CLINICAL PRACTICE GUIDELINE

Ductal Pancreatic Adenocarcinoma

Surgery, Pathology Work-up, and Neoadjuvant, Adjuvant, and Palliative Treatments

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SUMMARY

Background: Ductal adenocarcinoma of the pancreas is the fourth most common cause of death from cancer in men and women in Germany: about 15 000 persons die of this disease each year.

Methods: The S3 guideline on exocrine pancreatic carcinoma was updated with the aid of systematic literature reviews on the surgical, neoadjuvant, and adjuvant treatment of ductal pancreatic carcinoma, and on treatment in the metastatic stage. These reviews covered the periods 2002 to February 2012 (for radiotherapy) and 2006 to August 2011 (for all other topics).

Results: The criteria for borderline resectable pancreatic tumors are the same as those of the guidelines of the National Comprehensive Cancer Network. Preoperative biliary drainage with a stent is recommended only if cholangitis is present or if a planned operation cannot be performed soon after the diagnosis is made. When a pancreatic carcinoma is resected, at least 10 regional lymph nodes should be excised, and the ratio of affected to excised nodes should be documented in the pathology report. Gemcitabine and 5-fluorouracil are recommended for adjuvant therapy. Neither of these drugs is preferred over the other; if the one initially given is poorly tolerated, the other one should be given instead. When gemcitabine and erlotinib are given for palliative treatment, erlotinib should be given for no longer than 8 weeks if no skin rash develops. In selected patients, the folfinox protocol yields markedly better results than gemcitabine. Moreover, the new combination of nab-paclitaxel and gemcitabine can be used as first-line treatment. In the event of disease progression under first-line treatment, second-line treatment should be initiated.

Conclusion: In recent years, new chemotherapeutic protocols have brought about marked improvement in palliative care. Further trials are needed to determine whether the perioperative or adjuvant use of these protocols might also improve the outcome of surgical treatment with curative intent.

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There are about 16 000 new cases of ductal pancreatic carcinoma in Germany every year (1), with men and women affected equally often. Pancreatic cancer is the ninth most common type of cancer (in terms of incidence) among men and the seventh most common among women. It usually arises in elderly persons (mean age at onset, 71 years for men and 75 years for women). In 2010, ductal pancreatic carcinoma caused approximately 15 500 deaths in Germany and was thereby in fourth place among all types of cancer; it was responsible for 6.7% of cancer deaths in men and 7.9% in women (1). Its incidence and annual mortality are numerically very close, and its 5-year survival rate of 8% is the lowest among all types of cancer in Germany (1). Late diagnosis, early metastasis, and the resulting low number of curative resective procedures contribute to the high mortality of this disease.

The S3 guideline created by the joint oncologic guideline program of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF), German Cancer Aid (Deutsche Krebshilfe e.V., DKH), and the German Cancer Society (Deutsche Krebsgesellschaft, DKG) contains evidence-based recommendations issued by expert panels on the basis of a consensus procedure. All medical specialty societies and patient organizations involved in the care of patients with ductal pancreatic carcinoma participated in the updating of the guideline (*Box 1, eTable*).

The update concerned the topic areas IV (surgical treatment), V (adjuvant and neoadjuvant treatment), and VI (palliative treatment). In this article, we present and discuss the recommendations that are particularly relevant to clinical practice and the main changes contained in the update. The complete S3 guideline update of 2013 was published in the German-language journal *Zeitschrift für Gastroenterologie* (2), and the entire S3 guideline of 2007/2013 (in German) can be found on the Internet via the websites of the AWMF, the DGVS, and the DKG.

Method

Systematic literature search

The literature search on radiotherapy was performed by the German Agency for Quality in Medicine (Ärztliches Zentrum für Qualität in der Medizin, ÄZQ) in two

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steps, with a search for aggregate evidence (systematic reviews, meta-analyses, and HTA reports from 1 January 1980 onward) on 8 December 2011, followed by a search for primary literature (from 1 January 2002 onward) on 23 February 2012. The guideline secretariat performed the literature search for all other topics on 29 August 2011 (for publications from 1 January 2006 onward). In both cases, the search was carried out in the Medline, Embase, and Cochrane databases (the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Health Technology Assessment Database). The course of the systematic literature searches is depicted in *Figure 1*. New data that became available between the above closure dates and the date of printing are also included.

Surgery with curative intent

Surgery is the only potentially curative treatment for pancreatic carcinoma (level of evidence [LOE] 1b–). Thus, patients with a pancreatic carcinoma that is considered to be resectable should not be treated with chemotherapy, radiotherapy, or a combination of these two without surgery (good clinical practice [GCP]) (3).

A staging laparoscopy can be performed if a patient has been found to have a pancreatic carcinoma that is considered resectable; this is appropriate mainly in cases where the imaging studies are not conclusive and peritoneal carcinosis is suspected on clinical grounds (significant ascites, very high CA19–9 value) (recommendation grade [RG] 0, LOE 1b) (4). In about 30% of cases, staging laparoscopy yields findings that rule out a curative resection (5).

The goal of surgical resection and histopathological classification

The goal of surgery is total resection of the pancreatic carcinoma with clean margins (R0) (RG A, LOE 1a–) (6–8), as this affords the patient the greatest chance of long-term survival (6, 7). There are various different definitions of “total resection” of a pancreatic carcinoma; there is no evidence base for any particular “minimal resection margin” that should be respected or for the related prognostic implications. The goal is curative tumor removal with a maximal safety margin. The size of the tumor margin should be documented in the pathology report. In general, the farther away the tumor is from the resection margin, the better the prognosis.

In defining R categories, the guideline uses the criteria of the UICC classification: R0 means that no carcinoma cells are demonstrable at the resection margin, and R1 means that there are carcinoma cells at the resection margin.

In order to maintain a clear distinction between classification systems (such as the R classification) and parameters of putative prognostic relevance (distance from the resection margin), and to enable unambiguous and reproducible documentation of the histologic findings, a standardized histopathological

BOX 1

Medical societies and other organizations participating in the updating of the guideline*

- German Society for Digestive and Metabolic Diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, DGVS)
- German Society for Radiation Oncology (Deutsche Gesellschaft für Radioonkologie, DEGRO)
- German Society for Hematology and Medical Oncology (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie, DGHO)
- Association of Medical Oncology (Arbeitsgemeinschaft Internistische Onkologie, AIO) of the German Cancer Society (Deutsche Krebsgesellschaft, DKG)
- German Society of Pathology (Deutsche Gesellschaft für Pathologie, DGP)
- Association of Surgical Oncology (Chirurgische Arbeitsgemeinschaft Onkologie, CAO-V)
- German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie, DGAV)
- Radiation Oncology Working Group (Arbeitsgemeinschaft Radiologische Onkologie, ARO) of the DKG
- German Society of Clinical Chemistry and Laboratory Medicine (Deutsche Vereinigte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin, DGKL)
- Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften, AWMF)
- Oncological and Pediatric Oncological Nursing Conference (Konferenz Onkologischer Kranken- und Kinderkrankenpflege, KOK)
- Working Group of Pancreatectomized Patients (Arbeitskreis der Pankreatektomierten, AdP)

* In addition, the following medical societies were offered participation in the guideline-updating process: the German Radiological Society (Deutsche Röntgengesellschaft), the German Nutrition Society (Deutsche Gesellschaft für Ernährung), and the German Society of Palliative Medicine (Deutsche Gesellschaft für Palliativmedizin). These three societies either saw no need to participate in the update or did not respond to the offer of participation.

work-up of the relevant resection margins and a conceptual extension of the R classification with the circumferential resection margin (CRM) classification are recommended. The circumferential resection margin comprises an anterior, a medial, and a posterior resection surface and takes the distance of the tumor from the resection margin (in millimeters) into account. R0-resected pancreatic carcinomas are

FIGURE 1

Flow diagram of the systematic literature search (aggregated evidence and primary sources)

called CRM-positive if there are tumor cells within 1 mm of the resection margin, but not at the margin (R0 narrow). If there are no carcinoma cells within 1 mm of the definitive margin of resection, then the situation is classified as CRM-negative R0 (R0 wide). The application of this concept shall make it possible for the first time to estimate the risk of recurrence and the overall prognosis more accurately and to assess different surgical treatments of pancreatic carcinoma.

The pT, pN, and M categories and tumor grade should be stated in the pathology report along with the R status (RG A, LOE 2b) (16, 20, 21), as should

lymphatic vessel invasion, perineural infiltration, and blood vessel invasion (RG B, LOE 2b) (8).

Criteria for resectability

Infiltration of neighboring organs

A pancreatic tumor may be totally resectable even if it infiltrates into the neighboring organs (RG 0, LOE 3). An extended R0 resection does not confer a worse prognosis than a standard resection. Thus, locally advanced carcinoma can, in some cases, be resected en bloc with the infiltrated neighboring organs (9).

Vascular infiltration

No tumor resection should be performed if the primary tumor infiltrates into the celiac trunk or the superior mesenteric artery (GCP). The National Comprehensive Cancer Network (NCCN) guidelines (10) contain a criterion for the maximal extent of vascular infiltration at which resection can still be reasonably attempted (*Box 2*): tumors surrounding more than 180° of the circumference of the celiac trunk or the superior mesenteric artery are considered unresectable. This criterion is derived from expert consensus alone but can serve as a decision aid for clinical practice. Infiltration of either of these two vessels is not an absolute contraindication to resection in a technical, surgical sense (11), but resection in such cases is associated with higher perioperative morbidity and mortality and does not improve survival (12).

Infiltration of the portal vein, the superior mesenteric vein, or the splenic vein does not contraindicate resection (RG B, LOE 2b) (6, 11–14). The morbidity and mortality after en bloc resection of pancreatic tissue together with segments of the portal vein or the superior mesenteric vein are no higher than after resections not involving these veins (6, 13). The long-term prognosis after resection when one or both of these veins are infiltrated by tumor has not been found in clinical studies to be any worse than when they are not infiltrated (12, 14). Infiltration of more

BOX 2

The definition of borderline resectable tumors according to the NCCN guidelines (10)

- no distant metastases
- infiltration of the superior mesenteric vein and/or the portal vein, i.e., direct contact of the tumor with the vessel, with or without luminal narrowing in imaging studies
- encasement of the superior mesenteric vein and/or the portal vein without simultaneous encasement of the neighboring arteries
- occlusion of a short segment of vein by tumor thrombus or tumor encasement, but with suitable vessels proximal and distal to the occlusion permitting safe resection and reconstruction
- encasement of the gastroduodenal artery up to the hepatic artery, with either encasement of a short segment of the hepatic artery or direct contact with the hepatic artery, but without extension to the celiac trunk
- tumor surrounding no more than 180° of the circumference of the superior mesenteric artery

than 2–3 cm of the portal vein is, however, considered prognostically unfavorable.

There are no clearly defined criteria for the resectability of a pancreatic carcinoma. The sensitivity and specificity of imaging studies are less than perfect. Due to this and depending on their surgical experience, two visceral surgeons (or surgical centers) may differ in their assessments of the resectability of a pancreatic carcinoma. Thus, the guideline committee considers it reasonable for centers with a low caseload of pancreatic tumor surgery to get a second opinion from a tertiary reference center specializing in such surgery if a tumor is judged to be locoregionally unresectable on the basis of imaging studies or open exploration (GCP).

Distant metastases contraindicate resection of the primary tumor

If distant metastases (organ metastases, peritoneal carcinosis, or lymph node metastases counting as distant metastases) are found, then the primary tumor should not be resected (RG B, LOE 2b). Resection does not improve the prognosis (15, 16).

Management of preoperative cholestasis

Painless jaundice is a common presentation leading to the diagnosis of pancreatic carcinoma. After endoscopic retrograde cholangiopancreatography (ERCP) and stenting, up to 73% of patients have biliary infections (17); when pancreatic resection is performed, such infections are associated with increased morbidity (18). Thus, preoperative biliary drainage with a stent should only be performed if cholangitis is present (RG B, LOE 1b) or if resective surgery cannot be performed within 2 weeks of the time of diagnosis (GCP).

Lymphadenectomy

At least 10 regional lymph nodes should be removed during resection of a pancreatic carcinoma in order to meet the criteria of the TNM classification (GCP). Extended lymphadenectomy is not recommended, as it does not prolong survival (GCP) (19). The ratio of affected to excised nodes (the lymph node ratio, LNR) should be documented in the pathology report (RG A, LOE 2b). An LNR of 0.2 or higher is prognostically unfavorable (20, 21).

Resection of distant metastases

If previously undiagnosed distant metastases are discovered at surgery, no resection should be performed, even if the lesion is resectable (RG B, LOE 4). In the few publications that have addressed this question to date, it has been reported that resection in this situation yields little or no prolongation of survival, at the cost of increased morbidity (22).

Laparoscopic surgery for pancreatic carcinoma

The role of laparoscopic left pancreatectomy in the treatment of ductal adenocarcinoma is currently unclear. Laparoscopic surgery should only be

Figure 2: Resection margin—Moderately differentiated ductal adenocarcinoma of the pancreas; the resection margin is marked in blue. The distance of the tumor from the resection margin should be measured under the microscope and documented in the pathology report. Hematoxylin-eosin (H&E) stain, distance scale in figure

Figure 3: Perineurial infiltration—Tumor cells of pancreatic adenocarcinoma are seen in a nerve in the peripancreatic fat. H&E stain, distance scale in figure

TABLE

Recent randomized and controlled trials on combination chemotherapy showing a survival advantage over gemcitabine monotherapy in the palliative setting

Reference	N	Treatment regimen	Progression-free survival	Overall survival	1-year survival rate	EBM grade
Moore 2007 (35)	569	gemcitabine + erlotinib versus gemcitabine	3.75 versus 3.55 months (HR 0.77, $p = 0.004$)	6.24 versus 5.91 months (HR 0.82, $p = 0.038$)*	23% versus 17% ($p = 0.023$)*	1b
Conroy 2011 (36)	342	folfinirinox versus gemcitabine	6.4 versus 3.3 months (HR 0.47, $p < 0.001$)	11.1 versus 6.8 months (HR 0.57, $p < 0.001$)	48% versus 21% ($p < 0.001$)	1b
Von Hoff 2013 (37)	861	gemcitabine + nab-paclitaxel versus gemcitabine	5.5 versus 3.7 months (HR 0.69, $p < 0.001$)	8.5 versus 6.7 months (HR 0.72, $p < 0.001$)	35% versus 22% ($p < 0.001$)	1b

* In the subgroup analysis of overall survival for patients with rash $\geq$ grade 2, 10.5 months (HR 0.74, $p = 0.037$) and 1-year overall survival rate 43% ($p < 0.001$). HR, hazard ratio

performed in the setting of a clinical trial (23, 24) (RG B, LOE 2b).

Adjuvant treatment of pancreatic carcinoma

The 5-year survival rate after resection of a ductal pancreatic carcinoma with curative intent is limited by local recurrences and distant metastases (6). Thus, after R0 resection of a pancreatic carcinoma in UICC stage I, II, or III, adjuvant chemotherapy should be given (RG A, LOE 1b), as it significantly improves cancer-free and overall survival compared to surgery alone (5-year survival 20.7% vs. 10.4%, 10-year survival 12.2% vs. 7.7%) (25). There is no chronological age limit for adjuvant chemotherapy (25).

Either gemcitabine or 5-fluorouracil (5-FU) can be given as adjuvant chemotherapy (RG A, LOE 1b) (26, 27). Neither is preferred over the other; either drug can be given initially, and, if it is poorly tolerated, the other can be given instead (GCP). The gemcitabine protocol has lower mucosal toxicity, but causes thrombocytopenia somewhat more often than 5-FU bolus administration in the Mayo protocol (26, 27).

Adjuvant chemotherapy should be given for six months, which was the duration of administration in published trials (GCP). In analogy to the situation in colorectal carcinoma, and in the absence of directly relevant prospective trials, the guideline contains a recommendation that adjuvant chemotherapy should be begun within six weeks of surgery, if possible (GCP). Nonetheless, it was reported very recently, in an evaluation of the ESPAC-3 trial, that the completion of adjuvant chemotherapy has greater prognostic significance than its early initiation. Initiating chemotherapy up to 12 weeks after surgery did not shorten survival (28).

After R1 resection of a pancreatic carcinoma, additive chemotherapy with gemcitabine or 5-FU should be given for 6 months (RG B, LOE 2b). In a subgroup analysis of the CONKO-01 trial, patients treated with gemcitabine after R1 resection had significantly longer disease-free and overall survival than patients in the control group (mDFS [median disease-free survival] 15.8 vs. 5.5 months, $p < 0.001$, mOS [median overall survival] 22.1 vs. 14.1 months, $p = 0.07$) (26).

The role of adjuvant/additive radiochemotherapy

After R0 resection of a pancreatic carcinoma, no adjuvant radiochemotherapy should be given except in the setting of randomized controlled trials (RG B, LOE 1b–), as there is no clear evidence for the benefit of such treatment (27, 29). Nor should additive radiochemotherapy be performed after R1 resection of a pancreatic carcinoma, except in randomized controlled trials (RG B, LOE 2b–).

Neoadjuvant and intraoperative therapies

Neoadjuvant radiotherapy, radiochemotherapy, or chemotherapy should not be performed in patients with a pancreatic carcinoma that is considered to be resectable, except in clinical trials (RG B, LOE 2a–), as the published studies do not document any prolongation of recurrence-free and overall survival with these treatments compared to surgery alone (30).

Neoadjuvant systemic chemotherapy for resectable pancreatic carcinoma seems reasonable from the tumor-biological point of view, as such tumors tend to metastasize early (31). Patients undergoing neoadjuvant chemotherapy might, however, have tumor progression during the treatment. Randomized controlled trials on this matter are expected in the future, particularly with new chemotherapeutic protocols (e.g., folfinirinox).

On the basis of retrospective analyses, it is stated in the updated guideline that a sequential treatment approach with chemotherapy and radiotherapy can be applied in patients with locally advanced, inoperable tumors, because patients with local tumors that remain stable under initial chemotherapy can additionally benefit from radiochemotherapy given immediately afterward (RG 0, LOE 3). A conflicting result was obtained, however, in the LAP07 trial, in which patients with locally advanced pancreatic carcinoma were treated with gemcitabine or gemcitabine/erlotinib and the outcomes with or without radiochemotherapy were followed prospectively. In this trial, only patients with stable, non-metastatic disease or responders were randomized to radiochemotherapy. It was found that

radiochemotherapy conferred no advantage over gemcitabine treatment without radiation (32). The findings of further trials must be awaited for a definitive answer to this question.

Isolated local recurrence

In case of an isolated local recurrence, all options for local therapy should be considered (GCP).

Small, retrospective case studies have shown that tumor resection or radiochemotherapy can be effective and are well-tolerated in this setting (33). It is realistic to expect such procedures to prolong tumor-free survival, but cure remains unlikely.

Palliative treatment of pancreatic carcinoma

Metastatic or locally advanced pancreatic carcinoma with an ECOG performance status of 0 to 2 should be treated with palliative chemotherapy (RG A, LOE 1a), as this prolongs survival and improves quality of life (34). Chemotherapy should be begun as soon as the disease is diagnosed. For patients in poor general condition (Karnofsky index <70%, ECOG performance status >2), the benefit of chemotherapy is doubtful.

Gemcitabine in a conventional dosage (1000 mg/m² in a 30-minute infusion) is standard for the treatment of locally advanced and/or metastatic pancreatic carcinoma (RG B, LOE 1a). The 1-year survival rate is 18–20% (34). There is only a grade B recommendation for gemcitabine, as two more effective treatments exist for defined patient groups, namely folfinox and a combination of gemcitabine with nab-paclitaxel.

As an alternative to gemcitabine monotherapy, combination therapy with gemcitabine and the EGF-receptor tyrosine kinase inhibitor erlotinib can be used for patients with metastatic pancreatic carcinoma (RG 0, LOE 1b) (35). Without the occurrence of a skin rash (a typical side effect of anti-EGFR treatment) within 8 weeks of initiation of treatment with erlotinib, erlotinib treatment should be discontinued, as patients have not been found to benefit from longer treatment with erlotinib under these conditions (RG B, LOE 4) (35).

A combination of 5-FU/folinic acid, irinotecan, and oxaliplatin (the folfinox protocol) can be used in patients with metastatic pancreatic carcinoma who have a favorable risk profile (ECOG status 0–1, bilirubin value <1.5 times the upper limit of normal, age up to 75 years) (RG 0, LOE 1b). This protocol significantly prolongs overall survival compared to gemcitabine (median survival 11.1 vs. 6.8 months, $p < 0.0001$, hazard ratio [HR] 0.57) (36). It likewise prolongs progression-free survival from 3.3 to 6.4 months and has a higher response rate than gemcitabine (31.6%, compared to 9.4%). It is, however, also more toxic (grade III/IV neutropenia, 45.7% vs. 18.7%; febrile neutropenia, 5.4% vs. 0.6%; grade III/IV diarrhea, 12.7% vs. 1.2%) (Table).

Gemcitabine combined with nab-paclitaxel (G+nab-P) is a further new treatment option for metastatic pancreatic carcinoma that was just approved

for use in the European Union. In a phase III trial, this combination was found to improve median progression-free survival (PFS), overall survival (OS), and tumor response rates significantly in comparison to gemcitabine alone (PFS: G+nab-P: 5.5 months vs. G: 3.7 months, HR=0.69 [95% confidence interval (CI), 0.58–0.82]; $p < 0.001$; OS: G+nab-P: 8.5 months; G: 6.7 months, HR=0.72 [95% CI, 0.62–0.83]; $p < 0.001$; response rate [RR] G+nab-P: 23%, G: 7%) (37). Grade III/IV hematotoxicity, fatigue, neuropathy, and diarrhea were all more common in the combination group.

Combinations of gemcitabine with oxaliplatin, cisplatin or capecitabine should not be used as standard first-line therapy for metastatic or locally advanced pancreatic carcinoma (RG B, LOE 1a), as a significant prolongation of survival with such combinations in comparison to gemcitabine monotherapy has been documented only in meta-analyses (34, 38).

Second-line treatment

In case of disease progression under treatment with gemcitabine, second-line treatment with 5-FU and oxaliplatin should be given, as long as the patient has an ECOG status of 0–2 (RG B, LOE 1b–) (39). If folfinox treatment fails, gemcitabine can be given as second-line treatment (36).

Conflict of interest statement

Prof. Tannapfel has been paid for serving as a consultant and for preparing continuing medical education by the Roche, Merck, Amgen, Falk, Pfizer, Astra-Zeneca, and Celgene companies.

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CLINICAL PRACTICE GUIDELINE

Ductal Pancreatic Adenocarcinoma

Surgery, Pathology Work-up, and Neoadjuvant, Adjuvant, and Palliative Treatments

Thomas Seufferlein, Marc Porzner, Volker Heinemann,
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eTABLE

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