Secondary Neoplasia

12

12.1 Definition

The pancreas can be involved secondarily by extrapancreatic neoplasms, either by direct invasion (e.g., from the colon, stomach, or duodenum), or by metastatic spread along lymphatic channels, perineural clefts, or the blood stream.

In principle, the possibility of a secondary neoplasm should always be considered as a differential when diagnosing a pancreatic cancer. The distinction between ductal adenocarcinoma of the pancreas and ampullary, distal bile duct, or duodenal carcinoma involving the pancreatic head is discussed in detail elsewhere (see Chap. 9, Sect. 9.12.3). This chapter focuses on metastatic spread to the pancreas.

12.2 Clinical Features

Patients with metastatic tumor spread to the pancreas often present with clinical signs and symptoms that are similar to those of primary pancreatic tumors: weight loss, early satiety, abdominal pain, and jaundice if the tumor is located in the pancreatic head. Occasionally, pancreatitis may be the initial symptom. In some patients, pancreatic metastasis is clinically occult and becomes apparent during follow-up examination for the known extrapancreatic cancer. Fulminant upper gastrointestinal hemorrhage is a rare presenting feature that can occur in patients with a metastatic tumor in the pancreatic head causing ulceration of the duodenal mucosa.

Patients are usually elderly, 60–70 years old, that is, the age distribution is similar to that for ductal adenocarcinoma of the pancreas. Depending on the type of the primary tumor, metastasis to the pancreas can occur many years after diagnosis and/or resection of the primary.

Only a small selected group of patients will undergo pancreatic resection, which is never curative but may significantly prolong survival with good quality of life [1]. In most patients, however, palliative nonsurgical treatment is the only option. Not infrequently, metastasis is not limited to the pancreas but manifest also in other sites.

Secondary neoplasms of the pancreas are rare. Because surgical resection is performed in only a small subset of patients with metastatic disease to the pancreas, the frequency and site of origin of the malignancy varies between postmortem and surgical series, the latter partially reflecting a selection bias for malignancies with a more protracted course. The reported incidence of secondary neoplasms of the pancreas ranges from 1.6 to 11% in autopsy studies. In surgical series, these lesions account for up to 4% of pancreatic specimens. About one-third of these are clinically mistaken as primary pancreatic tumors [2].

Overall, carcinomas and malignant melanomas spread more commonly to the pancreas than sarcomas or hematopoietic neoplasia. The latter

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may include both myeloproliferative and lymphoproliferative disease (Fig. 12.1). Carcinoma of the kidney, lung, breast, and large bowel together with malignant melanoma are amongst the most frequent malignancies that spread to the pancreas. Some of these are discussed in more detail below.

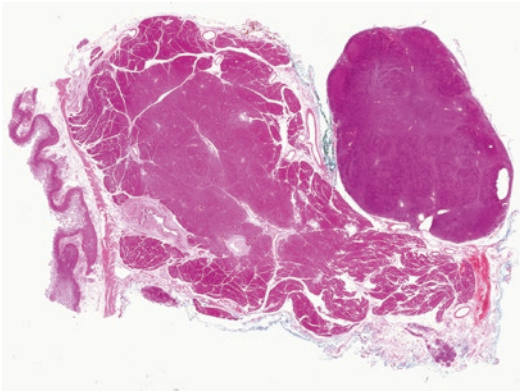

Fig. 12.1 Hodgkin lymphoma in a peripancreatic lymph node: a lymph node involved by Hodgkin lymphoma is prominently enlarged and indents the adjacent pancreas. On preoperative imaging this was misinterpreted as primary pancreatic cancer (whole-mount section)

12.3 Macroscopy

Metastatic tumor deposits in the pancreas tend to differ in their gross appearances from ductal adenocarcinoma of the pancreas, in as far as they are usually well-circumscribed, can exhibit significant hemorrhage, and may be partially cystic (Fig. 12.2). Although they are often of a considerable size, the surrounding pancreatic parenchyma is usually remarkably well preserved (Fig. 12.3). Metastasis can be solitary or multifocal (Fig. 12.4) and has usually no predilection for the head, body, or tail of the pancreas. Occasionally, the entire pancreas may be involved. Gross intraductal tumor growth, in the main pancreatic duct or common bile duct, may be seen and should not be interpreted as

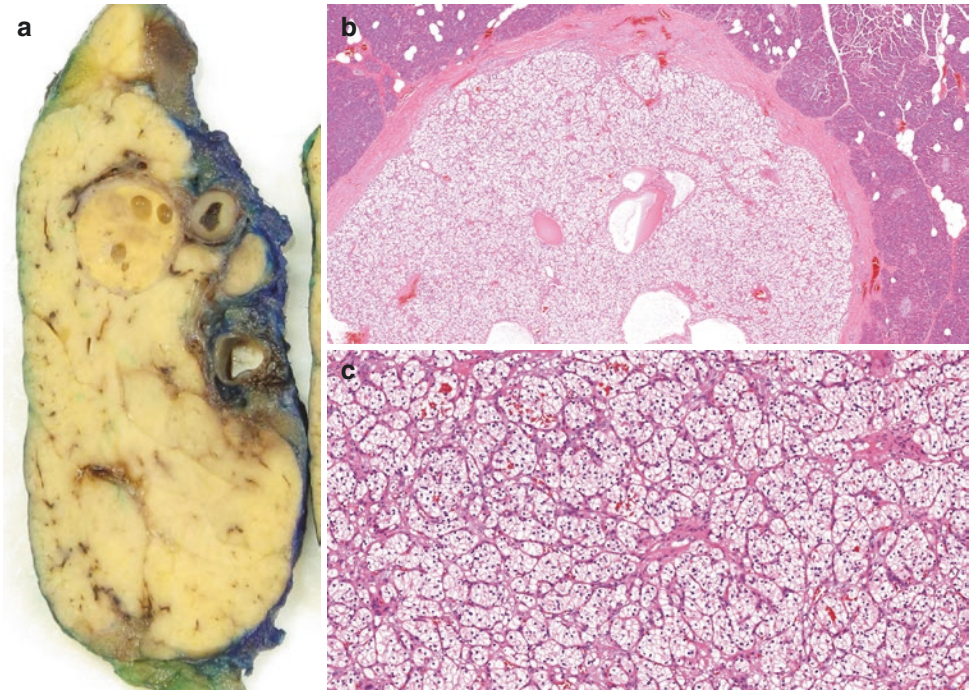

Fig. 12.2 Metastatic renal cell carcinoma: in contrast to primary pancreatic cancer, this metastatic deposit of renal cell carcinoma shows well-delineated pushing-type margins (**a**). Microscopically, the tumor has a fibrous capsule (**b**) and consists of densely packed clear cells (**c**)

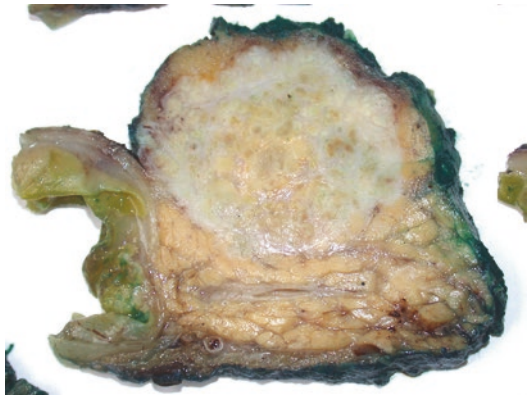

Fig. 12.3 Metastatic colonic adenocarcinoma: this metastasis of colonic cancer differs from primary pancreatic cancer by its remarkably well-defined contours. Note the normal appearance of the flanking pancreatic parenchyma and duct, despite the considerable size of the tumor

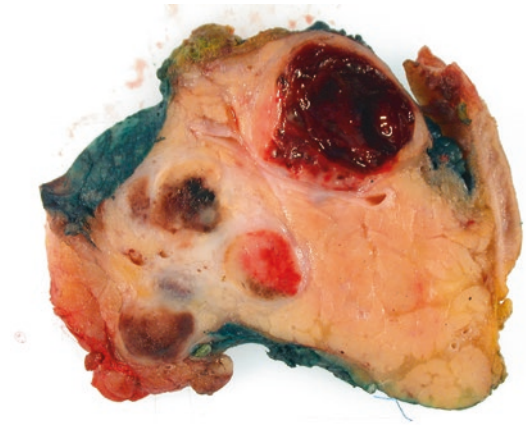

Fig. 12.4 Multifocal metastasis: the presence of multiple tumors within the pancreas raises the suspicion of metastatic rather than primary tumors

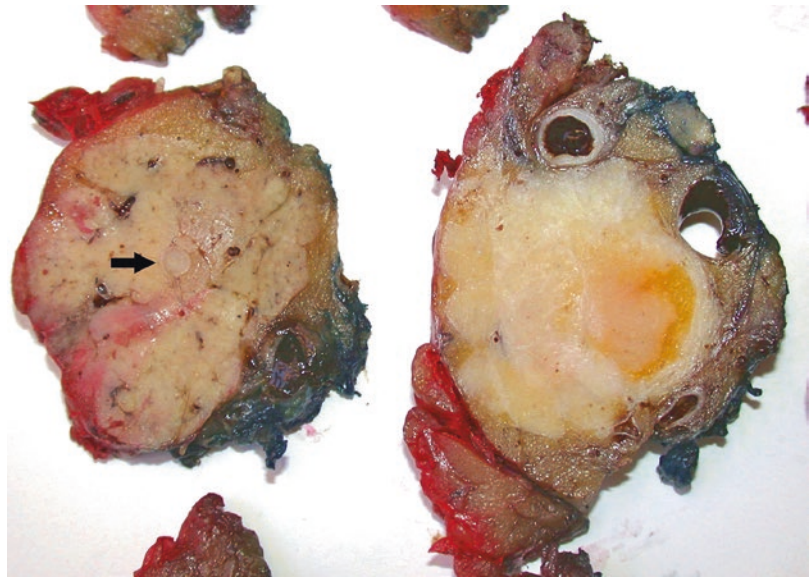

Fig. 12.5 Intraductal growth of metastatic tumor: this large metastatic deposit of colonic adenocarcinoma (*right*) extends beyond the main tumor mass by intraluminal growth within the main pancreatic duct (*left*, *arrow*)

an exclusion criterion for metastatic tumor (Figs. 12.5 and 12.6). Similarly, tumor occlusion of the splenic vein, which is commonly seen in pancreatic ductal adenocarcinoma, may occasionally also be found in metastatic cancer (Fig. 12.7).

Extensive hemorrhage and a yellow-orange color of the tumor tissue is characteristic of metastatic renal cell carcinoma, whereas dark brown-black pigmentation may be seen in the metastasis of malignant melanoma.

12.4 Microscopy

Depending on the type of the metastasis, the microscopic tumor appearances may by themselves raise the suspicion of metastatic rather than primary pancreatic neoplasia (Fig. 12.8). An abrupt transition from the neoplastic lesion to more or less pristine pancreatic parenchyma without convincing evidence of obstructive pancreatitis should also raise the suspicion of a metastatic process. Intraductal tumor propagation does not confirm a primary

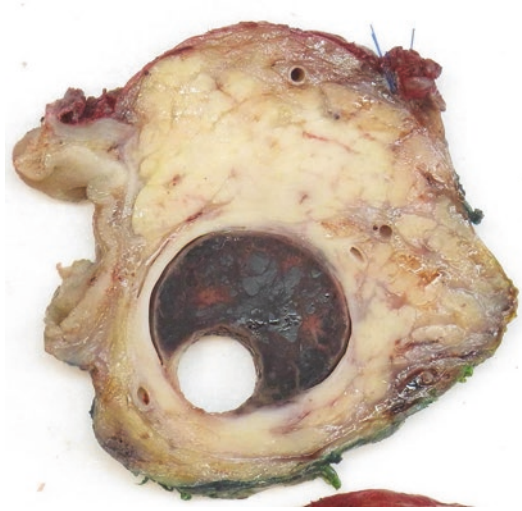

Fig. 12.6 Intraductal metastatic renal cell carcinoma: the common bile duct is grossly distended and obstructed by metastatic renal cell carcinoma growing within the duct lumen. Note the hemorrhagic tumor tissue and the punched-out hole due to a plastic biliary stent (removed)

Fig. 12.7 Metastatic renal cell carcinoma occluding the splenic vein: in this sagittal slice from a distal pancreatectomy specimen, the pancreatic body is almost entirely replaced by metastatic renal cell carcinoma, which also occludes and expands the splenic vein (*black arrows*). The splenic artery (*red arrow*) lies in contact with the tumor capsule but is not infiltrated

pancreatic origin, as metastastic tumor may also grow along pancreatic ducts of varying caliber, and on occasion mimic pancreatic intraepithelial neoplasia (PanIN).

12.5 Differential Diagnosis

Accurate information on the patient's medical history is essential to reach a correct diagnosis. Direct microscopic comparison of the pancreatic tumor with the previous extrapancreatic primary malignancy is helpful. However, the histomorphology of the primary tumor and metastasis may not always be entirely identical.

Immunohistochemistry may be helpful in many cases (Table 12.1) [3]. Probably the most difficult distinction to make is that between ductal adenocarcinoma of the pancreas and *metastatic colorectal cancer*, because a proportion of primary pancreatic cancers may exhibit an intestinal phenotype, both morphologically and immunohistochemically (see Chap. 9, Sect. 9.6.2). In addition, pancreatic ductal adenocarcinoma of pancreatobiliary type may assume intestinal features when infiltrating the duodenal wall, and in areas where it involves the duodenal mucosa, it may mimic dysplasia of the duodenal mucosa (see Chap. 9, Sect. 9.6.3, Fig. 9.20). *Metastatic breast cancer* of lobular type requires distinction from the rare signet ring cell subtype of ductal adenocarcinoma (Fig. 12.9) (see Chap. 9, Sect. 9.14.3). Distinction is important, because of the specific treatment options for metastatic breast cancer.

Renal cell carcinoma has a propensity to metastasize to the pancreas. If the *renal cell cancer* is *of clear cell type* (Fig. 12.2c), the differential diagnosis includes ductal adenocarcinoma with foamy gland or clear cell pattern, although the latter is usually only a focal feature within an otherwise conventional ductal adenocarcinoma. PAS-diastase staining or MUC1-immunohistochemistry may be helpful, as the clear cytoplasm in renal cell carcinoma contains glycogen, whereas in ductal adenocarcinoma it is mucin. Pancreatic endocrine neoplasia of clear cell type is a further important differential, which may be particularly difficult in patients with von Hippel-Lindau disease, who can also

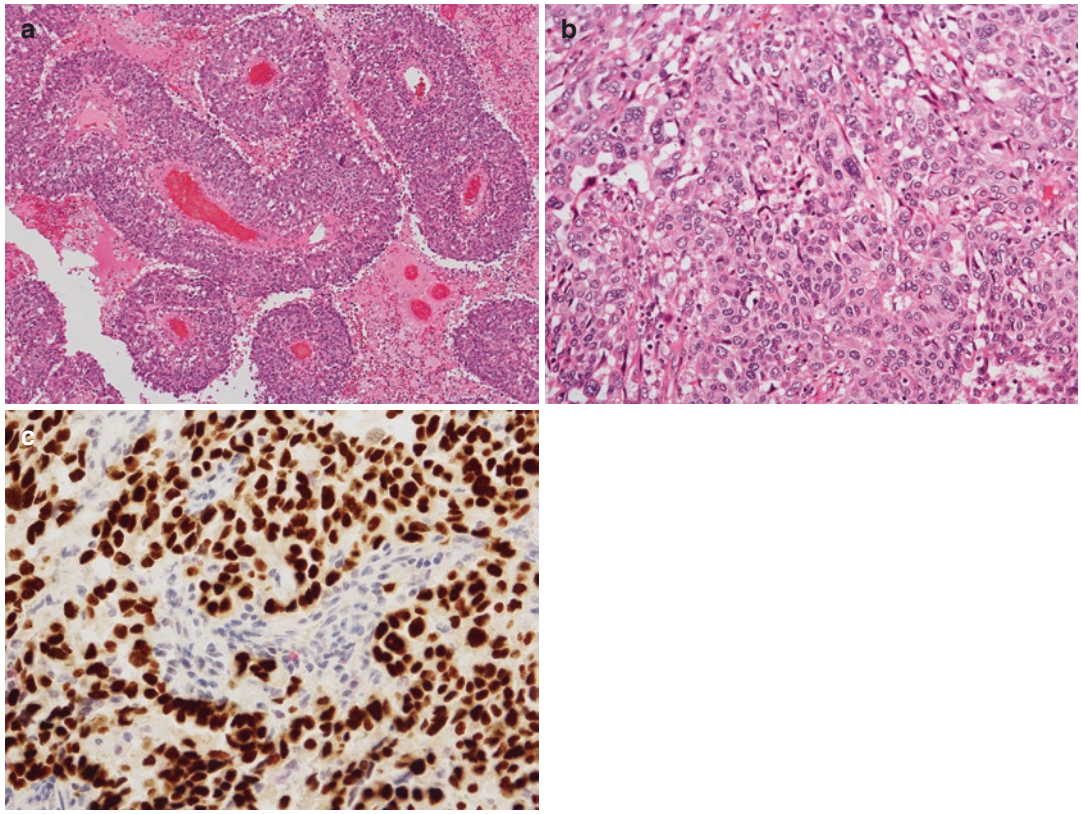

Fig. 12.8 Metastatic lung cancer: the growth pattern (**a**) and cytological features (**b**) of this tumor in the pancreatic body were not characteristic of ductal adenocarcinoma of the pancreas and raised the suspicion of metastasis in a patient with a history of lung cancer. Immunohistochemistry showed strong labeling for TTF-1 (**c**)

develop renal cell cancer (see Chap. 20, Sects. 20.9.1 and 20.12). PEComas, which are rare primary tumors of the pancreas, should also be distinguished. It should be borne in mind that the primary tumor and metastasis in renal cell carcinoma may differ in the extent of the clear cell features and the expression of various markers [4, 5]. For metastatic *renal cell carcinoma of non-clear cell morphology* (e.g., chromophobe), acinar cell carcinoma, pancreatic endocrine neoplasm, and solid pseudopapillary neoplasm are to be considered as a differential diagnosis, in particular if the metastatic renal cell carcinoma shows a trabecular or acinar growth pattern (Fig. 12.10). Very rarely, the renal cell carcinoma can be of a poorly differentiated or sarcomatoid morphology, in which case the pancreatic metastasis requires distinction from undifferentiated carcinoma of the pancreas (Fig. 12.11).

A further important differential diagnosis of poorly or undifferentiated pancreatic carcinoma is malignant melanoma. Diffuse sheets of noncohesive tumor cell growth, marked cellular atypia, and prominent nucleoli may be seen in both cancers (Fig. 12.12). Up to 10% of patients with malignant melanoma metastatic to the pancreas may not have a known primary. Immunohistochemistry usually aids in reaching the correct diagnosis (Table 12.1).

Table 12.1 Immunohistochemical staining of primary and secondary neoplasia of the pancreas [3–9]

	Ductal adenocarcinoma of pancreas	Pancreatic endocrine tumor	Renal cell carcinoma	Colorectal adenocarcinoma	Breast adenocarcinoma	Lung adenocarcinoma	Malignant melanoma
CK7	++	+	-/+ (clear cell, oncocytic) ++ (chromophobe, papillary)	-/+	++	++	-
CK20	-/+	-/+	-	++	-	-	-
CA125	+	-	-	-	-/+	-/+	-
CEA	++	-/+	-	++	-/+	+	-
CDX2	- (except intestinal type)	-/+	-	++	-	-	-
Pax8	-	++	++	-/+	-	-/+	ID
Mesothelin	-/+	-	-	-/+	-	-/+	-
Synaptophysin, Chromogranin	-	++	-	-	-	-	-
NSE, CD56	-	++	-/+ (except clear cell: +)	-	-	-	-
RCC	-	-	+ (except oncocytic:-)	-	-	-	-
TTF1	-	-	-	-	-	++	-
Napsin A	-	-	-/+	-	-	++	-
GATA3	-/+	-	-/+	-	++	-	-
GCDFP15	-	-	-	-	-/+	-	-
ER	-	-	-	-	+	-	-
WT1	-	-	-/+	-	-/+	-/+	++
Vimentin	- (except undifferentiated carcinoma)	-/+	++ (except chromophobe, oncocytic:-)	-	-/+	-/+	+
HMB45, Melan-A, S100	- -	- -/+	- -	- -	- -/+	- -	++ ++

Abbreviations: *ID* insufficient data, ++ >80% tumors stain positively, + 50-80% of tumors stain positively, -/+ 6-49% of tumors stain positively, - 0-5% of tumors stain positively

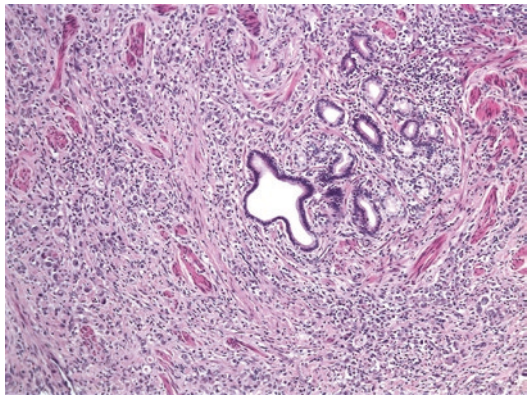

Fig. 12.9 Metastatic breast cancer: a metastatic deposit of lobular breast cancer shows microscopic similarity with the signet ring cell subtype of ductal adenocarcinoma

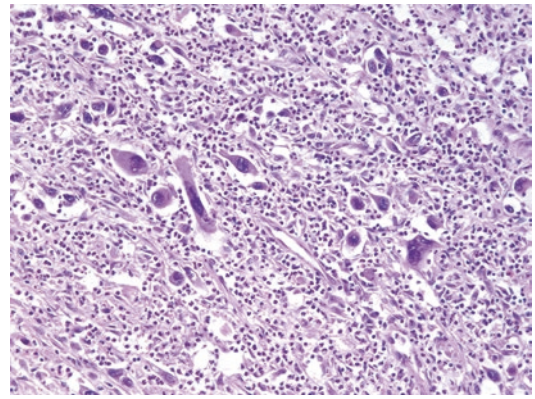

Fig. 12.11 Poorly differentiated metastatic renal cell carcinoma: the marked cytological atypia and nuclear pleomorphism, and the presence of bizarre tumor cells in this metastatic deposit of renal cell carcinoma may be mistaken as features of undifferentiated carcinoma of the pancreas

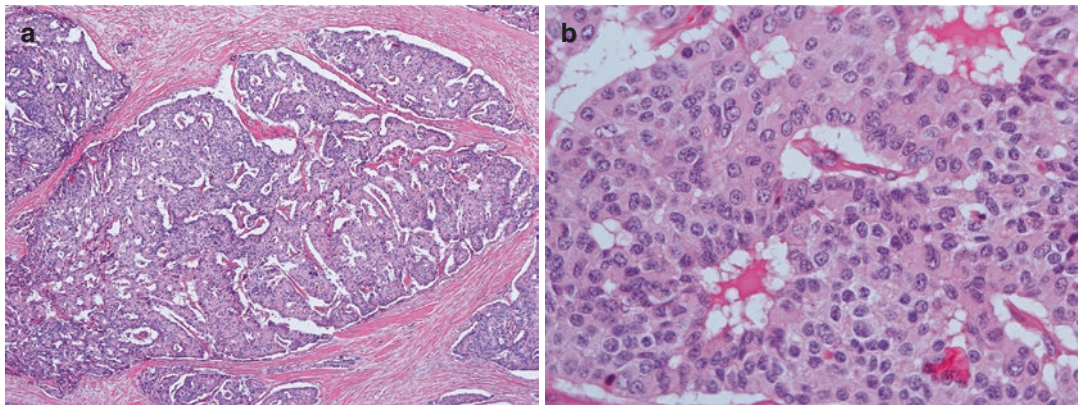

Fig. 12.10 Metastatic renal cell carcinoma of chromophobe type: the nearly organoid growth pattern of this tumor, its delicate vasculature, and cytomorphology raise the suspicion that this may be a pancreatic neuroendocrine tumor (**a**). However, the degree of nuclear pleomorphism, the irregular nuclear membranes, vesicular chromatin, and slightly prominent nucleoli are dissimilar from the nuclear features of endocrine tumors (**b**)

12.6 Synchronous Primary and Metastatic Cancer

On rare occasion, both primary pancreatic cancer and metastatic cancer of extrapancreatic origin may be present in the same resection specimen. This unusual finding may occur in patients with a hereditary cancer predisposition, for example, in patients with a germline *BRCA*-mutation, who may have both metastatic ovarian cancer and ductal adenocarcinoma of the pancreas. In such cases, the difference in tumor histomorphology and immunohistochemical profile, as well as the different location of both tumors (primarily intrapancreatic versus peripancreatic/peritoneal), will lead to a correct diagnosis (Fig. 12.13).

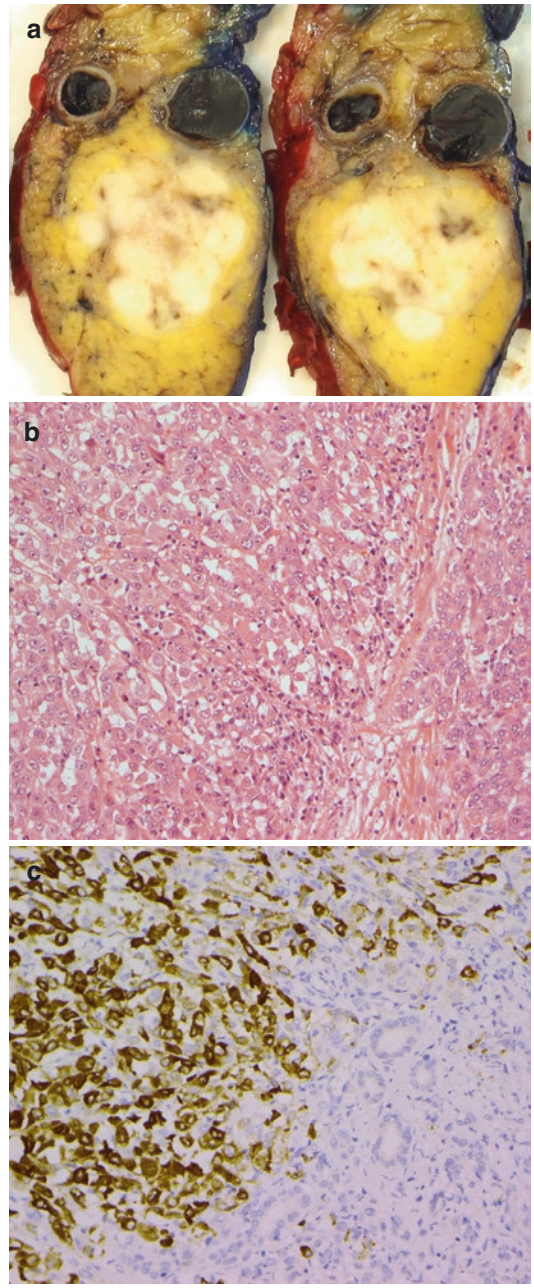

Fig. 12.12 Metastatic melanoma: a tumor in the body of the pancreas (**a**) consists of densely packed, large tumor cells with prominent nucleoli (**b**). Immunostaining for Melan-A shows strong labeling in the tumor cells, while the adjacent pancreatic parenchyma is negative (**c**)

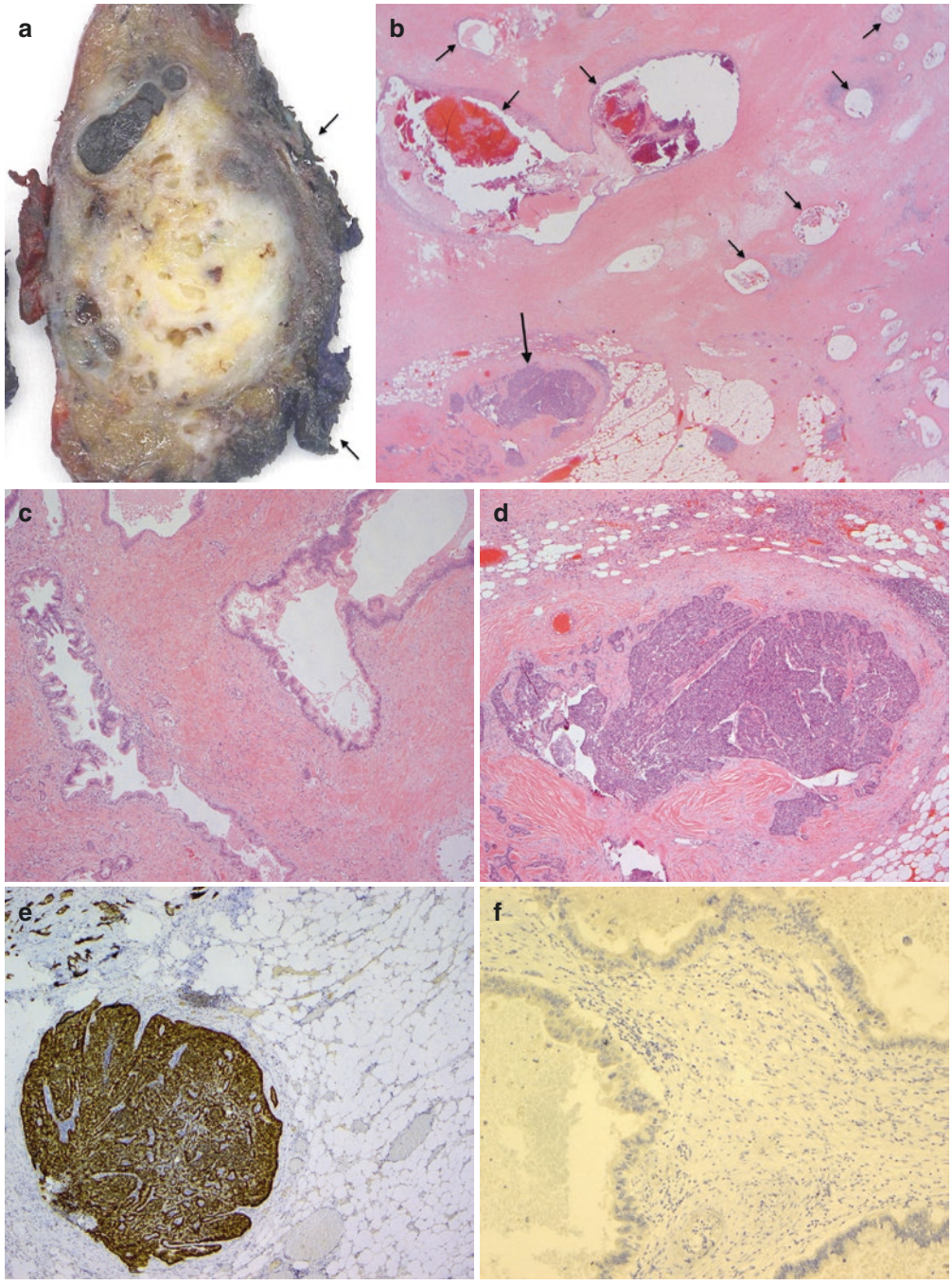

Fig. 12.13 Ductal adenocarcinoma and synchronous metastatic tubal cancer: a patient with a history of serous adenocarcinoma arising in the left fallopian tube underwent distal pancreatectomy for a tumor in the body of the pancreas. Note the irregular surface of the peripancreatic tissue posteriorly (*arrows*) (**a**). Histology revealed two tumors with distinct morphological features and a glandular (*short arrows*) and solid (*long arrow*) growth pattern (**b**). The former showed features characteristic of ductal adenocarcinoma of cystic-papillary pattern (**c**), while the latter consisted of compact solid and trabecular cell clusters suggestive of serous carcinoma (**d**). Immunostaining for PAX8 showed strong labeling of the compact tumor cell clusters, confirming the presence of metastatic tubal cancer in addition to primary ductal adenocarcinoma (**e**). PAX8 immunostaining was negative in the carcinoma with glandular growth pattern (**f**). Genetic analysis confirmed that the patient had a germline *BRCA1* mutation

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