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CICLO XXV ANNO 2008

TITOLO DELLA TESI DI DOTTORATO

PRIMARY NONAMPULLARY DUODENAL ADENOCARCINOMA

S.S.D. MED/18

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UNIVERSITY OF VERONA

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SURGICAL SCIENCE AND HEPATOBILIARY AND PANCREATIC DISEASES

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DECLARATION

No portion of the work referred to in this thesis has been submitted in support of

an application for another degree or qualification of this or any other university of in-

stitute of learning

DEDICATION

To my wife **Romina**, for her unconditional love and patience through the burden of this

thesis. To my wonderful children **Joseph** and **Emily**. Thinking of them makes me smile;

playing with them recharges my life.

I

1

Introduction and Aims of Research

1.1   INTRODUCTION

Primary Adenocarcinoma of the duodenum is a rare condition, accounting between 0, 3% and 0, 5% of all gastrointestinal malignancies [1-3].

Despite the duodenum is representing less than 10 % of the total length of the small bowel, this organ is the site of between 25% and 45% of the small bowel cancers [4]. However cancer of the duodenum appeared to be more frequent in the proximity of the Ampulla of Vater periampullary area [5], about 45 % of them demonstrated to arise in third and in fourth portions of this organ. Since the symptoms of this cancer are non-specific and similar to other benign conditions, the diagnosis is often difficult and delayed.

Nonetheless, duodenal carcinoma has a reported 5-year survival rate for resected tumours   between 25% and 75% [6-10] which is significantly better than that for cancer of the ampulla (46%) [11] and the head of pancreas (10%) [12, 13].

In the last decade different studies evaluated the correlations between clinical, pathological and treatment variables in order to identified specific prognostic factors associated with survival [14-19].

Those recent studies showed that histological grade, transmural involvement, tumour size, lymph node involvement and distant metastasis can influence the survival in patients with duodenal adenocarcinoma.

However, due to a low incidence of this disease in the general population, the debate on prognostic factors in duodenal adenocarcinoma is still open. Therefore, questions have been raised especially on the prognostic significance of the absolute number and ratio of involved lymph nodes. A recent study has led an increased interest on perineural invasion as single independent prognostic factor for patients with primary duodenal cancer [20].

1.2   Aims of research

The aim of this thesis was to improve understanding of specific prognostic factors associated to survival in primary duodenal adenocarcinoma.

A retrospective review of 37 patients diagnosed with primary duodenal adenocarcinoma between 1989 and 2009 was performed at Hepato-pancreatico-biliary department, General Surgery B, Verona University, Borgo Roma Hospital. Data were acquired then analysed for impact on recurrence and 5-year overall survival rate.

From this retrospective study, evidence will be generated to improve knowledge on potential prognostic factors in primary duodenal adenocarcinoma.

2

Anatomy, Physiology of the Duodenum and Embryology of Midgut

2.1   ANATOMY OF THE DUODENUM

The length of the duodenum varies from 20 to 25 cm and is the shortest and widest part of the small bowel. The duodenum extends up to the duodenuoje-junal junction and lies mostly in the upper retroperitoneum with only the proximal 2.5 cm of its length located in the intraperitoneal cavity. The duodenum is anatomically divided into four parts and curves in the shape of the letter C around the head of the pancreas.

2.1.1 FIRST (SUPERIOR) PART

The first is the most mobile part of the duodenum and is about 5 cm long. The first 2 cm of the duodenum is frequently referred to as the duodenal "cap" since is often visible in the plain radiographs of the abdomen as an isolated triangular gas shadow to the right of the first or second lumbar vertebra.

The first part of the duodenum lies anterior to the gastroduodenal artery, common bile duct and portal vein and anterosuperior to the head and neck of the pancreas.

The junction of the first and second parts of the duodenum lies posterior to the neck of the gallbladder.

2.1.2 SECOND (DESCENDING) PART

The second part of the duodenum is 8-10 cm long. It starts at the superior duodenal flexure and runs inferiorly in a gentle curve, convex to the right side of the vertebral column and extending to the lower border of the third lumbar vertebral body. It is covered by peritoneum only on the upper anterior surface, lies posterior to the neck of the gallbladder and the right lobe of the liver at its start, and is crossed transversally by the transverse colon. The common bile duct and pancreatic duct enter the medial wall of this portion of duodenum obliquely and usually united to form the common hepatopancreatic ampulla. The narrow distal end opens on the summit of the major duodenal papilla called ampulla of Vater which is situated on the posteromedial wall of the second part, 8-10 cm distal to the pylorus.

2.1.3THIRD (HORIZONTAL) PART

The third portion of the duodenum starts from the inferior duodenal flexure and is approximately 10 cm long. It runs from the right side of the lower border of the third lumbar vertebra, angled slightly superiorly, across to the left, anterior to the inferior vena cava, becoming continuous with the forth part in front of the abdominal aorta.

It lies posterior to the transverse colon, the origin of the small bowel mesentery and the superior mesenteric vessels.

The third part is anterior to the right ureter, right psoas muscle, right gonadal vessels, inferior vena cava and abdominal aorta, and inferior to the head of the pancreas.

2.1.4 FOURTH (ASCENDING) PART

The fourth part of the duodenum is 2.5 cm long. It stars just to the left of the aorta, runs superiorly and laterally to the level of the level of the upper border of the second lumbar vertebra, and then turns sharply anteroinferiorly at the duodenojejunal flexure to become continuous with the jejunum. At its left lateral end, the forth part becomes covered in peritoneum on its superior and inferior surfaces, such that it is suspended by a double fold of peritoneum, the ligament of Treitz, at the start of the duodenuojejunal flexure.

2.1.5 BLOOD SUPPLY AND LYMPHATIC DRAINAGE

The main vessels supplying the duodenum are the superior and inferior pancreaticoduodenal arteries. The first and the second parts also receive contributions from several sources including the right gastric, supraduodenal, right gastroepiploic, hepatic and gastroduodenal arteries.

The duodenal veins drain ultimately into the portal vein through the superior and inferior pancreaticoduodenal veins.

Duodenal lymphatics run anterior and posterior pancreatic nodes that lie in the anterior and posterior grooves between the head of the pancreas and the duodenum: these nodes drain widely into the suprapyloric, infrapyloric, hepatoduodenal, common hepatic and superior mesenteric nodes.

2.1.6 INNERVATION

The duodenum is innervated by both parasympathetic and sympathetic neurones.

Preganglionic sympathetic axons originate from neurons in the interomediolateral columns of the grey matter in the fifth to the 12th thoracic spinal segments. They travel via greater and lesser splanchnic nerves to the celiac plexus where they synapse on neurones in the coeliac ganglion. The sympathetic nerves are vasoconstrictor to the duodenal vasculature and inhibitor to the duodenal musculature.

The preganglionic parasympathetic supply is carried by vagal axons that are distributed via celiac plexus and which synapse on the neurones in the duodenal wall. The parasympathetic supply is secretomotor to the duodenal mucosa and motor to the duodenal musculature. The sympathetic nerves are vasoconstrictor to the duodenal vasculature and inhibitory to the duodenal musculature.

2.1.7 HISTOLOGY OF INTESTINAL WALL

The mucosa of the duodenum and small bowel is thrown into a series of folds by the plicate are the valvulae conniventes. This greatly increases the surface area available for absorption within the small bowel.

The mucosa of the small bowel contains intestinal villi which are covered by simple columnar epithelium and broken into microvilli. The wall of the small intestine is divided into the lamina propria, and this is divided from the submucosa by the muscularis mucosae. Within the lamina propria there is an extensive network of capillaries which transports respiratory gases and absorb material to the hepatoportal circulation.

In addition, there are capillaries and nerve endings within the lamina propria and each villus also contains a terminal lymphatic called a lacteal. The name lacteal refers to the cloudy appearance of the lymph contained within these channels. The lacteals themselves transport materials that fail to enter the local capillaries because they are unable to cross the capillary wall. Examples would be of fatty acids and proteins which are too large to diffuse into the bloodstream. These lipoproteins form small partials called chylomicrons which pass through the lymphatic system and account for the milky appearance within the lacteal.

2.1.7.1.1 INTESTINAL CRYPTS

 Within the columnar epithelium there are goblet cells which produce mucus onto the intestinal surfaces. At the base of the villi there are also found entrances to the intestinal crypts. These extend deep into the underlying lamina

propria. Within the intestinal crypts there are a number of different cell populations including stem-cell divisions which continue to produce new generations of columnar and goblet cells.

These new cells are continuously displaced towards the intestinal surface and within a few days will reach the tip of the villi, where they will be shed or exfoliated into the intestinal lumen. It is this process of exfoliation of the intestinal cells which ensures that the epithelial surface continues to be renewed. This also adds intracellular enzymes to the intestinal contents. One of these enzymes would be *enterokinase*, which although it does not does not directly participate in the digestion of food, is important because it activates proenzymes secreted by the pancreas. Cells within the intestinal crypts also contain enteroendocrine cells.

These are responsible for the production of several intestinal hormones including cholecystokinin and secretin.

2.2 PHYSIOLOGY OF DUODENUM

The duodenum has very little absorptive function and acts mainly to neutralise the acidic contents delivered to it by the stomach. The duodenum receives the chyme from the stomach and its essential function is to buffer the gastric acid and enzymes before delivering the contents to the jejunum. The histological characterisation of the duodenum reveals abundant presence of mucus secreting glands. These submucosal glands, known as *Brunner's glands*, assist in the production of copious amounts of mucus. The secretion of this mucus is to pro-

tect the duodenal mucosa and also to neutralise the acid pH of the chyme. The submucosal glands are most abundant in the proximal duodenum and decrease in number towards the jejunum.

The pH of the duodenal contents rises from a pH of 1–2 to 7–8 by the time it is delivered to the jejunum. In addition, the chyme is diluted by mixing with the intestinal, pancreatic and hepatic secretions. The duodenal ampulla lies within the wall of the second part of the duodenum and allows for the delivery of bile and pancreatic enzymes to initiate the digestion and breakdown of the chyme. Absorption may occur; it is more effective under these conditions and the increase in the surface area of the duodenum in its third and fourth parts supports this increased absorptive capacity.

2.2.1 INTESTINAL HORMONES

The enteroendocrine cells within the duodenum produce hormones which coordinate the secretory activity of the stomach, duodenum, liver and pancreas.

Enterocrinin is a hormone which is released by the duodenal mucosa when the acid chyme from the stomach enters the small intestine. There are many other hormones secreted which have both primary and secondary effects, and which act in a complementary fashion. The three most important hormones involved in the regulatory activity of the small intestine are *secretin*, *cholecystokinin* and the glucose-dependent *insulinotropic peptide*.

2.2.1.1 Secretin

Secretin is produced in response to the presence of acid within the duodenum.

The primary effect of secretin is to increase the production of water and buffers by the pancreas and liver. It also has an effect on stimulating the duodenal submucosal glands.

2.2.1.2 Cholecystokinin (CCK)

The duodenal mucosa is stimulated to produce cholecystokinin when chyme arrives within the lumen of the duodenum and particularly when it contains lipids and partially digested proteins. This hormone has a target effect both on the pancreas and on the liver. The pancreas is stimulated to produce and secrete digestive enzymes, and the hormone also increases the passage of bile by stimulating the gall bladder to contract. The net effect of cholecystokinin is to increase the secretion of pancreatic enzymes and stimulate the production of bile. However, in high concentration both secretin and cholecystokinin have the additional effect of producing gastric motility and secretions.

2.2.1.2 Glucose-dependent Insulinotropic Peptide (GIP)

This peptide is released by the duodenal mucosa in response to fats and glucose entering the duodenum.

This peptide stimulates the release of insulin from the pancreatic islet cells, although at high concentration it can also inhibit gastric activity. (Originally this was named the gastric inhibitory peptide)

2.2.1.3 Vasoactive Intestinal Peptide (VIP)

Several other hormones are produced in small quantities in response to chyme entering the duodenum.

For example, relatively large amounts of undigested proteins will stimulate the release of gastrin by the duodenal cells. Vasoactive intestinal peptide or VIP is also produced and it stimulates the secretion of the intestinal glands whilst inhibiting acid production within the stomach. Previously, it was considered that the enzyme called enterogastrin was responsible for inhibiting gastric activity. However, it is now considered that this inhibition of gastric motility is the product of GIP and VIP. The number and diversity of the hormones produced by the small bowel are well recognised, but poorly understood. Many of the hormones have a similar chemical structure and it is difficult to differentiate the primary effects of these various hormones. Analysis has led to an increased number of hormones being identified, although their specific functions are poorly understood [21].

2.3 EMBRIOLOGY OF THE MIDGUT

In the adult the midgut starts immediately distal to the point where the bile duct enters the duodenum and it terminates at the junction of the proximal two-thirds of the transverse colon with a distal third.

The superior mesenteric artery supplies the entire length of the midgut.

Within the 5-week-old embryo the midgut is suspended by a short mesentery from the posterior abdominal wall and it communicates with the yolk sac by way of the

vitello-intestinal duct. At the apex of the midgut loop there is a connection with the yolk sac via the vitelline duct.

The proximal or cephalic limb of the loop becomes the distal part of the duodenum, the jejunum and part of the ileum, and the cordal or distal portion of the loop becomes the ileum, caecum, appendix, ascending and proximal transverse colon. With the rapid growth and expansion of the liver and the elongation of the midgut, the abdominal cavity becomes too small to contain the intestinal loops. For a period during the sixth week of development, the intestinal loops enter an extra-embryonic cavity within the umbilical cord; this is considered to be a physiological umbilical herniation.

By the tenth week the herniated intestinal loops are returning to the abdominal cavity. The precise factors responsible for this are not known although as the mesonephric kidney regresses and there is a reduced growth of the liver with some expansion of the abdominal cavity, space becomes available to allow for the return of the midgut to the abdomen.

As the midgut retracts into the abdomen it also rotates and with the expansion of the caecal bud, which appears around the sixth week, the characteristic placement of the midgut within the abdominal cavity occurs.

The distal midgut expands and there is some separation into the small and large intestine. A small narrow diverticulum is formed from the caecal bud which develops into the appendix.

 The mesenteries of the intestinal loops are produced during the changes and rotation of the midgut around the superior mesentery vessels.

With fusion of the mesenteric layers the small intestine retains a long and mobile mesentery; however, the caecum and ascending colon become fused with the posterior abdominal wall.

Associated with the embryological development of the small intestine a number of abnormalities can occur.

Abnormal rotation of the intestinal loop may occur and this results in a volvulus where the blood supply to the loop is compromised, particularly when the base of the small bowel mesentery is shortened. On occasions there can be reverse rotation of the intestinal loop and the small intestine is found towards the right side of the abdomen, with the caecum and the large intestine to the left.

Further abnormalities may include duplication of the intestinal loop with cysts. These cysts are most frequently found within the region of the ileum and they may vary from a long segment to a short one with a small diverticulum. Other abnormalities of the small intestine may be associated with defects within the abdominal wall.

An omphalocele (exomphalos) involves the herniation of the abdominal viscera through a defect within the umbilical ring.

This defect often contains small bowel, and liver, stomach, spleen and gall bladder may also be included. The defect is thought to be caused by failure of the bowel to return to the body cavity following its physiological herniation between the sixth and tenth week of development. This defect may occur in up to 2.5 per 10.000 births and it is associated with a high mortality[22].

3 Aetiology and Predisposing Factors for Adenocarcinoma of the Duodenum

3.1 INTRODUCTION

Primary Adenocarcinoma of the Duodenum arises from the Lieberkuhn epithelium of the duodenal mucosa and it is a rare condition, accounting between 0, 3% and 0, 5% of all gastrointestinal malignancies [1-3]. Despite the duodenum is representing less than

 10 % of the total length of the small bowel, this organ is the site of between 25% and 45% of the small bowel cancers. However cancer of the duodenum appeared to be more frequent in the proximity of the Ampulla of Vater periampullary area, about 45 % of them demonstrated to arise in third and in fourth portions of this organ.

Adenocarcinoma tend to arise in the duodenum rather than other parts of the small bowel maybe because is close to the ampulla of Vater. Although, ampullary carcinomas are usually classified as tumours of the extra-hepatic biliary tract rather than the small bowel, duodenal adenocarcinomas tend to gather in the periampullary region. This clustering may implicate bile or its metabolites in the aetiology of adenocarcinoma at this site.

The incident rate of small bowel cancer varies among populations. Small bowel cancer and duodenal cancer rates high among the Maori of New Zealand and among ethnic Hawaiians, and low in India, Romania, and other parts of Eastern Europe.

In most population-based registries, males have higher small bowel cancer incidence rates than females.

The incidence of the small bowel and duodenal cancer rises with age. The mean age at the diagnosis is typically about 60 +/- 10 years [23].

3.2 PREDISPOSING FACTORS

The predisposing factors for epithelial Neoplasms of the Duodenum can be divided in two groups:

- (a) Inflammatory Disorders, such as Crohn's disease

- (b) Genetic Disorders, familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC).

Other general factors including occupational hazards and lifestyle factors such as smoking and alcohol intake were investigated in two European multicentre case-control studies [24, 25]. A cohort of 70 patients diagnosed with small bowel adenocarcinoma (SBA) during the study period (1995–1997) was compared with 2070 matched controls. Beer and spirits intake were associated with small

bowel adenocarcinoma, with an odds ratio (OR) of 3.5 and 95% confidence intervals (CI) of 1.5–8.0.

However, there was no association between smoking or total alcohol intake and adenocarcinoma of the small bowel. In a second study of the same group, investigators identified occupational clustering of SBA. The strongest industrial risk factors for SBA were dry cleaning, manufacture of work wear, mixed farming (women), and manufacture of motor vehicles (men).

A significantly increased risk of SBA was found among men employed as building caretakers (OR 6.7; CI 1.7 to 26.0) and women employed as housekeepers (OR 2.2; CI 1.1 to 4.9); general farm labourers (OR 4.7; CI 1.8 to 12.2); dockers (OR 2.9; CI 1.0 to 8.2); dry cleaners or launderers (OR 4.1; CI 1.2 to 13.6); and textile workers (OR 2.6; CI 1.0 to 6.8)

TABLE 2.1

Inflammatory Conditions	Genetic Syndromes
Crohn's disease	Familial adenomatous polyposis
Coeliac Disease	HNPCC
	Peutz–Jeger
	Neurofibromatosis

3.2.1 CROHN'S DISEASE

Crohn's Disease is an inflammatory bowel disease that affects mainly people in their 3rd and 4th decade of life. It has long been associated with a high incidence of adenocarcinoma of the small bowel and colon. The first case of duodenal adenocarcinoma was reported in 1987 [26]. Interestingly, when the surgical approach to the treatment of Crohn's disease was changed from radical resection to bypass surgery, in literature has been described a high incidence of adenocarcinoma of duodenum in patients who underwent to bypass gastrojejunostomy for duodenal stricture [27, 28].

3.2.2 COELIAC DISEASE

Long standing coeliac disease is associated with an increased risk of malignancy, not only of intestinal lymphoma but also of duodenal adenocarcinoma. This is frequently manifested by loss of response to gluten withdrawn. It was suggested that the subgroup of coeliac patients not responding to gluten-free diet they were more prone to develop malignancy but this theory has never been scientifically proven [29,30].

3.2.3 FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

Familial adenomatous polyposis (FAP) is the most common adenomatous polyposis syndrome. It is an autosomal dominant inherited disorder characterized by

the early onset of hundreds to thousands of adenomatous polyps throughout the colon.

The genetic defect in FAP is a germline mutation in the adenomatous polyposis coli (APC) tumour suppressor gene, located on chromosome 5q21 [31, 32].

Multiple extra-colonic manifestations of FAP have been described, representing all three embryological layers. These manifestations can be either benign or malignant.

Endodermal lesions include duodenal and small bowel polyps and carcinomas.

Mesodermal abnormalities include desmoids tumours, osteomas, and dental abnormalities.

Ectodermal lesions localize to the eye, brain, and skin appendages.

Desmoid tumours of the abdominal cavity and duodenal adenocarcinoma are the most serious extra-colonic manifestations of FAP.

It is estimated that some 10% of all FAP patients will develop desmoids, whereas 50–90% of FAP patients will suffer from duodenal adenomas predomi-nantly concentrated on or around the major papilla. Desmoid tumours and duo-denal carcinomas are major causes of death in those patients in whom a pro-phylactic proctocolectomy has been performed [33].

Although some investigators suggest that the adenoma–carcinoma sequence, which is generally accepted for colorectal adenomas, also applies for the duodenal adenomas in FAP patients, it is not clear whether these patients should be screened for upper gastrointestinal adenomas.

Since these polyps are usually small, multiple, and difficult to remove, the benefit of endoscopic surveillance would be the early detection of cancer. Endoscopic surveillance programmes grade the severity of the duodenal disease according to the Spigelman classification (stages 0-IV) to identify patients at risk of developing adenocarcinoma. Duodenoscopy can also be used therapeutically to remove polyps and thus reduce a patient's Spigelman stage.

However, a recent study has demonstrated that patients down staged from Spigelman stage IV demonstrated an increased rate of progression to severe disease. Therefore, once a patient has been classified as having stage IV disease he should be treated as a high risk patient and a surgical treatment can be considered [34].

The preferable surgical procedure for a FAP patient is demonstrated to be a duodenectomy with pancreas preservation, and a pancreaticoduodenectomy only for a patient with proven malignancy [35].

3.2.4 HEREDEDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

Hereditary non polyposis colon cancer (HNPCC) also known as Lynch syndrome, is an autosomal dominant genetic disorder caused by germline mutations in mismatch repair (MMR) genes.

This can result in an increased risk of primary colorectal cancer, but also cancer of the breast, endometrium, and ovary. Patients with HNPCC may also have an increased risk of pancreatic cancer [36].

The genes involved in mismatch repair include MSH2, MLH1, PMS1, PMS2 and MSH6/GTBP [37].

The phenotype observed, as a result of defective DNA mismatch repair, appeared as Microsatellite Instability (MSI), which consists in a presence of instability at microsatellite regions in the MMR-deficient cells. Those microsatellite instability (MSI) is used as a diagnostic marker for loss of MMR activity in tumour cells.

However the risk of developing primary small bowel cancer in HNPCC patients has been demonstrated [38], only few case reports documented a clear correlation between duodenal cancer and hereditary non polyposis colorectal cancer [39].

3.2.5 PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by melanocytic macules of the lips, buccal mucosa, and digits; multiple

gastrointestinal hamartomatous polyps; and an increased risk of various neo-plasms, including PC.

It is often caused by mutations in the LKB1/STK11 tumour suppressor gene on chromosome 19p13. STK11 is a tyrosine kinase and is known to be located both in the nucleus and the cytoplasm of all human tissue. STK11's primary function is energy homeostasis and it is the primary kinase of AMP Kinase (AMPK) [40].

 As a tumour suppressor gene, STK11 has been shown to cause apoptosis in intestinal epithelial cells appearing as an important key-regulator of the G1-checkpoint.

In literature, cases of malignant transformation of solitary Peutz-Jeghers type hamartomatous polyp of duodenum have been reported [41, 42].

3.2.6 NEUROFIBROMATOSIS (von Recklinghausen's Disease)

 Neurofibromatosis type 1 (von Recklinghausen's disease) is an autosomal dominant genetic disorder characterized by cafe au lait spots, pigmented hamartomas (Lich nodules) of the iris, and cutaneous neurofibromas.

While the association between neurofibromatosis and neuroendocrine tumours is well described, there are numerous reports suggesting that the association between duodenal adenocarcinoma and neurofibromatosis may not be fortui-tous and that duodenal cancer should be considered in the differential diagnosis of gastrointestinal symptoms in patients with neurofibromatosis [43].

FIGURE 1

SPIGELMAN CLASSIFICATION

Points	Polyps	Polyps size (mm)	Histology	Dysplasia
1	1-4	1-4	Tubular	Mild
2	5-20	5-10	Tubulovillous	Moderate
3	>20	>10	Villous	Severe

STAGE I, 1-4 points; **STAGE II**, 5-6 points; **STAGE III**, 7-8 points; **STAGE IV**, 9-12 points

4
Clinical Presentation and Diagnosis

4.1 CLINICAL PRESENTATION

In general, primary duodenal cancer manifests itself with non-specific gastrointestinal symptoms. The main group of symptoms include pain, obstructive symptoms, symptoms related to bleeding, and symptoms related to effects on adjacent organs such as obstructive jaundice.

Other clinical symptoms and signs such as palpable mass, loss appetite and, weight loss are less frequent. However, a good proportion of the patients are asymptomatic at the time of diagnosis.

Abdominal pain is not specific, can be related to stretching of the serosa or neural invasion of the tumour. The pain is usually described as dull ache, intermittently associated to food intake, it can be radiated to the back and it is poorly localised.

The non specificity of the pain can mislead the clinician to consider as causes of this pain more common pathologies such as colonic diverticulosis, gallstones and "irritable bowel syndrome" and, therefore to delay the diagnosis.

Bleeding from duodenal cancer is rarely acute. Generally, patients with duodenal cancer have chronic microcytic iron deficiency anaemia with related symptoms of fatigue and weakness.

Obstructive bowel symptoms are rare and they can occur as result of luminal obstruction as concentric growing tumour. However, another reason for obstruction is intussusceptions. In literature, it has been described cases of duodenojejunal intussusceptions caused by distal carcinoma of duodenum [44].

Despite being a non-specific symptom, weight loss has been highlighted by Bakaeen as an indicator of poor outcome even after a potential curative resection. The reason of this it could be explained by the fact that weight loss appear as late symptom reflecting a late stage in the natural history of the disease [14].

4.2 DIAGNOSTIC MANAGEMENT

It is often difficult diagnose early duodenal cancer because of their non-specific and insidious presentation. The diagnostic work-up can be long, expensive and it always involves an invasive procedure. The choice of the diagnostic investigation depends on the presenting symptoms. Patient presenting with obstructive symptoms are investigated radiologically, while patients presenting with iron-deficiency anaemia will benefit from an endoscopic approach.

4.2.1 COMPUTED TOMOGRAPHY OF ABDOMEN

A Computed Tomography of the abdomen (CT) with intravenous and oral contrast can identified benign and malignant tumour of the proximal and distal duodenum. The value of a CT scan is not only to diagnose a cancer but also in all biopsy-confirmed cases in evaluation of the extension of the disease.

Upper gastrointestinal ulceration is quite common and the presence of malignancy in duodenal ulcer is rare. However, ulcer located in the distal part of the duodenum should be viewed as suspicious for malignancy.

The important value of CT scan is not only to diagnose duodenal abnormality but also to evaluate the extent of the disease and staging. The appearance of duodenal cancer on CT scan can be similar of the appearance of adenocarcinoma of the colon and includes: filling defects and polypoid mass.

4.2.2 BARIUM RADIOLOGY

Upper gastrointestinal barium radiology is still the most frequent modality used in the work-up of upper gastrointestinal symptoms. However, the correct diagnosis with barium radiology in patient with duodenal cancer is achieved in only 50% of cases. The main reason of this is due to suboptimal distensibility and the presence of overlapping segments.

4.2.3 OESOPHAGUS-GASTRO-DUODENOSCOPY (OGD)

The upper gastrointestinal endoscopy has become the first line examination for duodenal cancer related symptoms. The value of endoscopy as primary diagnostic method for the upper GI tract has been established. The introduction of fibreoptic endoscopy has extended the range of interventions undertaken in the duodenum such as endoscopic mucosal resection (EMR). However, the association of Familial Adenomatous Polyposis (FAP) with high risk of duodenal carcinoma has also raised the role of the upper GI endoscopy as surveillance tool [45, 46].

This new role of endoscopy showed an increased number of case reports of early duodenal cancer in the recent years [47, 48]. The macroscopic type of early duodenal carcinoma is classified by criteria similar to those used to classify early colorectal carcinoma. (Fig 1)

Detection of superficial epithelial flat lesions during conventional endoscopy remained a challenge, even for experienced endoscopists. In the last few decades Japanese researchers have advocated the use of dye spraying techniques. Magnifying Chromoendoscopy (MC) has revolutionised the detection of flat lesions in the mucosa and, when used in a targeted fashion, allows the unmasking of the type of lesion and its borderlines. Furthermore, the use of magnifying endoscopes during chromoendoscopy allows a detailed surface analysis of suspected lesions and prediction of the dignity of the lesions using the so-called pit pattern classification. (Fig2-4)

The efficacy of magnifying chromoendoscopy (MCE), not only in differentiating between epithelial neoplastic and non-neoplastic lesions, but also in accurately determining invasion depth of early cancer, has widely been demonstrated [49, 50].

However, magnifying chromoendoscopy (MCE) is operator-dependent and

labour-intensive, and requires the use of staining solutions, spraying catheters, and several water rinses. These requirements have hampered its wider acceptance, particularly in Western countries, despite its demonstrated effectiveness. Fig 5

Recent years have seen the advent of narrow band imaging (NBI) as new endoscopic technique to characterise epithelial lesions. This is an innovative optical technology that uses interference filters to spectrally narrow the bandwidth used in conventional white light medical videoscopy.

NBI, using optical filters, highlights surface structure and superficial mucosal capillaries. This can allow an enhanced appreciation of the mucosal pattern or 'pit pattern' and of superficial microvessel networks. This has led to NBI usefulness being assessed in many endoscopically accessible organs where superficial epithelial neoplasia may occur including the oro-pharynx, oesophagus, stomach, duodenal ampulla, lung, colon and bladder, with promising results [51, 52].

A meta-analysis by East et al. suggests that NBI may be considered an equivalent to chromoendoscopy for lesion characterization in both the oesophagus and colon as form of 'electronic dye-spray [53].

In a more recent study Sakamoto et al. comparing directly magnify chromoendoscopy with narrow banding imaging in evaluating the depth of invasion of colorectal studies, confirmed that NBI had comparable accuracy to pit pattern analysis using MCE [54, 55].

In conclusion, magnifying endoscopy with NBI or MCE improves the view of microvessels of the mucosa in early neoplastic lesions of the duodenum. These techniques can predict the depth of the mucosal lesion with the advantage to obtain more detail information about the lesion; information that are useful for the endoscopists in order to make a decision towards or against an endoscopic resection.

FIGURE 1

Protruded type		Ip	*Pedunculated*
		Isp	*Sub-pedunculated*
		Is	*Sessile*
Superficial type		IIa	*Flat elevated*
		IIb	*Flat*
		IIc	*Depressed*

Macroscopic classification of early duodenal adenocarcinoma

FIGURE 2

Pit Patterns classifications

FIGURE 3

Pit pattern type	Characteristics
I	roundish pits
II	stellar or papillary pits
III S	small roundish or tubular pits (smaller than type I pits)

III L	large roundish or tubular pits (larger than type I pits)
IV	branch-like or gyrus-like pits
V	non-structured pits

Characteristics of the different pit pattern types

FIGURE 4
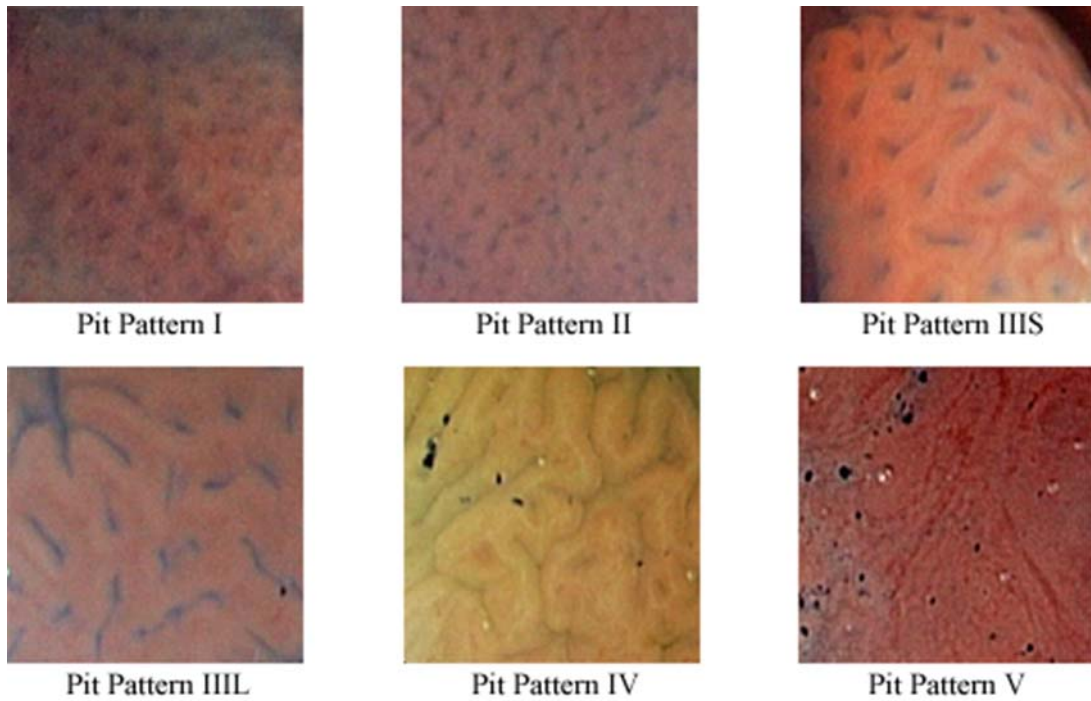
Real life pit pattern classification
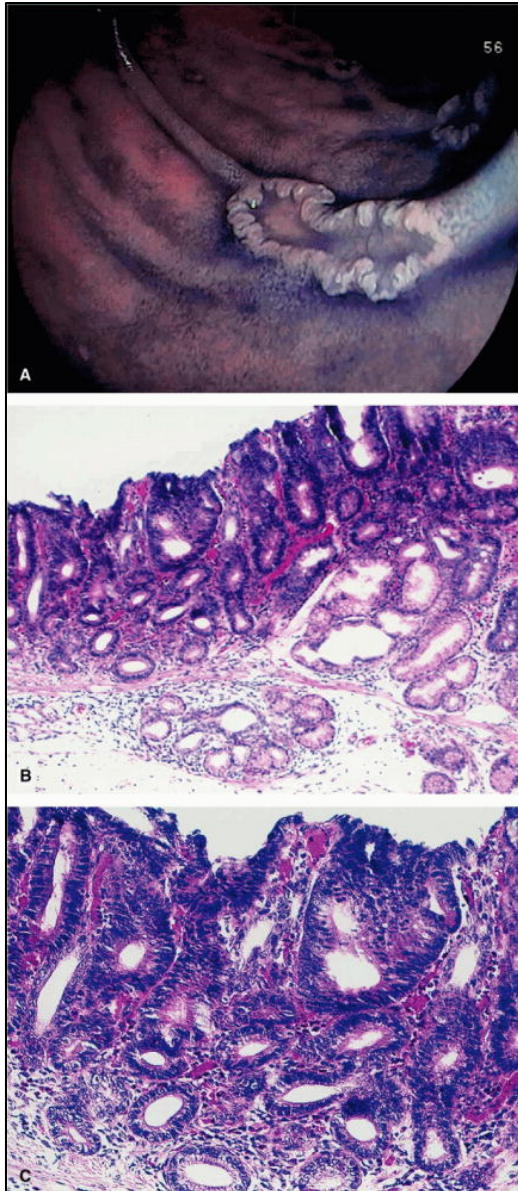
FIGURE 5 (A) Endoscopic findings of the depressed-type FAP-associated early duodenal carcinoma after the spreading of dye (0.1% indigo carmine). The tumour is located in the second portion of the duodenum, and the margin of the depressed lesion is irregular. **(B), (C)** Histologic findings of an endoscopically resected specimen. (H-E stain x20, x100, well differentiated adenocarcinoma in tubular adenoma, mucosal, ly0, v0)

4.2.4 DOUBLE BALOON ENDOSCOPY (DBE)

Total gastrointestinal examination has been possible with DBE using an endoscope for the small intestine. This endoscope was developed by Yamamoto et al.[55]. Such an examination was not possible using a conventional device. The total length is 2300 mm for the standard type, and the effective length is 2000 mm. A selection can be made between two types which differ in outer diameter.

This system has been developed for patients in whom insertion of the endoscope is difficult in the colorectal region. Therefore, all treatment devices for the large intestine can be used in this system. In addition, as this system has the regular DBE functions, stable manipulation is possible even in the deep portion of the duodenum. DBE has been proved to be useful for carrying out duodenal endoscopic treatment, especially in areas distal to the major duodenal papilla.

The double-balloon enteroscope features two balloons, one attached to the distal end of the scope and the other attached to a transparent tube sliding over the endoscope. When inflated with air, the balloons can grip sections of the small intestine and "shorten" the small intestine by pleating it over the endoscope. Sequential shortening of the small intestine over the endoscope and advancement of the endoscope enables a comprehensive examination of the entire small intestine. FIG 6

Recent studies concluded that the detection rate and complication rate of DBE are acceptable. They found that DBE is a valuable modality, with a pooled detection rate of 68.1 percent for all small intestinal disease.

Inflammatory lesions and vascular lesions are the common findings in patients with suspected mid-gastrointestinal bleeding in Eastern and Western countries, respectively, according to DBE. Although DBE failed to identify a proportion of lesions, the performance of DBE is acceptable because the symptoms of a significant proportion of patients without positive findings would not recur during follow-up. They noted that DBE is considered to be a safe procedure with few complications, most of which are minor.

FIGURE 6

Fig 1 - Double Balloon Enteroscope & Overtube System Fujinon Medical Inc.

TABLE 1

TNM Classification	
Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour invades lamina propria or submucosa
T2	Tumour invades muscularis propria or size >1 cm
T3	Tumour invades through the muscularis propria into the subserosa without penetration overlying serosa
T4	Tumour perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of the small intestine, mesentery, or retroperitoneum more than 2 cm, and the abdominal wall by way of the serosa; for the duodenum only, includes invasion of the pancreas)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
T1	No regional lymph node metastasis
T2	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M1	No distant metastasis
M2	Distant metastasis

TABLE 2

Stage Grouping using TNM system			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage III	T3	N0	M0
	T4	N0	M0
Stage IV	Any T	N1	M0
	Any T	Any T	M1

5

Molecular Pathogenesis and Prognostic factors of Adenocarcinoma of Duodenum

5.1 MOLECULAR PATHOGENESIS

Little has been published about carcinogenesis of duodenal adenocarcinoma due to rarity of this disease. Although the small intestine makes up approximately 75% of the length and 90% of the mucosal surface of the gastrointestinal tract, small bowel adenocarcinoma (SBA) occurs 50 times less frequently than colorectal adenocarcinoma [56].

Despite this intriguing biological difference in the incidence of small bowel adenocarcinoma (SBA) and colorectal adenocarcinoma, few investigations into the mechanisms of small bowel carcinogenesis have been conducted. A number of theories have been postulated to explain the relative protection of the small intestine from the development of carcinoma; however, none have been proven. Proposed protective factors have generally centred around two concepts. First, the rapid turnover of small intestinal cells results in epithelial cell shedding before the accumulation of the genetic damage critical to carcinogenesis.

Second, exposure of the small intestine to the carcinogenic components of our diet is limited because of the small intestine's rapid transit time, lack of bacterial degradation activity, and relatively dilute alkaline environment.

Stepwise progression of human cancer has been clinically well recognised. Several types of premalignant lesions, such as dysplasia and hyperplasia, can be detected in diverse organs prior the appearance of fully malignant tumours. The premalignant lesions are caused either by genetic alterations which include monoclonal expansions of the cells, or by environmental factors, such as viral infection, which include polyclonal expansion of the cells. Subsequently, accumulation of genetic alterations occurs in one or few of the premalignant cells and the cells convert into malignant ones of clonal origin and produce a primary tumour.

However, at early stage of primary tumour expansion, the cells are not invasive and metastatic. Then, new clones with invasiveness and metastatic ability appear as result of further accumulation of genetic alterations in the cells.

Since cancer is attributed to genetic alterations accumulated in the cells, it is indispensable to identify genes whose alterations accumulate during tumour progression to understand the molecular mechanism of progression of cancer.

FIG 1

FIGURE 1

○ : normal cell, ◐ : pre-malignant cell, ◑ : malignant cell without metastatic ability, ● : malignant cell with metastatic ability
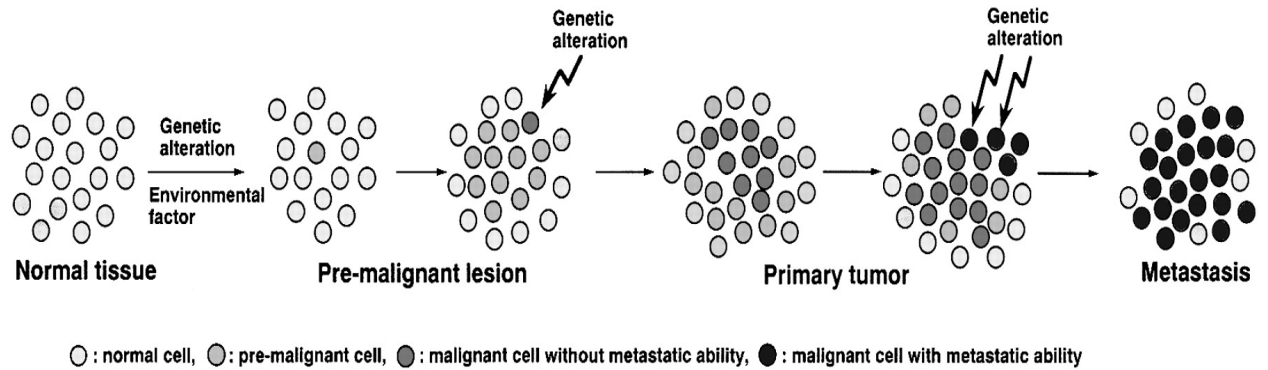
Stepwise malignant progression of human cancer associated with accumulation of genetic alterations in cells.

Over the last 3 decades, a number of genes that are genetically altered in human cancer cells have been identified.

In 1990, Fearon and Vogelstein proposed a model of successive genetic changes leading to colorectal cancer (CRC), in which a number of genes were involved, including APC (adenopolyposis coli), k-Ras, DCC, and p53 [57]. FIG 2

FIGURE 2
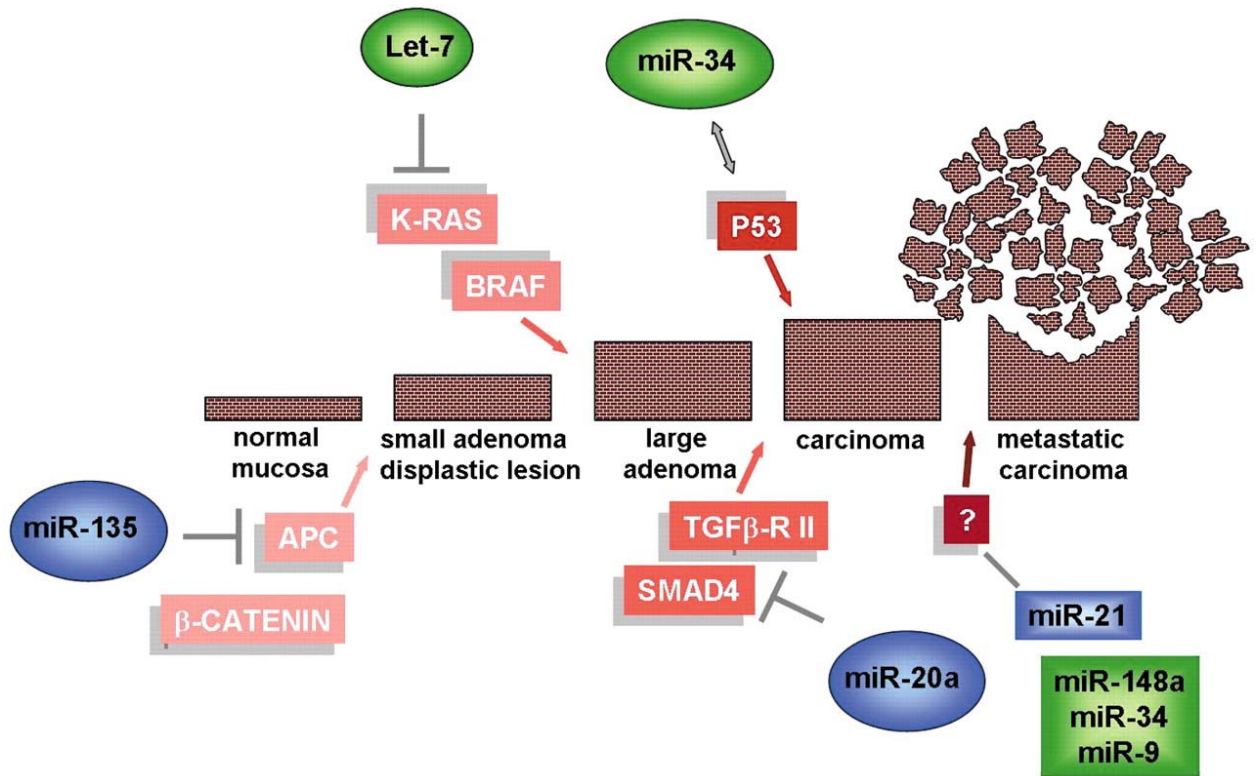
According to the model proposed by Vogelstein different genes are involved in each step of the progression from normal mucosa to metastatic cancer.

 The original proposal stressed that mutations in these genes were essential for the development of CRC, rather than specifying the exact sequence of changes.

Subsequent research over almost 10 years has revealed much information on the function of the key genes in the model, which will be reviewed first.

The APC gene product was originally thought to be involved in cell adhesion by binding to b-catenin, a known component of the adherent junction complex.

Later on, it appeared that APC co-localized with the microtubular system and bound to other molecules, such as EB-1; it was also, shown to induce apoptosis in APC-deficient cell lines.

Over the past few years, a role of APC in the Wnt signalling pathway has emerged. In this pathway, APC acts as a partner molecule of b-catenin, which is degraded and inactivated through binding to APC. Upon the binding of a Wnt peptide to its receptor, a signal is instigated, which through the dishevelled gene product inactivates glycogen synthase kinase 3β (GSK-3 β). This blocks phosphorylation of β-catenin and prevents its binding to APC;

β-catenin accumulates and starts acting as a co-transcription factor, providing the transactivation domain for the transcription factor Tcf-4. The mutated and truncated APC product is unable to bind and titrate b-catenin, so that Wnt signalling in an APC mutated cell becomes deranged [58,59].

More recently, one of the genes inappropriately activated in a deranged Wnt signalling system turned out to be c-myc [60]. This may shed light on the reason why this signalling pathway is so crucial for normal function of a colonic epithelial cell and may also explain some of the hitherto enigmatic effects of APC on, for example, apoptosis

The association of Familial Adenomatous Polyposis (FAP) with duodenal cancer has facilitated a better understanding the natural history of the duodenal polyposis and the risk of develop duodenal cancer [61].

In recent years, different hypothesis regarding the carcinogenesis of the duodenal cancer has been proposed.

It has been suggested two different pathways of carcinogenesis: one characterized by an adenoma-carcinoma sequence and the second one by a de novo cancer. Epidemiologic, histologic and histochemical observations of FAP-associated carcinoma suggest an adenoma-carcinoma sequence in the duodenum similar to that in the colon [62.63].

In that sequence, the inhibition of apoptosis through an altered expression of regulatory proteins plays an important role. As a result, regulatory proteins, such as p53, bcl-2, and cyclooxygenase 2 (COX2), have thus been suggested to be possible predictors of malignant transformation in colorectal adenoma.

However, somatic mutations of APC, K-ras, and p53 genes have been reported in duodenal adenomatosis, which differ from those found in colorectal cancer [64, 65].

Because carcinogenesis and tumour progression are considered to be the consequence of accelerated somatic alteration of oncogenes related to cell kinetics, such mutations may contribute to the increased risk of duodenal cancer in FAP subjects. It thus seems to be valid to identify proteins that are related to the cell kinetics of duodenal adenomatosis to elucidate their malignant potential.

Cell apoptosis is regulated by various inhibitors and promoters. In a recent study by Esaki et al., bcl-2 and p53 were selected as representative inhibitors of apoptosis since these proteins have been shown to play a key role in either the early or the late stage of colorectal carcinogenesis [64]. However, this study failed to demonstrate any difference in bcl-2 and p53 immunoreactivity between FAP and non-FAP subjects.

Those results indicated that duodenal adenoma in FAP subjects do not have a higher proliferative activity or a smaller degree of apoptosis when compared with those in non-FAP subjects. The inverse correlation between the endoscopic grade and the proliferative activity seems to be compatible with the static nature of ampullary adenoma in FAP.

Kashiwagi et al. [66] indicated a close correlation between p53 overexpression and a high-grade dysplasia of duodenal adenoma in FAP subjects. p53 may thus be a putative marker of duodenal adenoma and it thus requires a close surveillance in FAP subjects.

The adenomatous components have also been reported to be present in around 50 % of duodenal sporadic cancers [67]. However, there are few reports concerning the carcinogenesis of sporadic duodenal carcinoma.

Achille et al. [68] investigated 12 cases of sporadic duodenal carcinoma for genetic anomalies involved in the pathogenesis of gastrointestinal malignancy. Those anomalies included chromosome allelic losses; Ki-ras and p53 mutations; and microsatellite instability such as mismatch repair genes (MMR).

This study showed that the majority of cases had frequent chromosomal changes and mutations of Ki-ras and p53 genes, while widespread subtle alterations due to mismatch repair deficiency occurred in a minority.

The results proved that sporadic duodenal non-ampullary cancers share similar molecular pathogenic pathways to colorectal cancers. However, the small num-

ber of cases in the study did not allow the assessment of the prognostic value of the molecular variable through a survival analysis.

Although the prevalence of cancer of the duodenum is low compared with colorectal cancer, these similarities in the two cancers suggest that they may share many of the genetic changes of carcinogenesis.

If the two cancers differ in either the type of genetic changes or the frequency of these changes, then it may be hypothesised that the small bowel is resistant to the genetic events that occur in colorectal cancer.

As in colorectal cancer, a recent study suggested that small bowel adenocarcinomas are characterised by a defect in DNA mismatch repair (MMR), which results in DNA microsatellite instability (MSI) [69].

Microsatellite instability (MSI) is characterised by the accumulation of changes in the length of simple repeated nucleotide sequences known as microsatellites, caused by mutations in MMR genes such as MutS homologue 2 (hMSH2), MutL homologue 1 (hMLH1), post meiotic segregation increased 1 (hPMS1), hPMS2, and hMSH6. Although MSI is a hallmark of hereditary nonpolyposis colorectal cancer syndrome (HNPCC), in which mutations of one or more MMR genes are found in 90% of the cases, it has also been reported in approximately 10% of sporadic colorectal adenocarcinomas [70].

Recent studies counting early onset duodenal carcinoma in children showed presence of germline biallelic MMR mutations. Biallelic mutations in PMS2 accounted for majority of cases in families with MMR-D (25/50 families, 50%),

while MLH1 and MSH6 each accounted for 20% of families, and MSH2 accounted for 10% of families [71-74].

Other oncogenic signalling pathways that are active in colorectal cancer include the epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and phosphatidylinositol 3-kinase (PI3K)/AKT pathways.

A recent extensive study on small bowel adenocarcinoma suggested that alterations in DNA MMR pathways are common in SBAs, similar to what is observed in large bowel adenocarcinomas.

Furthermore, this study showed a high percentage of tumours expressing both EGFR and VEGF which suggests that patients with this rare cancer may benefit from therapeutic strategies targeting EGFR and VEGF receptor (VEGFR).

However, in recent study involving the role of β-catenin and E-cadherin in adenocarcinoma of small bowel, Wheeler et al. did not detect mutations in the Mutational Cluster Region MCR of the APC gene, and this suggests that adenocarcinoma of the small intestine may follow a somewhat different genetic pathway to colorectal cancer, although still often involving alterations associated with β-catenin and E-cadherin.

Over expression of p53 was a relatively frequent finding and, as in colorectal cancer, reflects its important role in the carcinogenesis of the small intestine [75, 76].

Those recent findings show intriguing differences from colorectal cancers with respect to APC mutations, suggesting that molecular mechanism leading to the

development of duodenal adenocarcinoma may be different than those leading

to colorectal cancers.

5.2 PROGNOSTIC FACTORS

Prognostic factors associated with survival in patients with primary adenocarcinoma of the duodenum still remain controversial.

Different retrospective series have evaluated the prognostic impact of specific clinico-pathological factors for duodenal adenocarcinoma. FIG 1

Considering the heterogeneity of the symptomatology of the primary duodenal adenocarcinoma, it is difficult to give to a specific symptom a particular prognostic value.

However, Hurtuk et al. [77] described how presenting symptoms can be indicative of advance disease, proving that patients presenting, at least with four symptoms had a worse outcome despite aggressive surgical resection.

In the literature, the presenting symptoms are related to the site of the duodenum involved by the tumour. However, jaundice at presentation seems to be reported as sing of advance disease and, therefore a symptom that can affect the survival after resection.

Rotman et al. [78] stressed the importance of anaemia as indicator of better prognosis, even though the data was not statistically significant. The explanation of this result can be explained by the fact that patients with anaemia come to the attention of the doctor sooner.

Bakaeen et al. found that weight loss was predictive of worse survival [14].

The length of the presenting symptoms has also a prognostic importance. Indeed, the adenocarcinoma of duodenum is normally presenting with non-

specific symptoms: causing an index of suspicious very low and, substantially a delay in the diagnosis.

In literature, the average symptoms were present before the diagnosis for a minimum of 3 months and in some cases up to 6-8 months.

Delcore et al. [79] reported that patients who had a length of symptoms of 4 months or longer before the diagnosis have a worse 2-year survival rate.

Chung et al. [18] recently reported White Blood Count (WBC) as an independent factor for survival from 1 through 5 years. WBC was not significant factor for survival only at 1 year, but tended to correlate with survival at 2 and 5 years.

In the univariate survival analysis, the white blood cell (WBC) was significantly correlated with survival at 6 months, 1, 2 and 5 years.

In literature, the issue on survival of patients with duodenal adenocarcinoma have still many areas of controversy: the prognostic significance of size and location of the tumour, histological grading, staging of the disease and nodal status.

The significance of the primary location in regard to the prognosis is still debatable. Lowell et al. [80] reported longer survival rate among patients with distal tumour, whereas

Schn et al. [81] and Stell et al.[82] reported longer survival in patients with proximal tumours. However, it seems evident in literature that the distal tumours have a better prognosis.

A better prognosis for distal tumour can have an embryological explanation. The proximal duodenum, which includes the supra-papillary and the peri-papillary

duodenum, is part of the foregut, while the distal or infra-papillary duodenum origins from the midgut. Tumours originating from the foregut are well known to be more aggressive of the one from the midgut.

Barnes et al. [7] found that adenocarcinoma of the duodenum behaves similarly to colon cancer, whereas Rose et al. [6] and Sarela et al. [15] reported a similarity to gastric cancer.

Ryder et al. [83] found that tumour size is an important independent prognostic factor, through a correlation between the diameter of the lesion and survival: greater the diameter, shorter the survival.

The hypothesis behind this results was supported by the fact that larger tumours have been present longer and having more time to metastasize and involve the adjacent structures. Interestingly, Hurtuk et al. [77] found that tumours larger of 3.5 cm were less likely to be invasive and on the contrary smaller tumours tend to be more aggressive.

Resection margins are considered as prognostic factor. In literature, patient who had an R0 resection (margins not involved) survives significantly longer than those with non-R0 resection (margin involved) independently from stage of the disease.

Lymph node status is a prognostic factor for survival, since nodal metastases have been associated with poor prognosis. Bakaeen et al. [14] reported a clear association between nodal metastasis and decrease survival (68% vs 22%).

The median number of nodes were higher in the radical surgery (6 nodes) compared with the limited resection group (2 nodes).

However, despite potential downstaging in the limited resection group no difference of survival was noted when compared with the radical resection group.

The importance to have an accurate lymph node staging in duodenal adenocarcinoma in comparison with antral gastric cancer was evaluated by Sarela et al. [15]. The incidence of nodal positivity was similar in the duodenal and in the antral gastric cancer groups. However, the duodenal cancer group had fewer patients with 15 or more lymph nodes assessed (47%vs 64%). The authors concluded that for the duodenal cancer, examination of 15 or more lymph nodes improved prognostic discrimination by the pN category.

The American Joint Committee on Cancer (AJCC) requires at least six regional lymph nodes assessment for duodenal or small bowel cancer.

Sarela et al. introduced the possibility of stage migration. The expectation of having an improvement in disease specific survival in both the node-negative and node-positive duodenal carcinoma group who have > 15 lymph nodes was not fulfilled. Indeed, in the node negative group there was a 25% improvement of in survival when > 15 lymph nodes were assessed, but surprisingly   the nodes positive group' patients who

had < 15 nodes had a 17% improvement of survival.

Therefore, the importance of total lymph node sampling remains unclear.

A recent study from Massachusetts General Hospital showed for the first time the superior prognostic importance of perineural invasion versus lymph node involvement. This single-centre retrospective study included 169 patients with duodenal adenocarcinoma.

They collected demographic, clinical and pathological data including the lymph node ratio (LNR) and the perineural invasion (PNI). In this study, univariate analysis demonstrated that nodal involvement, LNR, advance tumour stage, and perineural invasion were each associated with significant decrease in overall survival. However, a multivariate analysis identified perineural invasion as the most independent predictor of survival [20].

Perineural invasion (PNI) is the process through which cancer cells invade the perineural spaces of surrounding nerves and is frequently present in pancreatic and prostatic cancer. This process involves many signalling molecules from various signalling pathways; these signalling molecules called neurotrophins are produced by both the cancer cells and the nerves. Once the cancer cells have invaded the nerves, they are able to thrive within the neuronal spaces.

Several neurotrophins, including NGF, BDNF, and NT-3, have been implicated in promoting tumour cell invasion and may be key mediators in the pathogenesis of PNI [84].

 In a recent molecular study has been reported that chemokine CX3CL1/Fractalkine act as neurotrophic factors attracting receptor positive pancreatic tumour cells to disseminate along peripheral nerves [85].

In pancreatic cancer the incidence of PNI can account even for a 100 % involvement of intrapancreatic nerves and nearly 70 % of extrapancreatic nerves [85, 86].

In the Massachusetts General Hospital data the perineural invasion was present in 40% of the patients with duodenal adenocarcinoma.

These results were associated with an absence of concordance between perineural invasion and nodal involvement in more than one third of the patients raising the hypothesis which hat the perineural invasion may due to different pathogenic pathways.

TABLE 1

Overview of literature with analysis of prognostic factors for survival in patient after potentially curative resection for duodenal cancer

Author [ref] (year)	Number of cases	% 5-year OS	Predictors
Barnes [7] (1994)	36	29	**pN**
Rose [6] (1996)	42	60	**pN**
Santoro [8] (1997)	65	25	**pT** **Tumour location**
Sohn [81] (1998)	48	53	**Margin involvement** **Location**
Yeo [87] (1998)	17	59	**pN**
Ryder [83] (2000)	27	43	**pT** **Grading**
Bakaeen [14] (2000)	68 a	54	**pT** **pN** **Margin involvement** **Weight loss**
Tocchi [16] (2003)	47	23	**pN**
Sarela [15] (2004)	72	71a	**pN** **Age**
Hung [88] (2007)	11	16.6	**TNM stage** **Cytology** **Cigarette smoking** **AST**
Lee [89] (2008)	28	44	**pT** **pN**
Zhang [17] (2010)	59	33	**pN** **Margin involvement**
Poultsides [19] (2011)	122	48	**pN** **LNR**
Chung [18] (2011)	14	6.7	**Total bilirubin** **TNM stage** **Grading** **WBC** **CDT**
Cecchini [20] (2011)	103	42	**Perineural invasion**
Verona study (2012)	**25**	**71**	**POC** **Grade** **Margin involvement**

a Disease specific survival (R0 resection only), pN pathological nodes states, pT pathological tumour states, LNR lymph node ratio, WBC white blood cell count, AST Alanine transaminase, CDT cancer-directed-treatment, POC postoperative complications.

6

Early Duodenal Adenocarcinoma and Endoscopic treatments

6.1 INTRODUCTION

With the increasing prevalence of endoscopy, there have been an increasing number of reports of duodenal lesions. However, conventional surgery is often selected for duodenal adenoma because the incidence of duodenal cancer is relatively low, and its endoscopic treatment is difficult compared with that of the stomach and large intestine because of anatomical features and the long distance to the lesion.

6.2 ENDOSCOPIC TREATMENTS

Recent advances in the field of endoscopic examination have made possible not only to diagnose duodenal cancer at early stage but also to treat it.

6.2.1 ENDOSCOPIC MUCOSAL RESECTION (EMR)

Endoscopic mucosal resection is a method developed by Tada et al. [90] for the treatment of superficial stomach tumours.

At the present time, EMR provides for the safe resection of polyps, flat lesions of the stomach including adenoma and early adenocarcinoma. In this method, 0, 9% NaCl solution   or sodium hyaluronate solution are injected into the submucosal beneath a mass with endoscopic needle. Since the wall of the duodenum is thinner than that of the stomach, the injection of saline solution into the duodenal wall adjacent or beneath the tumour should aim to raise the tumour from the submucosal and serosal layers.

This method prevents the occurrence of intramural burns even if multiple pieces are removed in a piecemeal fashion.

Ulcers produced by electrocoaugulation after pre-injection of normal saline are all confined to the submucosal layers, whereas nearly half of those produced by electrocoaugulation without injection of saline involve the muscle or deep layer of the bowel wall. Those results confirm that this technique is safe for the treatment of intramural lesions of the intestine.

Despite the indications for endoscopic treatment of early cancer in the oesophagus, stomach and large bowel are been well defined, the indications for treatment of early cancer in the duodenum are still not established.
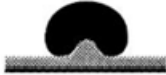
Satake et al. [91] reported that no lymph node metastasis was found in 14 patients with intra-mucosal carcinoma of the duodenum, whereas, it was detected in one of 18 patients (5.6%) with submucosal tumours.

Nagatani et al. [92] studied the indications for endoscopic treatment from the viewpoint of lymph nodes metastasis by analysing 128 lesions in 127 patients of early duodenal carcinoma reported in Japanese literature from 1968 to April 1992 [93]. They reported that the rate of lymph node metastasis is 0% for intra-mucosal cancers and 5% for sub-mucosal cancers.

These findings suggested that it is unlikely that intra-mucosal cancers are me-tastatasize to lymph node, although early cancer which infiltrates submucosal layers has high chance to have positive lymph nodes. Therefore, it has been established that endoscopic treatment for early duodenal cancer is indicated only for intra-mucosal cancers.

On the basis of these histological results, Nagatani supported that peduncolated tumours (Type Ip) of 20 mm or less in diameter, sessile tumour (Type Is) tumour of 5 mm or less, superficial lesions (Type IIa+ IIb) of 10 mm or less are indications radical endoscopic treatment of early duodenal cancer. FIG 1, 2

FIGURE 1

Protruded type		Ip	*Pedunculated*
		Isp	*Sub-pedunculated*
		Is	*Sessile*
Superficial type		IIa	*Flat elevated*
		IIb	*Flat*
		IIc	*Depressed*

Macroscopic classification of early duodenal adenocarcinoma.

However, another review of literature concluded that protruding or elevated tumours less than 50 mm can be removed completely but the Type II depressed lesions with or without marginal elevation of 10 mm or larger should be removed surgically since high chance to have lymph nodes metastasis [94].

 Taken together with previous studies, duodenal cancers appearing as a protruded lesion of 20 mm or less and a flat depressed tumour of 10 mm or less are considered to be indicators for radically curative endoscopic treatment.

The recognized complications of EMR include bleeding, pain, perforation, and stricture formation. Bleeding is the most common complication and usually occurs during or within 24 hours of the procedure. Early bleeding in the duodenum

has been reported in up to 33% of patients, and it is the most common complication associated with this procedure.

 The reported frequency of bleeding during an EMR for a duodenal adenoma range from 4% to 33%.[95-97].The frequency of delayed bleeding can be reduced by prevention measures such as APC or clipping. Primary closure of the resected area by clips is preferable to APC because it does not increase tissue injury after EMR.

FIGURE 2

Endoscopic images of the endoscopic mucosal resection (EMR) procedure. (A) Adenoma in the second part of the duodenum. (B) EMR procedure. (C) The site after the EMR

6.2.2 ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD)

More recently, Endoscopic submucosal dissection (ESD) has emerged as a novel technique for achieving en bloc resection for superficial neoplasms limited

to the mucosa. The advantage of this technique is to increase the ability to achieve en-bloc dissection. (Fig 3) Recent retrospective comparative trials showed that ESD achieved higher rates of en bloc resection and curative resection than EMR [98-100].

ESD is technically difficult procedure to perform because of the anatomical properties of the duodenum.

Honda et al. [101], recently described 9 duodenal lesion treated by ESD. All cases were limited to the mucosal layer and resected in en bloc with a mean time of operation 85.2 minutes, and localised in the second portion of duodenum. Five cases were carcinoma in adenoma and four were adenoma. A double balloon endoscope (DBE) was used in order to improve the control of the tip of the endoscope since it has been proven to be difficult to maintain the distance between the tip of the scope and the duodenal lesion. The mean diameter of the tumours was 23.8 mm (median 22 mm, range 12–39 mm) and that of the resected specimens was 32.4 mm. FIG. 3

They experienced duodenal perforation in two cases as a complication of ESD. In one case, it occurred during ESD and was immediately treated by clipping. In the other case, delayed perforation led to surgical treatment.

Delay perforation has a well know complication due to exposure of the duodenal wall to pancreatic juice and bile. Administration of protease inhibitors could be useful for prevention of delayed perforation.

Honda et al. advocated that the combine use of small-caliber-tip transparent hood

(ST hood) and hook knife can make possible to resect superficial duodenal lesion en block with ESD technique. However, ESD is difficult to standardize due to high level of endoscopic skills required to perform it; considering that endoscopist's experience affects the outcome of ESD.

FIGURE 3
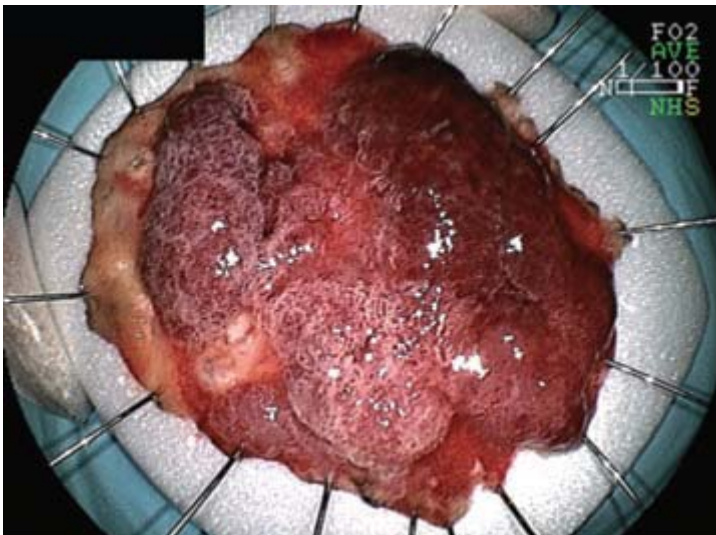
En-block resection of a 3.0 cm adenocarcinoma in adenoma by ESD technique.

6.3 SUMMARY

In conclusion, the majority of benign lesions in the duodenum can be resected using the standard EMR technique. This treatment method helps to reduce the

need for open surgery and offers an acceptable complication rate that can be managed by endoscopy.

However, in presence of early duodenal cancer presenting as protruded lesions bigger than 20 mm and superficial lesions bigger of 10mm endoscopic treatment should be abandon in favour to a surgical resection due to higher risk of nodal involvement. Some institutions indicate as first choice of endoscopic resection ESD for duodenal lesions exceeding 10 mm in diameter and in which en-bloc resection is desirable [102-103].

ESD is feasible and useful for superficial duodenal neoplasms. However, it is still a technically demanding, time-consuming procedure and associated with a high risk of complications.

7

Primary Nonampullary Duodenal Adenocarcinoma- Verona Experience

7.1 INTRODUCTION

Primary adenocarcinoma of the duodenum is a rare condition, accounting between 0.3% and 0.5% of all gastrointestinal malignancies [1]. Despite the duodenum is representing less than 10 % of the total length of the small bowel, it is the site of between 25% and 45% of the small bowel cancers [2]. Cancer of the duodenum appears to be more frequent in the periampullary area, but has been also shown to arise in the third and fourth duodenal portion [4]. Since the symptoms are non-specific and similar to other benign conditions, the diagnosis is often difficult and delayed. Nonetheless, duodenal carcinoma has a reported 5-year survival rate for resected tumours between 25% and 75% [5-10,17,18,20], which is significantly better than that for cancer of the ampulla of Vater (46%) and the head of pancreas (10%) [11,12]. In the last decade, different studies evaluated the correlations between clinical, pathological and treatment variables in order to identify specific prognostic factors associated with survival [13-20]. These studies showed that sex, age, tumour size and location, grade, stage, resection mar-

gins, weight loss, and white blood cells count can influence survival significantly.

However, due to a low incidence of the disease in the general population, the debate on prognostic factors in duodenal adenocarcinoma is still open. Therefore, questions have been raised especially on the prognostic significance of nodal status and of the absolute number and ratio of involved lymph nodes [15], and a recent report established perineural invasion as another important independent prognostic factor [20]. The purpose of the present study was to evaluate clinico-pathological features and analyse the main prognostic factors in patients with duodenal adenocarcinoma observed at our institution.

7.2 PATIENTS AND METHOD

This study was approved by the Institutional Review Board. The clinical records of all patients diagnosed with primary duodenal adenocarcinoma and referred to the unit of General Surgery B, University of Verona, between January 1990 and December 2009 were reviewed. The diagnosis was confirmed by histological examination of all resected specimens or by endoscopic biopsies. Patients with adenoma and malignant neoplasms other from adenocarcinoma were excluded. Demographic and clinical details, surgical and pathological data were collected from the patient notes. Pathological data included tumour size, grade, and stage. Pathological staging of duodenal adenocarcinoma was based on the American Joint Committee on Cancer (AJCC) system, 7th edition. A tumour

comprising two different degrees of differentiation was recorded as the category of poorer differentiation.

Lymph node ratio (LNR) was calculated dividing the total number of lymph nodes harbouring metastasis by the total number of resected nodes, cut-off points were chosen according to the existing literature [104]. Additional collected parameters included perineural invasion (defined as tumours cells within any layers of the nerve sheath or perineural space), and the presence of lymph-vascular invasion (defined as microscopic lymphatic invasion, vascular invasion, or both).

A curative resection was defined as a microscopically negative resection with no gross evidence of residual disease (R0 resection). A resection with curative intent was ultimately defined as a palliative intervention if the margin was micro-scopically (R1) or macroscopically (R2) positive. Palliative treatment also in-cluded biliary and gastrointestinal bypass, biopsy and exploration alone.

Postoperative morbidity and mortality were defined as occurrence of complica-tions and death within 30 days of the operation, respectively.

Postoperative pancreatic fistula (PF) was defined according to the International Study Group on Pancreatic Fistula (ISGPF) [105]. Follow-up information was ob-tained from our electronic database or through telephone interviews.

7.2.1 STATISTICAL ANALYSIS

Data were analyzed using the SPSS software (version 19.0; SPSS, an IBM company, Chicago, IL, USA). Distribution of continuous variables was reported as median and range. Categorical variables were presented as numbers and percentages.

Overall survival time was calculated from the date of operation/pancreatic resection to the date of last follow-up/death.

Cumulative event rates were calculated using the method of Kaplan and Meier. Univariate analyses were performed using the log-rank test to compare differences between categorical groups. A Cox proportional hazards model was developed using relevant clinico-pathologic variables in a direct enter fashion (univariate inclusion criteria of $p<0.150$) to determine the association of each with overall survival. P-values were presented with hazard ratios and 95% confidence intervals.

For univariate and multivariate analysis, the variables tumor size, resection margins, tumor grade and stage were dichotomized as appropriate (≤3 cm versus >3 cm, R0 versus R1-R2, G1 versus G2-G3, and Stage I-II versus Stage III-IV). Statistical significance was determined by a p-value of less than 0.05.

7.3 RESULTS

7.3.1 DEMOGRAPHIC

Thirty-seven patients with primary adenocarcinoma of the duodenum were identified. There were 21 men and 16 women with a median age of 57 years (range

38-83 years). Only one patient (2.5%) developed duodenal adenocarcinoma following colectomy for Familial Adenomatous Polyposis (FAP).

The majority of patients had cancer arising in the descending part of the duodenum- D2 (66.7%) and the remaining of the patients the cancer arose from the horizontal part of the duodenum- D3 (32.4%). Our data did not show any cases of duodenal adenocarcinoma located at the proximal and distal portion of the duodenum (D1 & D4).

The median Body Mass Index (BMI) was 22.6 (17.0-31.6), a median CA19.9 level at initial presentation was 24 U/ml with a range between 1 and 96.957 U/ml (Units per millilitre). TABLE 1

7.3.2 DIAGNOSIS

The most common presenting symptoms were non-specific upper abdominal pain (70.3%), weight loss (62.2%), jaundice (27%), episodes of maelena (16.2%) and anaemia (3%).

In patients who underwent palliative resection, the most frequent initial symptoms were weight loss (75%) and abdominal pain with vomiting (62.5%), compared to abdominal pain (72%) and Jaundice (36%) in patients with resectable disease.

7.3.3 OPERATIVE TREATMENT AND COMPLICATIONS

Twenty-five patients (68%) underwent potentially curative resection, 8 patients underwent to biliary bypass, 1 patient had an exploratory laparotomy, and 3 pa-

tients received a non surgical palliative treatment. Non surgical palliative treatment included chemotherapy with supportive treatment.

The 25 patients underwent curative resection were equally demographically distributed comprised 14 male and 13 female with a median age of 54 years (38-83 years).

Whipple's Procedure was performed in 9 patients (36%) and a Pylorus Preserving Pancreas Duodenectomy (PPPD) was performed in 16 patients, independently by the location of the tumour. 15 patients (60%) had tumours in the second portion of the duodenum while 10 (40%) patients had tumours in the third of the duodenum.

The overall length of surgery was 360 minutes with a range between 180-630 minutes.

The median length of stay for the curative resection patients was of 14 days (9-57), while the median length of stay after palliative treatment was 11.5 days (8-27).

Only 9 patients required postoperative blood transfusion. (26.5%)

 No postoperative mortality was reported following those pancreaticoduodenectomies. Overall postoperative morbidity was 52 % with a rate of 56% in the curative resection group and a rate of 50% in the bypass group.

 In the curative resection group the most common postoperative complication was pancreatic fistula involving 4 patients (11.8 %). Among the palliative group,

one or more complications developed in 4 patients (50%), with chest infection appearing to be the most common complication in this group of patients (25%).

The median length of stay for the curative resection patients was 14 days (9-57), while it was 11.5 days (8-27) after double bypass.

No postoperative mortality was reported following surgery in both groups of patients. (Table 2)

7.3.4 PATHOLOGICAL FINDINGS

This analysis was restricted to patients who underwent a potentially curative resection. Five patients (20%) were stage I, six (24%) were stage II, eleven (44%) were stage III, and three (12%) were stage IV. Among the three metastatic patients, one had a single lung metastasis, one had a single liver metastasis treated with concomitant wedge resection, and one had a proximal jejunal loop metastasis, which was excised with the pancreaticoduodenectomy specimen. Pathological data are summarized in table 4 .

17 of the curative resection were histopathologically confirmed as R0 (68%), six were R1 (24%) and only two resections (8%) were reported as R2. Nodal metastases (pN1) were identified in 24 patients (64.8%). The median number of lymph nodes retrieved was 19 (range 5-63), while the median number of lymph nodes excised from the pN1 patient group was 22 (range 10-61).

7.3.5 SURVIVAL

The overall median follow-up was 25 months (5-180). 13 patients (35.1%) had no evidence of disease, and these included three patients who are still alive for at least five years. Two patients (5.4%) died for an unrelated cause. Eight patients (21.6%) were alive with recurrent or stable disease, while 14 patients (37.8%) died of recurrent disease, of these only one patient survived more than 5 years.

The median survival of the overall population (N=37) was 70 months (95% CI 41.7-98.2), the 5-year survival rate was 58.5%.

The median survival time for patient undergoing curative (R0) surgery was significant longer (180 months, 95% CI NA) than those undergoing palliative surgery (35 months, 95% CI 11.9-58.0), with 5-years survival rates of 76.6% and 35.4% respectively (p=0.013, Figure 1). Univariate and multivariate analysis was restricted to the 25 patients who underwent potentially curative resections. TABLE 3

Median follow-up in this subgroup was 27 months (6-180), with a median survival of 70 months (95% CI 14.0-125.9) and a 5-year survival rate of 71.1%. Univariate analysis showed tumour grade (p=0.05), the occurrence of postoperative and of abdominal complications (p=0.05 and p=0.013) to be significantly associated with survival (Figure 2,3). In particular, median overall survival was 180 months (95% CI NA) in patients with G1 tumours and 70 months (95% CI 50.4-89.5) in patients with G2-G3 tumours. Five-year overall survival was 100% for G1 tumours and 61.6% for G2-G3 tumours. Median overall survival was 180

months (95% CI NA) in patients with an uneventful postoperative course and 70 months (95% CI 10.7-129.2) in patients with a complicated course.

Five-year overall survival was 100% for an uneventful postoperative course and 53.3% for a complicated postoperative course. Median overall survival was 180 months (95% CI NA) in patients who did not develop abdominal complications and 52 months (95% CI 22.5-129.4) in patients who develop abdominal complications.

Five-year overall survival was 100% in the absence of abdominal complications and 60% in patients who develop abdominal postoperative morbidity.

The best regression model resulted in same three variables being independently associated with survival. Hazard ratios were 1.345 (95% CI 1.28-1.91, p=0.03) for tumour grade, 1.781 (95% CI 1.10-2.89, p=0.037) for the development of postoperative complications, and 1.878 (95% CI 1.21-3.08, p=0.029) for the development of abdominal complications.

7.4 DISCUSSION

The aim of this study was to address factors influencing the long term survival in patients with duodenal adenocarcinoma through a retrospective analysis of our institution in a 20 year period.

The debate regarding prognostic indicators for primary duodenal adenocarcinoma is still open, likely because of the very low incidence of this malignancy

and the small number of studies published in the last two decades [14-16,19],[82-83,88-89].

In the present paper we retrospectively evaluated the clinical features of patients with primary duodenal adenocarcinoma observed at our institution and addressed the prognostic relevance of different surgical and pathological factors after potentially curative pancreaticoduodenectomy.

Duodenal adenocarcinoma usually presents with non-specific symptoms, which may be attributed to more common gastrointestinal disorders (such as peptic ulcer) or malignancies (such as gastric adenocarcinoma).

In our series, the most common presenting symptoms were abdominal pain, nausea and weight loss, although 27% of patients developed jaundice. Similarly to other reports, tumors occurred more frequently in the second portion of the duodenum (67.6%) [17].

At a median follow-up of 25 months, overall survival of the study population, which included patients undergoing pancreaticoduodenectomy, double bypass, or best supportive care, was 70 months. 5-year survival rate was 58.5%. As expected, overall survival was significantly longer after R0 resections (180 months) when compared to palliative resections (R1/R2) and bypass operations (35 months).

Survival rate after curative surgery was substantially greater than in the study by Zhang et al, who reported a median survival of 45 months, with a 5-years survival rate of 49.3% [17].

In the study by the Massachusetts General hospital group, median survival of resected patients was 44 months (88% of R0 resections), with a 5-years survival rate of 42% [20]. A number of factors have been considered to be of prognostic value after potentially curative resection, including sex, age, tumor size and location, grade, stage, resection margins status, LNR, perineural invasion, weight loss and biochemical parameters (white blood cells, alanine aminotransferase). However, not all these findings were consistent among different reports.

The first factor which in our study was found to be related to survival on multivariate analysis was histological grade, with a hazard ratio of 1.345 and a p-value of 0.03.

In particular, 5-year overall survival was 100% in well differentiated tumors (G1) and 61.6% in moderately to poorly differentiated tumors (G2-G3). Data from other gastrointestinal malignancies generally support the relationship between the degree of differentiation and survival, but only few other papers confirmed this concept in primary duodenal adenocarcinoma, both in the resection specimen and endoscopic biopsy.

The most relevant finding of the present analysis was that postoperative complications impact significantly on survival.

Five-year overall survival was 100% in patients with an uneventful postoperative course, and 53.3% in patients who experienced complications (hazard ratio on multivariate analysis of 1.781, p=0.037). Being abdominal complications the most relevant after pancreaticoduodenectomy, they were analyzed separately

and found to be likewise associated with survival (hazard ratio on multivariate analysis of 1.878, p=0.029).

The most frequent abdominal complication was PF, with an incidence of 16%, followed by postoperative bleeding (8.8%). The influence of postoperative morbidity on survival after tumor resection has been reported for patients with oesophageal and colorectal cancer [106-110].

In this study, the specific mechanism through which postoperative complications impact on long-term results can only be speculated.

Postoperative complications can induce a systemic inflammatory response and the release of cytokines and growth factors which, in turn, may affect tumor growth and influence the survival [111].

The degree of host inflammatory cell activity can be measured indirectly by markers related to inflammatory response. High systemic level of C-reactive protein has been associated with poor survival in patient undergoing potentially curative resection for pancreatic and colorectal cancer, and – similarly – an elevated neutrophil/lymphocyte ratio has been shown to influence the disease recurrence rate in oesophageal and colorectal cancer [112-114]. However, given the retrospective nature of this analysis, these markers of inflammatory response could not been evaluated.

A recent study has also shown that a prolonged period of immunosuppression and angiogenic stimulation caused by intra- and post-operative blood transfusion was independently associated with earlier cancer recurrence and reduced

survival after pancreatoduodenectomy for pancreatic ductal adenocarcinoma [115]. However, we did not find any correlation between blood transfusions and survival.

Another potential cause of worse survival in patients with postoperative morbidity and prolonged hospital stay may be a delay in adjuvant therapy. Other papers have reported an improved median survival for patients with adjuvant therapy [116], but our series was unable to demonstrate a benefit. In particular, the frequency of adjuvant therapy was not different between patients with or without postoperative complications (data not shown).

Despite patients who did not experience complications were referred to the Oncologist earlier, this did not seem to affect survival (data not shown). These results, however, have to be interpreted with caution, and larger studies are necessary to clarify the role of adjuvant therapy for primary duodenal adenocarcinoma.

Tumor stage was not a significant prognostic factor in our study. Three M1 patients were resected, in two of them (one with a single liver metastasis and one with a jejunal metastasis) the tumors could be completely resected. Furthermore, the presence of lymph node metastases did not show a significant association with decreased survival. These findings suggest that lymph node involvement should not preclude an aggressive surgical resection as a potential curative treatment. Contrarily to our findings, different studies have reported an important impact of nodal status and LNR on survival.

Interestingly, Sarela et al. [15] described the importance of accurate lymph node staging in duodenal adenocarcinoma, raising the hypothesis that examination of 15 or more lymph nodes can improve diagnostic discrimination by the pN category.

Resection margin status, which is generally believed to be critical to survival in duodenal adenocarcinoma, did not result to be a significant prognostic factor in the resected population.

A recent large single-institution study of 169 patients from Massachusetts General Hospital reported perineural invasion (which was present in 40% of resection specimens) to be the strongest independent predictor of recurrence and overall survival. LNR and size of tumor failed to stratify prognosis [20].

Contrary to this finding, the present study did not show a significant association between perineural invasion (present in 48% of resection specimens) and overall survival. Similarly, we demonstrated no difference in survival based on tumor size, lymph-vascular invasion, and LNR.

As with any retrospective study, this analysis has certain drawbacks. A lack of defined criteria for determining the operative or chemotherapeutic modalities was a major limitation, along with the small number of patients included in the study. With this in mind, we remark that postoperative morbidity may influence long-term outcomes after potentially curative pancreaticoduodenectomy for primary duodenal adenocarcinoma. Despite substantial advancements in surgical

techniques, this operation is still demanding and should be performed in high

volume centers, where an appropriate postoperative care can be delivered.

TABLE 1

Demographic and clinical details of patients with duodenal adenocarcinoma

Study population (N=37)	N (%)
Sex	
Male	21 (56.8)
Female	16 (43.2)
Age, median (range)	57 (38-83)
Body mass index, median (range)	22.6 (17.0-31.6)
Presenting symptoms	
Abdominal pain	26 (70.3)
Nausea/Vomit	13 (35.1)
Jaundice	10 (27.0)
Anemia	3 (8.1)
Melena	6 (16.2)
Weight loss	23 (62.2)
Ca 19.9, median (range)	24 (1-96957)
Tumour location	
D2	25 (67.6)
D3	12 (32.4)
Preoperative tumor stage (AJCC, rTNM)	
Stage I	5 (13.5)
Stage II	7 (18.9)
Stage III	16 (43.2)
Stage IV	9 (24.3)

TABLE 2

Surgical and pathologic details of patients operated (N=34) with duodenal adenocarcinoma

	N (%)
Surgical treatment	
Exploratory operation	1 (2.7)
Palliative bypass	8 (21.6)
Pancreaticoduodenecomy	25 (67.6)
Surgery not performed	3 (8.1)
Length of surgery, median, minutes (range)	360 (180-630)
Blood transfusion	
Yes	9 (26.5)
No	25 (73.5)
Tumor size, median, mm (range)	25 (10-65)
Postoperative complications	
Yes	18 (52.9)
No	16 (47.1)
Pancreatic fistula	
Yes	4 (11.8)
No	30 (88.2)
Hospital stay, median, days (range)	14 (9-57)
Adjuvant therapy	
Yes	18 (52.9)
No	16 (47.1)
Pathological details, resected patients (N=25)	
	N (%)
Lymph nodes resected, median (range)	19 (5-63)
Lymph node ratio	
0	11 (44.0)
>0 and <0.2	11 (44.0)
≥0.2	3 (12.0)
Resection margins	
R0	17 (68.0)
R1	6 (24.0)
R2	2 (8.0)

Lymph-Vascular invasion	
Yes	10 (40.0)
No	15 (60.0)
Perineural invasion	
Yes	12 (48.0)
No	13 (52.0)
Tumor grade	
G1	7 (28.0)
G2	10 (40.0)
G3	8 (32.0)

TABLE 3

Variables with a potential influence on survival in patients undergoing resection for duodenal adenocarcinoma

Factor	Univariate analysis (p-value)	Multivariate analysis (p-value)
Sex	0.280	
Abdominal pain	0.761	
Nausea/Vomit	0.918	
Melena	0.376	
Jaundice	0.793	
Fever	0.220	
Weight loss	0.616	
Anaemia	0.868	
Grade (G1 vs G2-G3)	0.050	0.912
R-Status (R0 vs R1-R2)	0.152	0.071
AJCC stage (II-II vs III-IV)	0.937	
Lymph node ratio	0.299	
Vascular invasion	0.250	
Perineural invasion	0.419	
Postoperative morbidity	0.050	0.087
Adjuvant therapy	0.700	

TABLE 4

stage * resection

	RESECTION		
	Yes	No	Total
STAGE I	5	0	5

II	6	1	7
III	11	5	16
IV	3	6	9
Total	25	12	37

TABLE 5

Overview of literature with analysis of prognostic factors for survival in patient after potentially curative resection for duodenal cancer

Author [ref] (year)	Number of cases	% 5-year OS	Predictors
Barnes [7] (1994)	36	29	pN
Rose [6] (1996)	42	60	pN
Santoro [8] (1997)	65	25	pT Tumour location
Sohn [81] (1998)	48	53	Margin involvement Location
Yeo [87] (1998)	17	59	pN
Ryder [83] (2000)	27	43	pT Grading
Bakaeen [14] (2000)	68 a	54	pT pN Margin involvement Weight loss
Tocchi [16] (2003)	47	23	pN
Sarela [15] (2004)	72	71a	pN Age
Hung [88] (2007)	11	16.6	TNM stage Cytology Cigarette smoking AST
Lee [89] (2008)	28	44	pT pN
Zhang [17] (2010)	59	33	pN Margin involvement
Poultsides [19] (2011)	122	48	pN LNR
Chung [18] (2011)	14	6.7	Total bilirubin TNM stage Grading WBC CDT
Cecchini [20]	103	42	Perineural invasion

(2011)			
Verona study (2012)	**25**	**71**	**POC Grade Margin involvement**

a Disease specific survival (R0 resection only), pN pathological nodes states, pT pathological tumour states, LNR lymph node ratio, WBC white blood cell count, AST Alanine transaminase, CDT cancer-directed-treatment, POC postoperative complications.

FIGURE 1

Kaplan-Meier survival curves of patients undergoing radical surgery (R0 pancreaticoduodenectomy, n=17) versus palliative surgery (R1/R2 pancreaticoduodenectomy or bypass, n=16)
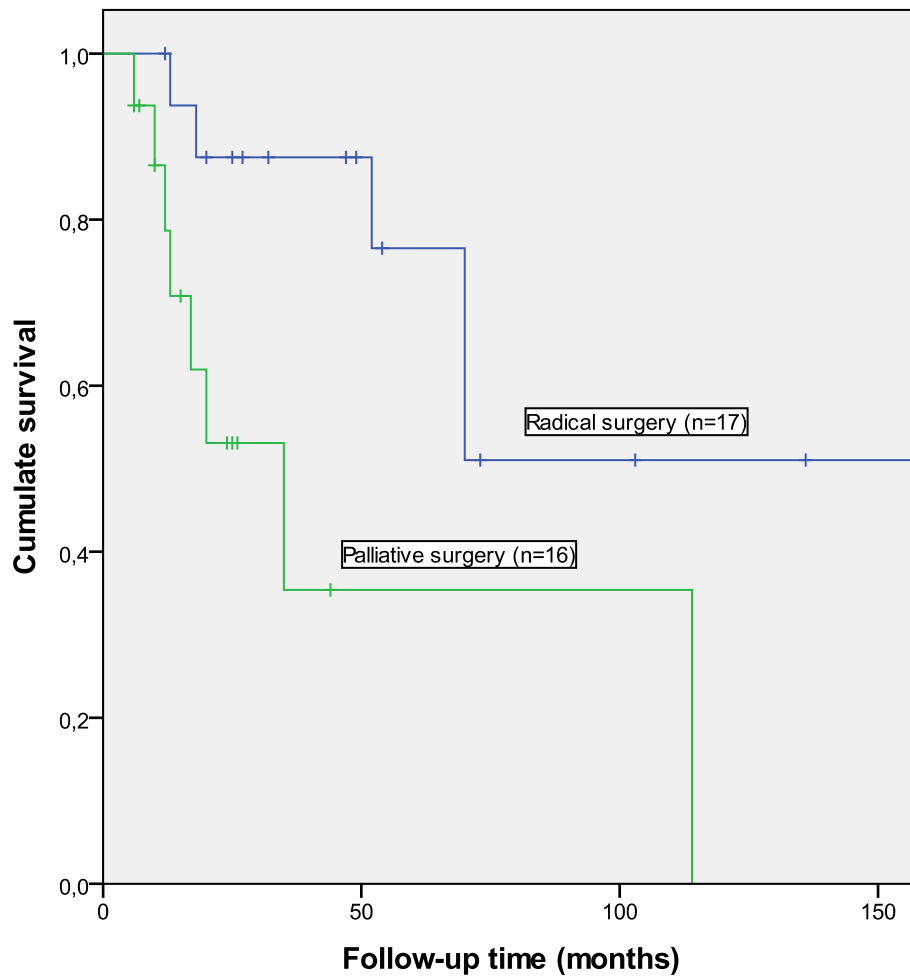
Radical surgery: median overall survival = 180 months (95% CI NA)

Palliative surgery: median overall survival = 35 months (95% CI 11.9-58.0)

p=0.013 (Log-rank test)

NB: the patient who underwent exploratory laparotomy was not included in the analysis (17+16+1=34)

FIGURE 2

Kaplan-Meier survival curves comparing patients within the resection group by tumour grade. Five-year overall survival 100% vs. 61.6% for G1 and G2-G3 tumours, respectively.
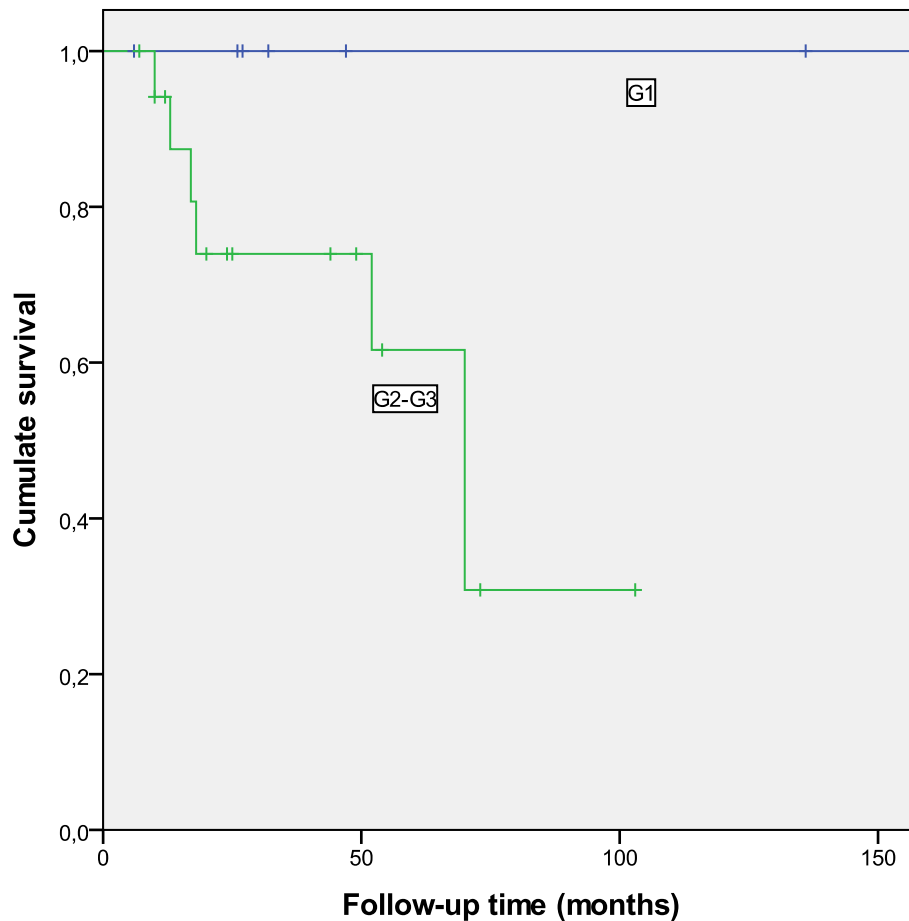
G1: median overall survival = 180.0 months (95% CI NA)

G2-G3: median overall survival = 70.0 months (95% CI 50.4-89.5)

p=0.050 (Log-rank test)

FIGURE 3

Kaplan-Meier survival curves comparing patients within the resection group by postoperative recovery (uneventful/complicated). Five-year overall survival 100% vs. 53.3% for uneventful and complicated postoperative course, respectively
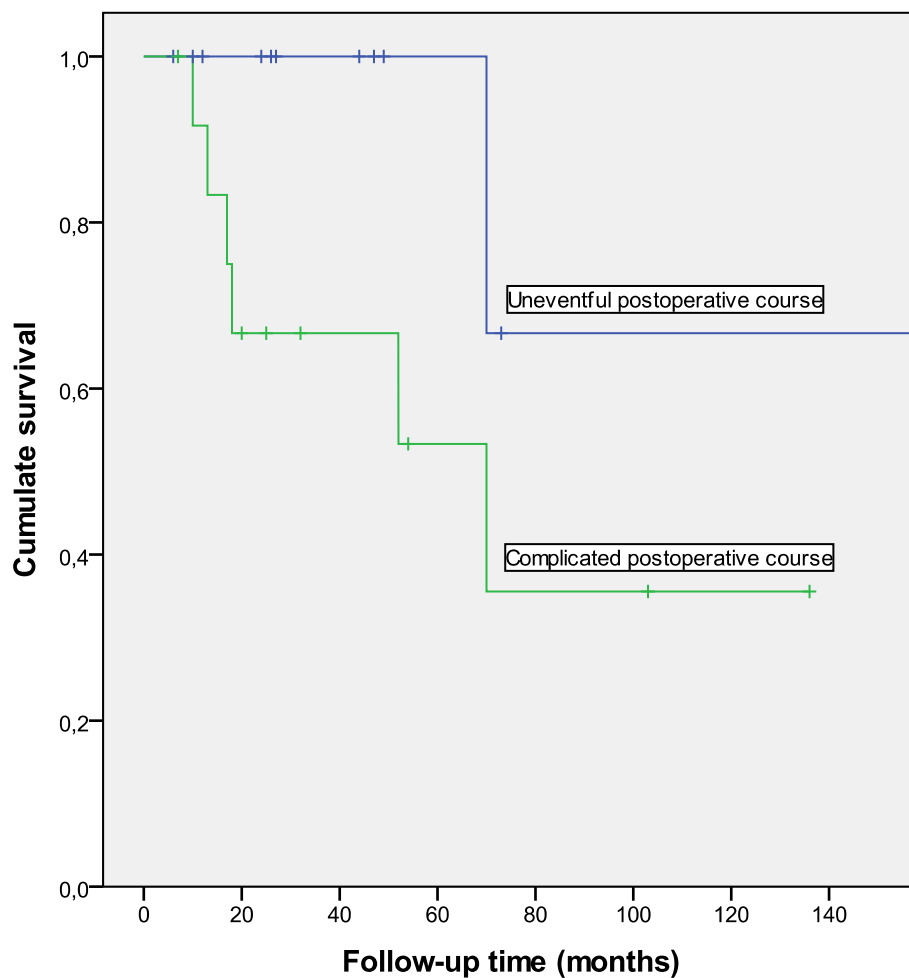
Uneventful course: median overall survival = 180.0 months (95% CI NA)

Complicated course: median overall survival = 70.0 months (95% CI 10.7-129.2)

p=0.050 (Log-rank test)

8

The Role of chemo-radiotherapy & Palliative endoscopic stent in Duodenal Adenocarcinoma

8.1 INTRODUCTION

Primary malignancy of the duodenum is rare. As result, our knowledge of the natural history, ideal management and prognosis of patients with primary duodenal cancer is limited compared to other gastrointestinal malignancies. Previously published data suggests that radical surgery with curative intents is the only curative treatment.

In literature, the involvement of periduedenal structures and distant metastasis appear to be the main reason for non resectability of the lesion.

In this chapter we will analyse the effects of adjuvant chemotherapy in influencing the overall survival of patients underwent potentially curative surgery. We will also consider the value of palliative duodenal stent in patients with non-resectable disease reported in literature.

8.2 THE ROLE OF CHEMO-RADIOTHERAPY IN DUO-DENAL

ADENOCARCINOMA

Little information exists in literature about the effect of adjuvant chemotherapy and radiotherapy on overall survival in patients with node-positive duodenal adenocarcinoma treated with pancreaticoduodenectomy. The cause of this poor reporting in literature is mainly due to the rarity of the disease in the general population.

The results with chemotherapy seem to be disappointing in term of improving the overall survival in patients underwent to potentially curative surgery. Additionally, very few data on the activity of anticancer agents are also available for patients with advanced disease.

In different studies on small bowel adenocarcinoma, only a small percentage of patients underwent adjuvant chemo-radiotherapy.

In the largest retrospective series of small bowel adenocarcinoma from the National Cancer Data Base, only 15% of patients with duodenal adenocarcinoma received radiotherapy, while 21% received chemotherapy [117].

Retrospective studies have indicated that chemotherapy prolongs overall survival in patients with advanced small bowel adenocarcinoma but there is no

agreed frontline regimen owing to a lack of randomized trials [118,119]. Most available data from literature are case reports or small retrospective studies involving old chemotherapy regimens.

In a large multicentre study involving 11 hospitals, Zaana et al. [120] studied three different chemotherapy regiments to treat 154 patients with advanced small bowel adenocarcinoma.

One group of patients underwent to infusion of Leucovorin and 5-fluorouracil (5-FU) alone or with cisplatin (LV5FU2 regiment, LVFU2-cisplatin); FOLFIRI subgroup including Leucovorin, 5-fluorouracil, and irinotecan; the FOLFOX regimen with Leucovorin, 5-fluorouracil and oxaliplatin or cisplatin. This study showed that overall survival was best in the FOLFOX subgroup, although the difference did not reach statistical significance, due to lack of power.

 The other important finding of this study was that in the platinum-based chemotherapy subgroup, the overall survival was significantly longer with FOLFOX than with LV5FU2-cisplatin.

Another study reported that treatment with 5-FU and a platinum agent was highly effective and recommended this combination as frontline treatment for patients with metastatic small bowel adenocarcinoma [125].

A recent prospective phase II trial enrolling 30 patients, has evaluated the benefit of capecitabine in combination with oxaliplatin (CAPOX) in patients with advanced adenocarcinoma of small bowel.

This therapy combination (CAPOX) has given interesting results with a median time to pregression of 11.3 months, and a medial overall survival of 20.4 months.

Since the combination therapy CAPOX has been well tolerated and highly effective, the author suggested that this combination should represent a new standard for the treatment of patients with advanced small bowel adenocarcinoma.

These results indicate that small bowel adenocarcinoma is more sensitive to oxaliplatin than to cisplatin that its behaviour may resemble that of colorectal cancer more than that of gastric tumours. Indeed, survival of patients with advanced colorectal cancer was improved by combining 5-FU with oxaliplatin [126] but not with cisplatin [127]. Conversely, both oxaliplatin and cisplatin are active on advanced gastric cancer [128,129].

A recent study from the Johns Hopkins Hospital analysed the effects of the adjuvant chemo-radiotherapy in patients with node-positive duodenal adenocarcinoma. All 14 patients received adjuvant external beam radiation therapy, and all were offered fluorouracil-based concurrent and maintenance chemotherapy.

Only one patient received concurrent fluourouracil and cisplatin. The median follow-up was 12 months for patients who died and 42 months for those who survived. The median survival for all patients was 41 months, with a 5-year survival rate of 44%. Local control for patients treated with adjuvant chemo-radiation therapy in this study was 93%.

Although this study is underpowered due to small number patients, it appears the adjuvant chemotherapy for node positive duodenal adenocarcinoma after pancreaticoduodenectomy may improve local control and median survival but does not appear to improve overall survival [130].

As previously described for small bowel adenocarcinoma, new chemotherapy strategies are reported in literature. Unfortunately, those data are mainly coming from case reports and small retrospective studies.

In a small retrospective analysis of 32 patients with duodenal adenocarcinoma, Kelsey et al.[128] assessed the influence of preoperative and postoperative chemo-radiotherapy (CT-RT) on overall survival comparing with patients who had only surgical resection without further adjuvant therapy. 16 patients received either preoperative (n = 11) or postoperative (n = 5) chemo-radiotherapy. Median radiotherapy dose was 50.4 Gy (range, 12.6-54 Gy). All patients treated with radiotherapy also received concurrent 5-fluorouracil-based chemotherapy. In his series, 2 of the 11 patients underwent preoperative chemotherapy had a complete pathological response, suggesting that duodenal adenocarcinoma may be chemo-radiation sensitive.

 The main result of this study was a non significant difference on overall survival between patients receiving chemo-radiotherapy versus surgery alone (57% vs. 44%, p = 0.42).

 However, in patients undergoing R0 resection, CT-RT appeared to improve overall survival (5-year 83% vs. 53%, p = 0.07) [128]. Therefore, comparing pa-

tients who had CT-RT with patients who had surgery alone, the view is that CT-RT can have favourable outcomes in patients underwent radical surgery with clear margins (R0) can be supported.

As previously described for small bowel adenocarcinoma, new chemotherapy strategies are reported in literature. Unfortunately, those data are mainly coming from case reports and small retrospective studies.

Catania et al. [129] described a case of a patient with duodenal adenocarcinoma who underwent pancreatoduodenectomy followed by adjuvant chemotherapy. The tumour seemed to be resistant to eight bi-weekly cycles of 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX-4), and a subsequent 5-FU 200 mg/m2/ die continuous-infusion concomitant with radiation therapy. However, a clinical complete tumour response to a second-line chemotherapy regimen with 5-fluorouracil/leucovorin/irinotecan (FOLFIRI) was demonstrated. This case report suggests that duodenal adenocarcinomas refractory to oxaliplatin could be highly sensitive to irinotecan-containing chemotherapy combinations.

Another case report from Manfredi et al.[130], described a patient with duodenal adenocarcinoma who at the time of the laparotomy the tumour was found to be invading the superior mesentery and therefore only a palliative bypass was performed. Palliative chemotherapy with FOLFOX 4 regiment (combination of oxaliplatin and infusional 5-FU/FA) was given for 4 months.

 Since patient had a full clinico-radiological response from FOLFOX 4 regiment, a complete R0 duodeno-jejunal resection of the mass and reconstruction of the

mesenteric artery was performed. Surgery was followed by a 3 month course of adjuvant chemotherapy. Patient has been reported to be alive 27 months after surgery.

Although it is case report, these findings suggested FOLFOX 4 regiment as potential neoadjuvant therapy with the aim to down-staging or even complete radiological response of patients with locally advanced duodenal adenocarcinoma.

The role of neoadjuvant chemo-radiotherapy in the management of unresectable duodenal adenocarcinoma has been studied recently. Onkendi et al.[131] published a report in 2011 of 10 patients with localized advanced adenocarcinoma treated with neoadjuvant chemotherapy. In this series, not all 10 patients had neoadjuvant chemotherapy and radiotherapy combined. Four patients underwent curative R0 resection after chemotherapy alone. One patient did not have response to the neoadjuvant chemotherapy with FOLFOX.

 Six patients received intraoperative radiotherapy (IORT); 4 of them survived more than 1 year, with 75% of these patients surviving more than 2 years. These outcomes are suggesting that intraoperative radiotherapy (IORT) may potentially prolong survival in this patient population.

At present, there is no clear evidence showing a benefit from the use of adjuvant chemotherapy following curative resection in patients with duodenal adenocarcinoma.

All available data are drawn from small single-institution retrospective studies and case reports, which are all limited by significant selection bias.

Recent studies investigating the effect of colorectal regiments of chemotherapy (FOLFOX, FOLFIRI, combination of irinotecan, oxaliplatin and capecitabine with radiotherapy), showed an increased activity against tumour progression. It is likely that the proven benefit of adjuvant chemotherapy in colorectal cancer is being applied to clinical decision making for patients with duodenal adenocarcinoma.

Although, standardized chemotherapy protocols are not acknowledged in literature recent studies suggested a potentially beneficial effect of chemo-radiotherapy regiments as neoadjuvant therapy with rescue surgery in an otherwise unresectable and lethal disease. A multi-institutional trial is needed to further elucidate the role of adjuvant and neoadjuvant therapy in this disease.

However, the main challenge for the near future is to identify a molecular marker involved in duodenal carcinogenesis with which to predict chemosensitivity and thus to improve survival. Targeted therapy with mAbs against vascular endothelial growth factor or epidermal growth factor receptor (EGFR) has already shown significant efficacy on metastatic colorectal cancer and small bowel adenocarcinoma [132].

8.3 THE ROLE OF PALLIATIVE ENDOSCOPIC STENT IN DUODENAL ADENOCARCINOMA

Malignant gastric outlet obstruction (GOO) is a late complication of gastric, pancreatic and duodenal carcinoma which can cause significant morbidity through persistent intractable nausea and vomiting, intolerance of oral feeding, and associated weight loss. Patients affected by GOO are at risk of aspiration and pneumonia. Obstruction reduces greatly the quality of life in these patients who have a limited life expectancy.

The palliative treatment has the goal of maintaining the best quality of life possible during the terminal phase of the illness.

When the life expectancy is predicted to be more than few days, traditionally palliative surgery through a gastrojejunostomy (GJ) has been the standard treatment. This treatment modality is associated with undoubted good functional outcome and relief of symptoms in almost all patients [133,134]. Nevertheless, this carries a peri-operative morbidity as high as 35% and a mortality rate of about 2% in later studies [134]. Most patients also have delayed gastric emptying which often causes a prolonged hospital stay [135].

During the last two decades, however, endoscopically placed self-expandable metallic stent (SEMS) have been increasingly used as minimally invasive modality for the palliative treatment of malignant duodenal obstruction.

Palliative endoscopic treatment of GOO with endoluminal self-expanding metallic stents was first reported by Topazian et al. in the early 1990s [136].

Stent placement for GOO has been suggested to be less invasive with a faster relief of symptoms compared to open or laparoscopic GJ. As a consequence, hospital stay should be shorter in the majority of patients with many of them being able to eat soft solids after 1–4 days. In several studies, this treatment has been evaluated as safe and efficient with a technical success rate of 90–100%, a clinical success rate of 67–100%, a rate of severe complications about 7% and non-severe complication rate about 20% [137,138].

In literature, there are three recent systematic reviews [134,140] and two meta-analysis [141,142] to assess the role of duodenal stent in patients with GOO, which showed a positive influence of implementing endoscopic duodenal stent in this group of patients.

Only three randomized controlled trial comparing surgical gastro-jejunostomy (GJ) and endoscopic stent placement for palliation of malignant gastric outlet obstruction are reported in literature [143-145.] All these randomized controlled trial showed that duodenal stenting is a safe means of palliating malignant gastric outflow obstruction. However, the Dutch SUSTENT Study Group suggested that the choice between surgical palliation and endoscopic stent is regulated by the life expectancy of the patients.

In this randomized controlled study they recommended that despite slow initial symptom improvement, GJ was associated with better long-term results and is therefore the treatment of choice in patients with a life expectancy of 2 months or longer. Because stent placement was associated with better short-term outcomes, this treatment is preferable for patients expected to live less than 2 months [147].

Recurrent obstructive symptoms, necessitating a reintervention, seem occurring more frequently after stent placement than after GJ. The majority of recurrent obstructive symptoms after stent placement are caused by stent occlusion from either tumour in- or overgrowth, or food obstruction.

Duodenal stent obstruction by tumour in- or overgrowth remains a problem, especially when non-covered stents are used. The use of covered stents in the duodenum may however lead to a higher incidence of stent migration and may also lead to an increased incidence of biliary obstruction and even pancreatitis due to obstruction of the common bile duct and/or pancreatic duct by the covered device.

Stent migration seems to occur in a shorter time period (range: 1–121 days) after stent placement than recurrent obstructive symptoms caused by tumour in- or overgrowth or food debris (range: 11–273days). In addition, stent migration seems to occur at a shorter time period and more frequently after placement of a covered stent (19%) than after placement of an uncovered stent.

Zheng et al. [142] in a recent meta-analysis suggested that GJ is a more expensive procedure than endoscopic stent; however, there was inadequate data available to evaluate the potential cost savings of endoscopic stent over GJ.

Rate of gastric emptying are, however, only recorded after stenting, and the quantitative effect of stenting was thus not revealed. More detailed data on the effect of stenting on rate of gastric emptying is thus required, and can be used to improve the knowledge on the relation between GOO and obstructive symptoms. This is an important issue, since the relation between gastrointestinal symptoms and gastric emptying might be rather weak.

Gastric emptying is a complex process involving grinding and emptying of the meal, and it is not likely that the re-establishment of passage is followed by a more rapid rate of gastric emptying in all subjects treated. In literature, only few studies analysed the predictive factors of survival in patients with malignant gastric outlet obstruction.

In a recent study, Jeurnink et al [134], collected prognostic factors on patients with malignant GOO, such as WHO performance status, prior or concurrent treatment of obstructive jaundice, extend of disease and weight loss. After a multivariable analysis, the WHO performance status appeared to be the only significant prognostic factor for survival.

Therefore, the authors suggested that patient with a short survival (WHO 3-4) will benefit from the optimal short term outcomes of duodenal stent placement.

Patients with a longer survival (WHO 0-1) should however be considered for GJ.

In palliative cancer care, improvement of QoL is a main treatment goal, and data on this issue are missing in most of the retrospective and prospective studies in literature.

Objective evaluation of gastric/duodenal function after stenting is still limited and only few studies have performed quantitative tests of gastric emptying.

In conclusion, endoscopic stent is a safe and effective, minimally invasive and cost-effective option for the palliation of malignant GOO. However, larger randomized controlled trials with longer follow-up data are needed to confirm these positive findings on endoscopic stent in palliative settings.

9
Conclusion

Non ampullary duodenal adenocarcinoma is a rare cancer representing less than of 0.5% of gastrointestinal malignancies and approximately 45 % of small bowel adenocarcinomas.

The natural history of the duodenal adenocarcinoma is poorly understood, in comparison with the stomach and colo-rectum, the duodenum and small bowel seem to be relatively resistant to carcinogenesis. Although the small intestine provides the majority of the mucosal surface of the gastrointestinal tract, small intestinal adenocarcinoma is approximately 100 times less frequent than colo-rectal cancer.

Several reasons have been discussed for this disparity, which mainly focus on a reduced carcinogen exposure of the small intestine due to the rapid transit and the highly diluted nature of its nutritional contents. However, recent molecular studies have showed that the molecular pathways of sporadic tumorigenesis differ in the small intestine compared to the large intestine.

Hereditary syndromes or conditions that can predispose to duodenal adenocarcinoma include neurofibromatosis, hereditary non polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP) and its variants such as Gardner's Syndrome, Celiac Sprue, Puetz-Jeghers, Crohn's Disease and Juvenile Polyposis Syndrome.

Primary duodenal adenocarcinomas are much rarer than those that arise from a secondary neoplastic process. Metastasis from the stomach, ovary, colon and uterus can involve the small bowel by direct means or via peritoneal involvement.

Metastatic tumours from breast, melanoma and lung appear to spread to the duodenum by blood and lymphatic pathways.

Primary duodenal adenocarcinoma has a poor prognosis most likely due in part to a delayed diagnosis, which results from the difficulty making diagnosis, as patients often present with non-specific symptoms or signs not suggesting the need for upper gastrointestinal endoscopy.

Surgical resection is the only potentially curative treatment, but not all the patients in whom the tumour is removed will survive long term. Surgical intervention has shown to provide a curative resection in 40-65% of patients.

The five year survival rate for non resected tumours being is 15-30% compared to 40-60% survival rate for those who had resection.

However, the prognosis for curatively resected duodenal adenocarcinoma is substantially better (5-year survival, 60%), than that for cancer of the ampulla (46%), distal bile duct (27%), or head of pancreas (10%).

Due to the low incidence of the duodenal adenocarcinoma in the general population, it has been difficult to determine which factors can influence the overall survival.

An assessment of the literature shows that our knowledge about duodenal adenocarcinoma is based only on retrospective single or multi-centre studies. The aim of these studies was to determine those factors that influence the survival. The debate about the importance of the different factors on overall survival is still open.

Therefore, several controversial issues remain to be studied including the significance of the depth of invasion and degree of differentiation, the prognostic value of nodal involvement and the perineural invasion, the indications and type of adjuvant treatments.

Our study is a retrospective review of 37 patients with diagnosis of primary duodenal adenocarcinoma referred to the Hepato-Pancreato-Biliary Institution of Borgo Roma Verona University Hospital (BRH) between January 1989 and December 2009.

The   main aim or our study was to determine prognostic factors in patients who underwent potentially curative resection of their duodenal adenocarcinoma.

A potentially curative resection was performed in 25 patients with a median age median age of 54 years (38-83 years). Perineural and lymph-vascular were present in the 48% and the 40% of patients, respectively. Nodal metastasis (pN1) was identified in 13 patients (52%).

Overall 5-year survival were 58.5% considering all the 37 patients

Survival was significant higher for patients who underwent curative resection (median overall survival 180 months; 5-year survival 71%) than those who underwent palliative procedure (median overall survival 35 months) (p=0.013).

Tumour grade (p=0.050), positive resection margins (p=0.152) and postoperative complications (p=0.050) had a significant negative effects on the survival of the patients who underwent curative resection according to univariate analysis.

Our series is the first study to evaluate postoperative morbidity as a potential prognostic factor of survival and recurrence after potential curative resection of duodenal adenocarcinoma.

The influence of postoperative morbidity on long term survival after tumour resection has been reported for patients with oesophageal, colorectal cancer.

The evidence from our study suggests that resectability of primary duodenal adenocarcinoma and a lower   tumour grade are associated with increase survival. However, postoperative morbidity seems to influence the overall long term survival in patient underwent curative resection of primary duodenal adenocarcinoma.

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