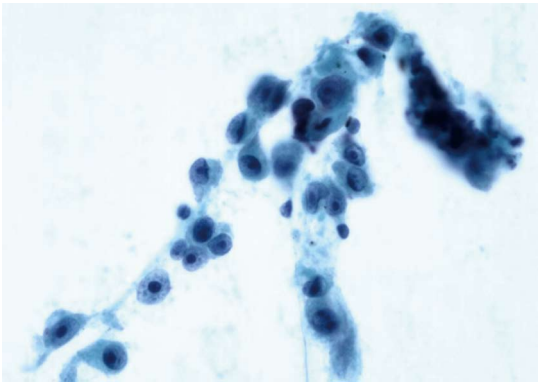

Figure 3 Photomicrograph of cytologic specimen obtained by EUS-guided showing a poorly differentiated carcinoma with histological features consistent with a metastasis from his previous hepatocellular carcinoma (Papanicolaou stain, × 200).

plasms of the pancreas is problematic in individual cases. Tissue diagnosis can be established before surgery with fine-needle aspiration biopsy, ultrasonography guided[16], CT guided[17], or endoscopic ultrasonography guided[18,19]. These techniques allow definitive tissue diagnosis, as well as an assessment of resectability. In the case of a pancreatic mass, rare causes, such as pancreatic metastasis, should also be taken into consideration besides the most common diagnosis, adenocarcinoma pancreas with its dismal prognosis. In particular, in cases where a patient is not undergoing surgical resection, a biopsy is mandatory to determine a definite diagnosis.

Surgical treatment of solitary pancreatic metastases from neoplasms other than renal cell cancer carries a poor prognosis, because they often signal the onset of disseminated metastatic disease[7,20]. Although resectable pancreatic metastasis is uncommon[7], metastatic pancreatic tumor from renal cell carcinoma is one of the favorable indications for radical surgery because it may offer a better prognosis for the patient[8,21,22]. Results of surgical extirpation of isolated metastases to the pancreas, not only from renal cell carcinoma but also from various primary tumors, provide improvement in long-term survival, revealing a clearly better prognosis than for primary pancreatic cancer[23,24]. This positive outcome suggests that solitary pancreatic metastases must not be regarded as accidental initial manifestations of impending diffuse metastatic disease and that a point must be made to correctly diagnose solitary pancreatic metastases and subject them to radical resection.

The result of treatment for extrahepatic recurrent HCC is poor[2,25,26]. Most metastases of HCC are multiple and are not amenable to surgical resection. Solitary metastases may be encountered occasionally. If considered resectable, the patient should be examined to exclude the presence of other metastasis, especially in the liver remnant, before embarking on surgery. Resection of isolated extrahepatic recurrences of HCC has been shown to prolong survival in selected patients[27-30]. The unusually positive outcome after treatment prompted a research group to question, rightfully, whether the positive outcome was really attributable to the successful removal of the metastases or whether it reflected an extremely protracted natural history of solitary pancreatic metastases.

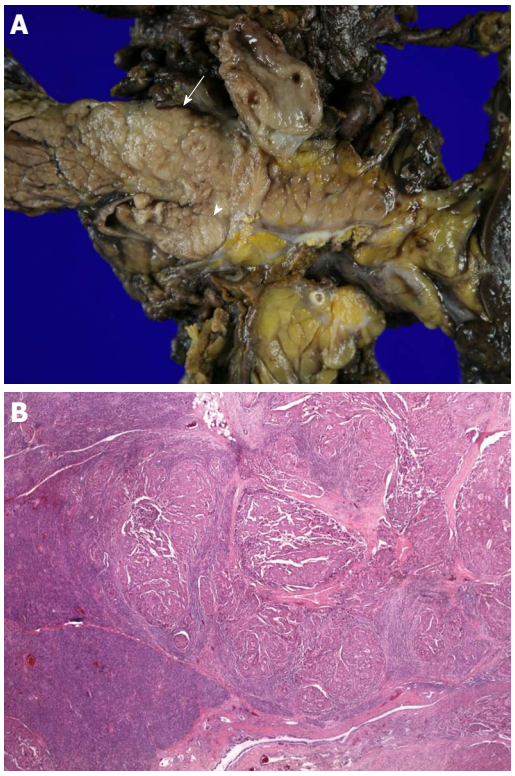

Figure 4 Surgical specimen. A: The tumor was 4.5 cm × 3.4 cm × 2 cm in size in the tail of the pancreas (arrow) and invaded the splenic vein (arrow head); B: Microscopic examination revealed metastatic hepatocellular carcinoma in the pancreas (HE, × 40).

To our knowledge, this is the first case of solitary pancreatic metastases of HCC that developed after curative resection. Our patient developed solitary pancreatic metastasis, which was documented 28 mo after resection of HCC. In patients with a pancreatic mass and history of HCC, the possibility of metastasis to the pancreas should also be taken into consideration besides the most common diagnosis, adenocarcinoma pancreas with its dismal prognosis.

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Meetings

Events Calendar 2010

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AGA Clinical Congress of Gastroenterology and Hepatology
The Venetian And Palazzo, 3355 Las Vegas Blvd South, Las Vegas, United States
http://www.gilearn.org/clinicalcongress

January 16-17, 2010
The Symposium on Clinical Interventional Oncology
Hollywood, Florida, United States

January 22-24, 2010
ASCO Gastrointestinal Cancers Symposium
Orlando, FL, United States

February 05-09, 2010
Cancer Genomics, Epigenomics & the Development of Novel Therapeutics
Waikoloa, HI, United States

February 19-20, 2010
8th International Symposium on the Evolution of Supportive Care in Oncology: the Era of Targeted Agents
New York, NY, United States

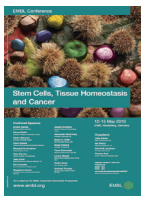
March 04-07, 2010
2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri 63101, United States
http://www.surgonc.org/

March 05-07, 2010
Genitourinary Cancers Symposium
San Francisco, CA, United States

March 07-11, 2010
16th International Conference on Cancer Nursing
Atlanta, GA, United States

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

April 17-21, 2010
101st Annual Meeting of the American Association for Cancer Research
Washington, DC, United States



May 12-15, 2010
Stem Cells, Tissue Homeostasis and Cancer
EMBL Heidelberg, Germany
http://www.embl.de/training/courses_conferences/conference/2010/STM10-01/

May 15, 2010
Digestive Disease Week 2010
American Association for the Study of Liver Diseases Ernest N. Morial Convention Center, 900 Convention Center Blvd, New Orleans, LA 70130, United States
http://www.ddw.org/

June 04-06, 2010
American Society of Clinical Oncologists Annual Meeting
Chicago, IL, United States

June 09-12, 2010
13th International Conference on Emergency Medicine
Singapore, Singapore

August 28-31, 2010
10th OESO World Congress on Diseases of the Oesophagus 2010
Boston, Massachusetts, United States

September 23-25, 2010
2010 Gastrointestinal Oncology Conference
The Sheraton Philadelphia City Center, Philadelphia, PA, United States
http://www.isgio.org/isgio2010/program.html

September 23-26, 2010
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases
Prague, Czech Republic

October 15-20, 2010
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting
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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and posi tioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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