

## Original articles

# Primary duodenal carcinoma

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### Summary

**Eight cases of primary duodenal carcinoma in a district general hospital are presented. The cases highlight the advanced state of the disease at presentation, the difficulty in diagnosis, and its poor prognosis. Duodenal carcinoma occurs in both sexes worldwide with no predisposing factors in the majority of cases. There is an increased risk in patients with familial adenomatous polyposis and adenomas of the duodenum. Duodenal carcinoma occurs about 22 years from the diagnosis of familial adenomatous polyposis in about 2% of patients, forming over 50% of upper gastrointestinal cancers occurring in these patients. Carcinomatous changes occur in 30 to 60% of duodenal villous adenomas and much less in tubulo-villous and tubular adenomas. These categories of patients should be screened and adequately followed up.**

**Aggressive and radical surgery, even in the presence of locally advanced disease and lymph node involvement, gives a better outcome. When curative surgery is not possible, chemotherapy must accompany palliation with or without radiotherapy. Pre-operative chemotherapy may facilitate a curative radical resection. The general five-year survival is 17–33% but some centres have achieved a five-year survival of 40–60% with aggressive management of these patients.**

**Keywords:** duodenal carcinoma, predisposing factors, treatment

Primary duodenal carcinoma is rare, but it is the commonest duodenal malignancy.<sup>1</sup> It forms 60–100% of all duodenal malignancies and between 11 and 24% of all small bowel malignancies.<sup>2–7</sup> In England and Wales in 1987, small bowel malignancies (including duodenal) were 0.93% of all bowel cancers registered with a rate of 0.7 per 100 000 of population.<sup>8</sup> Presentation is late, diagnosis is often difficult and despite improved survival from some centres, prognosis is still poor. Because of their rarity, duodenal carcinomas are reported in the literature as case reports or a collection of few cases; management therefore varies from one hospital to another. We present eight cases diagnosed in the Pathology Department of a district general hospital over a five-year period and review the current literature.

### Patients and result

The clinical and pathological records of eight patients with duodenal carcinoma were reviewed retrospectively. The patients were diagnosed between June 1988 and June 1993 in the Pathology Department of Kings Mill Hospital, Sutton-in-Ashfield, Nottinghamshire. There were six females and two men with a median age of 63.5 years (range 31–87). Six patients presented with abdominal pain, four with intestinal bleeding (two acute and two chronic) and three with weight loss. Two patients had duodenal obstruction and jaundice and another had a change in bowel habit. Both patients with jaundice had direct invasion of the pancreatic head. Median time of presentation after the onset of symptoms varied from one day to two years (median 3.5 months).

Seven patients had upper gastrointestinal endoscopy, five of whom had biopsies and duodenal carcinoma diagnosed. The two patients without biopsy had peptic ulcer diagnosed and both needed a second endoscopy, only one had a biopsy and a correct diagnosis. The other patient, diagnosed at laparotomy, had a previous barium meal which showed duodenal obstruction due to a post peptic ulcer benign stricture. The other patient not to have an initial biopsy had a barium meal; this showed an apple core lesion in the third part of the duodenum. The only patient not investigated with endoscopy had a barium meal and active duodenal ulcer diagnosed. One patient had computed tomography (CT) scanning – this revealed a duodenal mass with nodal involvement – before being subjected to endoscopy. Six patients had a correct pre-operative diagnosis made, and in five this was within a month of presentation.

One patient had segmental resection, three had palliative duodenal bypass and one each had biliary stenting and Whipple's procedure. Two patients had no procedures because of the extent of the disease. The patient who had Whipple's procedure had a direct invasion of the pancreatic head and lymph node infiltration; he survived for 18 months. The patient who had segmental resection had infiltration of the subserosal adipose tissue but no lymph node involvement. He developed a recurrence 18 months later with lymph node involvement, diagnosed on CT scan. He was treated with chemotherapy but died six months later. Another patient had adjuvant chemotherapy with 5-fluorouracil but survived for only five months.

Six patients had peritoneal and visceral

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metastasis and two had local invasion. Seven patients had lymph node involvement at presentation. There were one well-differentiated, three moderately differentiated and four poorly differentiated tumours. Median survival time was six months (one to 24) with three patients (38%) surviving for one year. The median survival of four patients with poorly differentiated carcinoma was five months (four to eight) and for those with moderately differentiated tumour, 18 months (12–24).

## Discussion

### EPIDEMIOLOGY

Primary duodenal carcinoma, first described by Hamburger in 1746,<sup>9</sup> occurs worldwide.<sup>1–6,10–14</sup> It affects females marginally more at a ratio of 1.1–1.5:1.<sup>1,9,11,15</sup> It is commonest in the sixth to eighth decades of life, peaking in the seventh.<sup>9,15,16</sup> It occurs earlier in the fifth and sixth decades<sup>17,18</sup> in patients with familial adenomatous polyposis. There are sporadic cases in the third decade of life.<sup>9,15</sup>

The true prevalence is difficult to determine. In newly diagnosed cancers recorded by the Office of Population Censuses and Surveys<sup>8</sup> in England and Wales in 1987; the incidence of small bowel cancers was 0.7 per 100 000 of population. From reviewed series, duodenal carcinoma forms 11 to 24% of all small bowel malignancies and a crude estimate of the incidence in England and Wales is 0.08–0.17 per 100 000 of the general population. This compares with figures from the US of 1.7 per million people.<sup>19</sup>

There is no evidence of an increase incidence of duodenal carcinoma. Analysis of 11 500 autopsy specimens over 60 years ago, yielded 0.05% of duodenal carcinoma<sup>20</sup> and this is similar to figures of 0.019 to 0.5% quoted in reviews<sup>1,9</sup> 40 years later. In England and Wales, the reported incidence of small bowel tumours including duodenal carcinomas has remained constant at 0.7 per 100 000 over the past 20 years while all other gastrointestinal tumours have shown an increase over the same period.<sup>8</sup>

### AETIOLOGY

Although most duodenal carcinomas occur without any predisposing factors,<sup>1–7,9,11–15,20</sup>

patients with familial adenomatous polyposis have a higher risk of duodenal carcinoma.<sup>17,18,21</sup> Fifty-one per cent of upper gastrointestinal carcinoma occurring in these patients are in the duodenum,<sup>17</sup> excluding the ampulla of Vater, with a relative risk of 330.82 (confidence interval (CI) 132.66–681.49).<sup>18</sup> The median interval from diagnosis of familial adenomatous polyposis to developing upper gastrointestinal carcinoma is about 22 years,<sup>17,22</sup> with duodenal carcinoma occurring in 2.3% of these patients.<sup>17</sup> Duodenal carcinoma is a common cause of cancer-related deaths in those patients who have had colectomy for familial adenomatous polyposis.<sup>22,23</sup> In a literature review of duodenal carcinoma from 1927 to 1986,<sup>23</sup> 30 out of 1320 patients with duodenal carcinoma (2.3%) had familial adenomatous polyposis.

Patients with solitary<sup>10,24–26</sup> or multiple<sup>27</sup> villous adenomas have a higher risk of duodenal carcinoma. This increases with size,<sup>24,28</sup>; 30% of adenomas greater than 1 cm are malignant.<sup>24</sup> Carcinomatous changes occur in 30 to 60% of duodenal villous adenomas.<sup>10,24–26, 29</sup> Tubulovillous and tubular adenomas also have increased risk of carcinomatous change but this is less than for villous adenoma.<sup>10,24</sup> The incidences of carcinoma in these two groups are 13–33% and 8–23%, respectively,<sup>10–24</sup> though after excluding ampullary adenomas, the risk is less. The risk is greater in patients with symptomatic polyposis.<sup>21</sup>

Carcinomas occur in post-gastrectomy duodenal stumps<sup>15,30</sup> and in post-traumatic duodenal scar.<sup>31</sup> They occur in duodenum affected with coeliac<sup>32</sup> and Crohn's diseases,<sup>33</sup> and in association with Torre's syndrome<sup>34</sup> and duodenal duplication cyst.<sup>16</sup> Terminal pancreatic or bile duct carcinomas<sup>1</sup> may spread to the duodenum as may distal gastric carcinoma<sup>35</sup> which occurs in about 24% of patients. Though peptic ulceration may be present in patients with duodenal carcinoma, there is no evidence that benign duodenal ulcers become malignant.<sup>1</sup>

### Pathology

Carcinoma occurs in all parts<sup>6,9,15,20,24,36–38</sup> but it is commonest in the peri-ampullary (32–50%) – excluding ampullary tumours – and infra-ampullary (32–56%) regions.<sup>1,9,11,24,36–39</sup> Supra-

#### Primary duodenal carcinoma: epidemiology and predisposing factors

- incidence 0.8–1.7/million people
- affects both sexes
- worldwide
- occurs in 6–8th decades, earlier in familial adenomatous polyposis, 5–6th decades
- no predisposing factors in the majority
- occurs in about 2% of patients with familial adenomatous polyposis
- 30–60% of duodenal villous adenomas become malignant
- less risk with tubular and tubulo-villous adenomas
- may occur in Crohn's and coeliac diseases affecting the duodenum

#### Primary duodenal carcinoma: clinical features and pathology

- insidious onset; anorexia, weight loss, etc.
- obstructive symptoms in two-thirds
- anaemia in majority, faecal occult blood in over two-thirds
- incidental finding at laparotomy or autopsy
- occurs in all parts of duodenum
- histologically adenocarcinoma
- macroscopically, polypoid, ulcerating, infiltrating
- majority moderately differentiated
- metastasis present in almost half at presentation

ampullary carcinomas form 7–14% of duodenal carcinoma, though in the series by Alwmark *et al*,<sup>15</sup> supra-ampullary carcinomas were the commonest (40%). In patients with familial adenomatous polyposis, carcinoma affects the peri-ampullary region most frequently.<sup>17,24</sup>

Peri-ampullary carcinoma consists of four types, ampullary (41%), pancreatic (35%), common bile duct (12%) and duodenal (12%).<sup>40</sup> Although weight loss is the commonest feature of presentation in duodenal peri-ampullary carcinoma (DPAC) and jaundice is the commonest feature in the other types (83–92 *vs* 33% in DPAC) clinical differentiation between the various types is difficult.<sup>40</sup> Ampullary and common bile duct carcinomas have a better prognosis<sup>40–42</sup> than DPAC.

Almost all duodenal carcinomas are histologically adenocarcinomas though adenosquamous carcinomas,<sup>43</sup> and adenocarcinomas arising from Paneth cells have been described.<sup>44</sup> Mucinous and signet-ring carcinomas occur but are rare.<sup>10,45</sup>

Moderate differentiated carcinoma occurs most frequently.<sup>10,37,39</sup> Macroscopically, tumours are polypoid, ulcerating, or infiltrating.<sup>15</sup> At presentation, over 45% of patients have metastasised<sup>9,15,38,39,46,47</sup> with 33–38% having hepatic involvement and/or mesenteric seeding.<sup>15,38</sup> In patients with invasive adenocarcinoma in villous tumours, metastasis occurs in about 36% of patients<sup>29</sup> at presentation, with approximately 9% hepatic involvement.

#### CLINICAL FEATURES

Most patients present with obstructive symptoms<sup>9,11,15,47</sup> such as nausea, vomiting, or postprandial fullness. Chronic blood loss occurs in the majority of patients<sup>1,4,9,11,47</sup> with over 66% positive for faecal occult blood<sup>19</sup> and about 44% have a haemoglobin level less than 10 g/l.<sup>36</sup> Massive haemorrhage occurs in less than 7% of patients<sup>9</sup> and jaundice occurs mainly in peri-ampullary tumours.<sup>15,40</sup> General symptoms, anorexia, malaise, and weight loss, are present in some of these patients.<sup>9,15</sup> A mass in the hypochondrium may be the presenting feature.<sup>11,15</sup> In about 25% of patients, diagnosis is made at autopsy;<sup>1,15</sup> in 20%, at exploratory laparotomy, or laparotomy for other reasons.<sup>15</sup> Less than 25% of patients present as emergencies.<sup>7</sup>

#### INVESTIGATIONS

There is an average of 4–8 months delay in the diagnosis of duodenal carcinoma from presentation,<sup>14,15,47</sup> in the series by Alwmark *et al*<sup>15</sup> an average of 17 months delay occurred in 35% of patients. Incorrect interpretations of results, inappropriate tests<sup>47</sup> and limiting investigations to stomach and the first part of the duodenum<sup>48</sup> contribute to this delay.

Anaemia occurs in the majority of patients with positive faecal occult blood. Electrolytes and urea may be deranged (eg, hypokalaemic, hypochloreaemic metabolic alkalosis). Barium studies are positive in less than 70% of

#### Primary duodenal carcinoma: features of barium studies

- multinodular filling defects
- ulceration with mucosal destruction
- rigidity and constriction of the lumen with loss of mucosal pattern in infiltrating lesions
- obstruction leads to proximal duodenal dilatation, gastric retention and dilatation

#### Primary duodenal carcinoma: endoscopic features

- firm or friable masses
- ulceration
- necrosis
- erosion
- bleeding
- about 13% may look benign

patients<sup>1,9,11,15</sup> with a normal report in 18–22% of patients with the disease.<sup>1,9,15</sup> A modified hypotonic duodenography involving catheterisation of the duodenal bulb offers better diagnostic accuracy.<sup>48</sup> Tumour antigens CEA and CA19-9, when detected, have been found useful in the diagnosis of duodenal carcinoma and in the assessment of response to treatment,<sup>49,50</sup> although in a study of 60 patients, only three (5%) had CEA > 5 ng/ml.<sup>36</sup>

Endoscopy is the mainstay of diagnosis<sup>9,38</sup> although up to 35% of patients may not have a definite diagnosis due to non-visualisation (3rd and 4th part) or a normal biopsy.<sup>10,25,29,38,46</sup> Frozen sections have high rates of false negative (28%) results.<sup>25,29</sup> Areas of malignancy are missed in up to 26% of polyps biopsied during endoscopy.<sup>29</sup> The combination of cytology and biopsy improves diagnostic accuracy.<sup>51</sup> Endoscopic ultrasonography is useful in assessing the depth of tumour invasion and nodal status.<sup>52</sup>

In a retrospective study,<sup>53</sup> CT scanning was accurate in predicting that a duodenal lesion was malignant in 82% of cases though it is not as accurate in determining the depth of invasion and nodal involvement. It is useful in tumours that do not affect the mucosa and may be missed by endoscopy.<sup>53</sup>

#### TREATMENT

Surgery is the definitive treatment. The tumour is resectable in about 70% of patients<sup>1,9</sup>

#### Primary duodenal carcinoma: treatment

- tumour resectable in about 70%
- definitive procedure is pancreatico-duodenectomy
- segmental resection in infra-ampullary tumours limited to the gut
- chemotherapy to be used in patients having palliative surgery

and palliation is possible in most of the others.<sup>9,39</sup> Pancreatico-duodenectomy is the procedure of choice.<sup>1,9,15,36,38,39</sup> Segmental resection is adequate in infra-ampullary tumours that have not spread,<sup>36,39,46</sup> endoscopic resection in early cases<sup>50,54</sup> and in carcinoma-in-situ,<sup>15</sup> which can be treated with strip biopsy.<sup>55</sup>

The use of chemotherapy is limited to a few cases,<sup>11,15,46,56,57</sup> most of which have been in post-operative patients<sup>11,15,46</sup> with metastasis or recurrence. 5-Fluoro-uracil is used most commonly<sup>11,15,46</sup> followed by cyclophosphamide.<sup>15</sup> Radiotherapy can be used with chemotherapy. Ohkusa *et al*<sup>56</sup> reported an advanced case primarily treated with a combination of tegafur, uracil and mitomycin that showed an objective reduction in primary and secondary tumours. The patient survived for three years. Yeung *et al* used pre-operative chemotherapy (5-fluorouracil and mitomycin C) and radiotherapy<sup>57</sup> and this facilitated complete resection in four out of five patients. Laser treatment is useful in palliating obstructing and bleeding duodenal carcinomas.<sup>36,58</sup>

#### PROGNOSIS

The trend in survival is difficult to assess because of overlap in the periods of studies and the small number of cases reported, but survival may be improving. Over two 15-year periods between 1960 and 1990, mean survival time rose from seven to 48 months.<sup>37</sup> This was attributed to the fact that in the second 15-year period, 95% of patients had curative surgical resection compared to 62% in the first 15 years. In this second period, 86% of patients had locally advanced disease and 64% had lymph node involvement.

Overall five-year survival is 17.5–33%<sup>9,15,26,36,38,39</sup> but in node-negative patients survival is over 40%.<sup>26,36–39</sup> Most patients with nodal involvement die within five years.<sup>38,39</sup> Some studies suggest that patients with distal tumours survive longer<sup>15,46</sup> but this is not borne out by others.<sup>36,37,39</sup> Melaena<sup>39</sup> and the involvement of local or regional lymph

nodes<sup>26,38,39</sup> carry a poor prognosis. The depth of transmural penetration<sup>29,38</sup> which relates to lymph node involvement and the degree of differentiation<sup>39,46</sup> affect survival. Carcinoma developing in an adenoma has a good prognosis.<sup>15</sup>

Less than 20% of patients having palliative surgery alone survived for two years<sup>9,11,15,36</sup> while 11 out of 18 (61%) patients with adjuvant chemotherapy, with or without radiotherapy, for advanced disease survived for more than two years.<sup>11,15,50,57,59,60</sup> This supports the assertion of the beneficial effects of adjuvant therapy in advanced disease put forward by Sakker and Ware<sup>11</sup> 20 years ago.

#### Conclusion

The prognosis of duodenal carcinoma is generally poor but there are encouraging reports from some centres that it is improving. Duodenal carcinoma is a slow-growing tumour; at presentation therefore, treatment should be aggressive and radical, even in the presence of locally advanced disease and lymph node involvement. Palliative surgery as a first line of treatment can be reduced to a minimum and in these patients chemotherapy with or without radiotherapy should be used. The role of adjuvant chemotherapy in patients undergoing a primary curative surgery needs to be investigated further in a multicentre trial. Available literature suggests that some patients with locally advanced disease can have their tumours debulked with chemotherapy and then offered a primary curative surgery.

Patients with familial adenomatous polyposis need screening for duodenal carcinoma and all patients with adenomas of the duodenum should have these excised and should be followed up. Finally, patients with chronic anaemia with a normal large bowel and stomach should have all parts of the duodenum visualised by endoscopy and, if necessary, barium meal or hypotonic duodenography should be done.

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