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Current Oncological Treatment of Patients with Pancreatic Cancer in Germany: Results from a National Survey on behalf of the Arbeitsgemeinschaft Internistische Onkologie and the Chirurgische Arbeitsgemeinschaft Onkologie of the Germany Cancer Society

Stefan Boeck[a] Christiane J. Bruns[b] Mirja Sargent[a] Claus Schäfer[c]
Thomas Seufferlein[d] Karl-Walter Jauch[b] Volker Heinemann[a]

[a]Department of Internal Medicine III, [b]Department of Surgery and [c]Department of Internal Medicine II, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, Munich, [d]Department of Internal Medicine I, University of Halle, Halle, Germany

Key Words
Chemotherapy · Pancreatic cancer · Survey, German Pancreatic Cancer

Abstract
Background: No data have previously been available regarding the current treatment of patients with pancreatic cancer (PC) in German hospitals and medical practices. ***Methods:*** Between February 2007 and March 2008 we conducted a national survey [on behalf of the Arbeitsgemeinschaft Internistische Onkologie (AIO) and the Chirurgische Arbeitsgemeinschaft Onkologie (CAO)] regarding the current surgical and oncological treatment of PC in Germany. Standardized questionnaires were sent via mailing lists to members of the AIO and CAO (n = 1,130). The data were analyzed using SPSS software (version 16.0). Pre-defined subgroup analysis was performed by grouping the results of each question with regard to the professional site of the responding physician and to the number of patients treated in their institution by year. ***Results:*** 181 (16%) of the oncological questionnaires were sent back. For 61% of the participating centers, a histological confirmation of PC diagnosis is obligatory. 21% of physicians offer neoadjuvant therapy to patients with potentially resectable PC. In the adjuvant treatment after curative-intent surgery, gemcitabine (Gem) is regarded as standard of care by 71% after R0 resection and 62% after R1 resection. For patients with locally advanced PC, 52% of the participating centers recommend systemic chemotherapy, 17% prefer combined primary chemoradiotherapy. Most centers (59%) base their decision of combination regimens for metastatic disease on the performance status of their patients. In patients with a good status, 28% apply single-agent Gem, 3% use Gem + capecitabine, 12% Gem + erlotinib, 16% Gem + oxaliplatin, and 8% Gem + cisplatin. Only 28% of the survey doctors offer second-line treatment to the majority of their patients with advanced PC. ***Conclusion:*** Not every PC patient in Germany is treated according to the present S3 guidelines. Diagnosis and treatment of PC in Germany still need to be improved.

Introduction

Pancreatic adenocarcinoma (PC) still remains a disease with a dismal prognosis. In 2007 in the United States, an estimated 37,170 new PC cases were diagnosed, with a

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Prof. Dr. Volker Heinemann
Department of Internal Medicine III, Klinikum Grosshadern
Ludwig-Maximilians-University of Munich, Marchioninistr. 15
DE–81377 Munich (Germany), Tel. +49 89 7095 2208, Fax +49 89 7095 5256
E-Mail volker.heinemann@med.uni-muenchen.de

nearly identical estimated rate of deaths (33,370) [1]. For patients with resectable disease at diagnosis, radical surgical tumor resection still is regarded as the only option for long-term survival or cure. In patients with locally advanced (unresectable) or metastatic PC, palliative systemic chemotherapy is the international standard of care [2, 3].

Since the introduction of the nucleoside analogue gemcitabine in the treatment of PC, several phase III trials have evaluated the role of a gemcitabine-containing combination treatment for patients with advanced disease [2, 4]. To date, only the combination of gemcitabine with the anti-EGFR tyrosine kinase inhibitor erlotinib provided a statistically significant (but clinically moderate) survival benefit compared to single-agent gemcitabine [5]. Promising efficacy results were also obtained with cytotoxic combinations of gemcitabine plus the oral fluoropyrimidine capecitabine or a platinum analogue [6–9]. However, based on the currently available data, it seems that only a subgroup of patients may derive a significant survival benefit from those cytotoxic combination regimens, e.g. those with metastatic disease and a good performance status at treatment initiation [10, 11]. For patients with locally advanced disease, the role of local radiotherapy (added to standard chemotherapy) still remains controversial [12]. Potentially, a sequential treatment approach (initial treatment with systemic chemotherapy for distant disease control, followed by chemoradiotherapy for local control) could be an effective therapeutic option for those patients [13, 14].

Based on clinical research conducted in patients with an advanced stage of disease, and on the poor prognosis of PC even after complete surgical resection, adjuvant treatment concepts have become a focus in recent years. Currently, adjuvant chemotherapy (e.g. with single-agent gemcitabine) is regarded as the standard of care (at least in European countries) after curative-intent surgery with a statistically significant benefit for disease-free and overall survival [15–17]. However, in the United States, there is still a trend towards the use of adjuvant chemoradiotherapy – despite the fact that this treatment approach has not shown a consistent survival advantage (compared to best supportive care only) in large randomized controlled trials to date [18, 19]. Phase III trials evaluating neoadjuvant treatment regimens for (potentially) resectable PC are currently under way, but to date only data from phase II neoadjuvant studies are available [20, 21]. Thus, a neoadjuvant treatment approach should have no place in the daily routine treatment of localized PC.

The aim of this study was to evaluate (based on a national survey using standardized questionnaires) the clinical practise of PC diagnosis, treatment and follow-up in German hospitals and medical practices. The obtained results were specifically analysed within the context of the recently published German S3 guideline 'exocrine pancreatic cancer', which contains consensus-based recommendations for prevention/screening, diagnosis and treatment of PC [3].

Materials and Methods

Survey Design and Questionnaire

From February 2007 to March 2008 standardized questionnaires regarding the surgical and oncological treatment of PC were sent by mail, fax and e-mail to German hospitals (university and community hospitals) and medical practices. The study questionnaire was designed by C.J. Bruns and K.-W. Jauch (surgical section) and S. Boeck and V. Heinemann (oncological section). In this paper, we report only on the results from the oncological part, as the surgical results from the survey will be published separately. The main goal of the questionnaire was to inquire into the local standards for PC diagnosis and treatment at the participating centers. The questionnaire was grouped in 3 parts. (1) Data of the participating physician: medical area of work (e.g. surgeon, gastroenterologist, medical oncologist), professional site (e.g. university or community hospital, private practice), and number of PC patients treated per year. (2) Questions on the local standard diagnostic procedures for PC. (3) Questions on the local treatment standards for resectable (including neoadjuvant and adjuvant therapy) and advanced PC. Both multiple-choice and open questions were part of the survey.

Participating Physicians

During the 1 year of evaluation, 1,130 questionnaires were sent out. The participating centers were not pre-selected, we contacted all members of the AIO gastrointestinal cancer study group and all members of the CAO of the German Cancer Society (DKG). All participating AIO/CAO physicians were contacted via e-mail lists. Additionally, all members of the project group 'Gastrointestinal Tumors' (chair: C.J. Bruns) of the Tumorzentrum München were contacted via mail and fax and participation in the national AIO/CAO survey was offered to physicians registered in this local project group.

Finally, the questionnaire was also published in the journal *Z Gastroenterol* (2007;45:1340–1342) of the Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten and the readers were encouraged to complete the questions and to fax them back to the study center at the University of Munich.

Statistical Analyses

All returned questionnaires were collected centrally at the University of Munich and data was entered into an electronic database. Study data was analyzed using SPSS® software (version 16.0) and the Microsoft Office® package (Excel database). Pre-defined subgroup analysis was performed by grouping the results of

each question with regard to the professional site of the responding physician (university hospital vs. community hospital vs. private practice) and to the number of patients treated in their institution by year (<5 patients vs. 11–30 patients vs. >30 patients).

Results

Participants in the Survey

From the 1,130 questionnaires that were sent out, 181 questionnaires (16%) concerning the onclogical part of the survey were completed and returned. The main responders were medical oncologists (35.4%), surgeons (30.4%) and gastroenterologists (15.5%). Further, 14.9% of the returned questionnaires were answered by interdisciplinary teams of physicians. Most of the participating physicians came from community hospitals (49.7%), followed by university hospitals (27.6%) and physicians in private practice (19.9%).

Of the responders, 9.9% stated that they treat fewer than 5 PC patients each year, 33.1% see 11–20, 19.3% see 21–30, 12.7% see 31–40, 6.6% see 41–50 and 17.7% treat more than 50 PC patients per year at their institution.

Diagnosis of PC

For the establishment of PC diagnosis, 60.8% of the responding physicians state that a histological confirmation is necessary. For 37.0%, an elevation of the tumor marker CA 19-9 plus a tumor in the pancreas (on imaging, e.g. CT or MRI) is sufficient for the diagnosis of PC. Most of the centers use a CT or ultrasound-guided method (80.7%) for tumor biopsy and histological assessment of the specimen; a further 54.1% also use endosonograpy techniques for needle biopsies of the primary tumor in the pancreas.

Resectable PC and Adjuvant Treatment

Only 1 doctor (0.6%) would not recommend a radical surgical resection for a patient with resectable PC; 29.3% would recommend a pylorus-preserving operation technique and 41.4% a classical Whipple procedure. For the remaining 25.4%, both procedures seem suitable as standard treatment for a patient with resectable disease.

Of the centers in this survey, 2.8% always perform a neoadjuvant treatment in each patient with resectable disease, whilst 30.4% never perform neoadjuvant treatments. Another 43.1% of physicians are treating their patients with neoadjuvant therapy only within clinical trials, for 17.7% the decision is individual in each case. If the centers decided to proceed to neoadjuvant therapy, most of them (57.7%) apply neoadjuvant chemoradiotherapy, 36.5% would prefer neoadjuvant chemotherapy alone.

Table 1. Adjuvant therapy after curative-intent resection of PC (n = 181)

Treatment decision	R0 resection	R1 resection[1]
No adjuvant therapy	27 (14.9%)	5 (2.8%)
Gemcitabine	129 (71.3%)	112 (61.9%)
5-FU/FA (Mayo regimen)	0 (0%)	0 (0%)
Chemoradiotherapy	4 (2.2%)	25 (13.8%)
Other treatment	20 (11.0%)	10 (5.5%)

[1] The remaining 27 physicians (14.9%) selected multiple answers.

Table 2. Palliative chemotherapy in patients with metastatic PC (n = 181)

Treatment decision	Good performance status (KPS 90–100%)	Poor performance status (KPS ≤80%)
Single-agent gemcitabine	50 (27.6%)	123 (68.0%)
Single-agent 5-FU	1 (0.6%)	3 (1.7%)
Single-agent capecitabine	1 (0.6%)	1 (0.6%)
Gemcitabine + capecitabine	6 (3.3%)	12 (6.6%)
Gemcitabine + erlotinib	21 (11.6%)	8 (4.4%)
Gemcitabine + oxaliplatin	28 (15.5%)	1 (0.6%)
Gemcitabine + cisplatin	15 (8.3%)	0 (0%)
Other treatment	49 (27.1%)[1]	17 (9.4%)[1]

[1] The remaining physicians (10 and 16, respectively) selected none of the above answers.
KPS = Karnofsky performance status.

The survey results for treatment decisions in the adjuvant setting are summarized in table 1.

Advanced PC

Locally Advanced Disease. In patients with locally advanced PC (unresectable, but without distant metastasis), 2.8% of the participating colleagues would recommend no antitumor treatment at all. For 51.9%, chemotherapy is the local standard of care in this patient population, 16.6% prefer a combined chemoradiotherapy. Ten doctors (5.5%) would treat their patients sequentially, 3 with radiotherapy followed by chemotherapy and 7 with chemotherapy followed by radiotherapy. No participant selected the term 'radiotherapy only'.

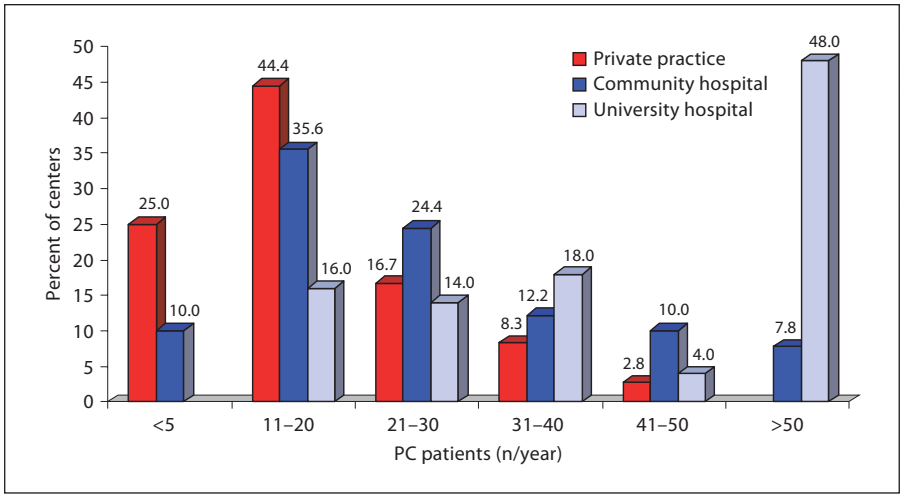

Fig. 1. Distribution of frequency of treating PC patients, by type of professional site.

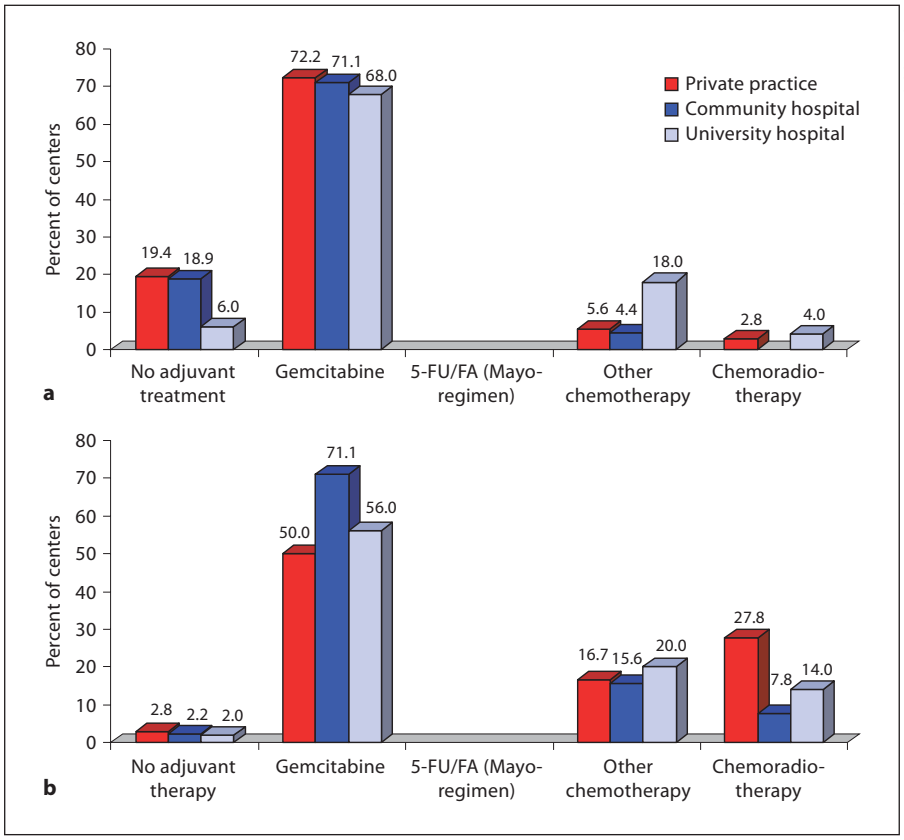

Fig. 2. Adjuvant treatment after curative-intent surgery for resectable PC, by professional site. **a** R0 resection. **b** R1 resection.

Metastatic Disease and Palliative First-Line Chemotherapy. In patients with metastatic PC, 23.2% of the responding doctors always treat their patients with a monochemotherapy regimen. 6.1% always apply combination therapy regimens, whilst a further 59.1% offer a combination treatment only to patients with a good performance status. The remaining centers selected the answer option 'other treatment'. The question when to start chemotherapy in this patient population was answered with 'after first diagnosis of metastatic PC' by 86.2%, and with 'if the patient shows clinical symptoms' by 7.7%.

The survey results for treatment decisions in the metastatic setting (subgroups based on performance status) are summarized in table 2.

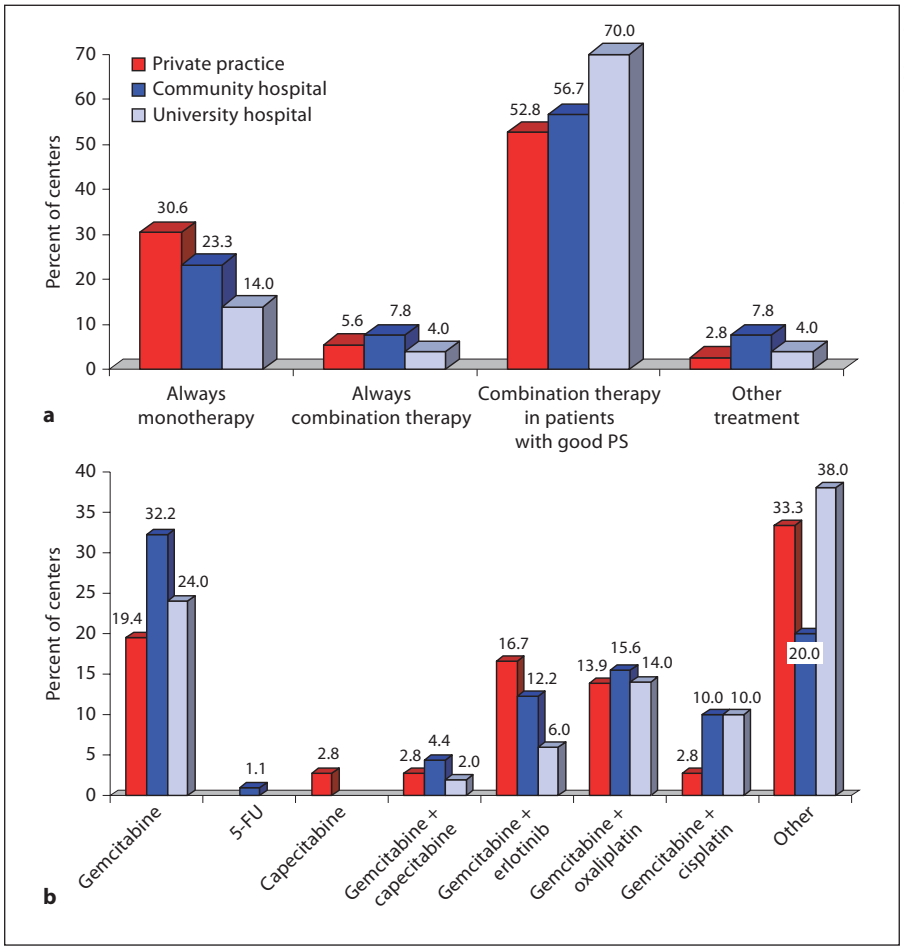

Fig. 3. Palliative treatment of PC patients with distant metastasis, by professional site. **a** Monotherapy vs. combination therapy. **b** Treatment regimens in patients with good performance status.

Concerning the duration of palliative chemotherapy in metastatic PC, 66.9% stated that they treat their patients until tumor progression, whereas 13.3% continue chemotherapy only until the control of tumor-related symptoms. Another 8.8% offer their patients a pre-defined number of treatment cycles.

Second-Line Chemotherapy. Only 2 responding centers (1.1%) always refuse to apply second-line treatment after failure of first-line chemotherapy. For most of the doctors (65.2%) second-line treatment is an individual decision based on the performance status of the patient; 27.6% offer second-line therapy to the majority of their patients. Regimens used in the second-line setting are single-agent 5-FU (8.3%), single-agent capecitabine (14.9%) or 5-FU/FA + oxaliplatin (34.8%).

Follow-Up

Imaging. For 6.6% of the participating centers, a clinical follow-up after curative-intent surgery for PC is not a local standard of care. The remaining centers offer their patients follow-up imaging investigations, mainly ultrasound (every 3 months, 31.5%) and CT scan (every 3 months, 16.6%). A smaller number of colleagues perform follow-up imaging with a prolonged time interval (4.4% ultrasound every 6 months, 12.2% CT scan every 6 months).

Serum Tumor Marker. Most of the responding centers also apply tumor markers (e.g. CA 19-9 or CEA) in the follow-up of patients after PC resection: 85.1% regularly measure tumor markers after surgery, only 9.4% do not use tumor marker monitoring at all.

Subgroup Analyses

Influence of the Professional Site of the Responding Physician on Treatment Decisions. In PC treatment, large-volume centers (>50 patients per year) are mainly located at German university hospitals (fig. 1). Most of the medical practices treat about 5–20 patients each year. The survey results for treatment decision in the adjuvant setting

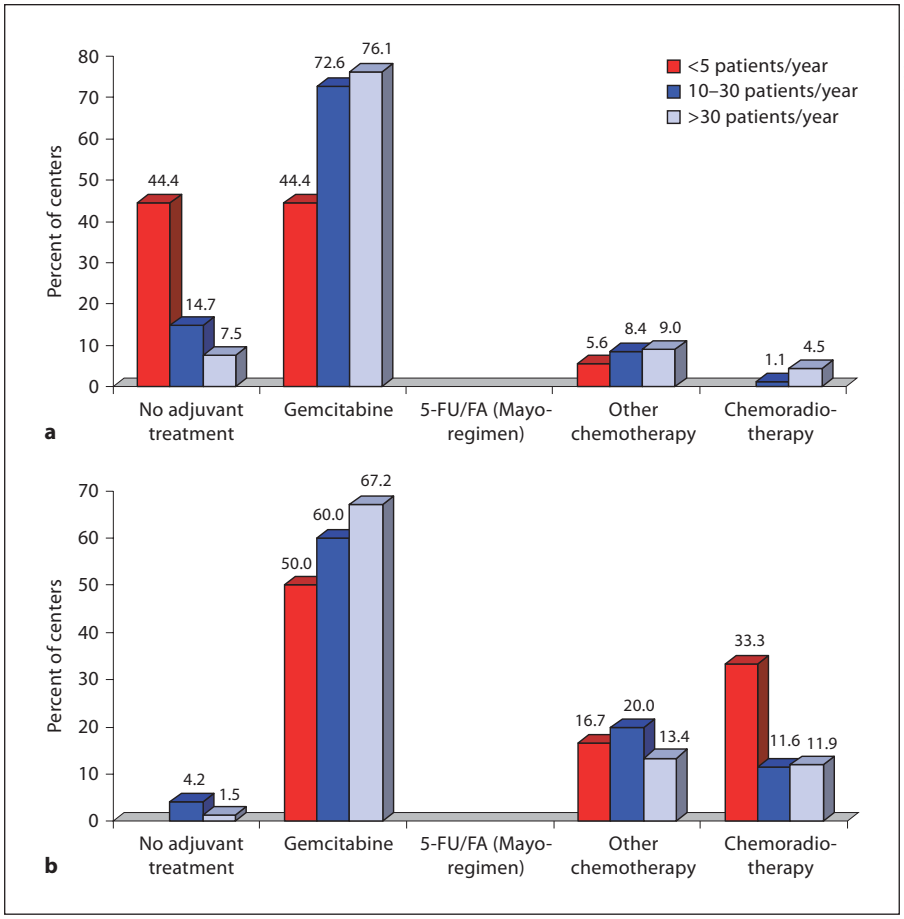

Fig. 4. Adjuvant treatment after curative-intent surgery for resectable PC, by number of patients (pts)/year. **a** R0 resection. **b** R1 resection.

(after R0 and R1 resections), subgrouped by professional sites, are summarized in figure 2. Figure 3 shows the local treatment standards of the participating centers for PC patients with metastatic disease by professional sites (fig. 3a) and the treatment regimens in patients with good performance status (fig. 3b).

Influence of the Number of Patients Treated at an Institution (by Year) on Treatment Decisions. As outlined in figure 4, the number of patients treated per year at an institution seems to have a significant impact on treatment decisions for adjuvant therapy. Centers with fewer than 5 patients/year more frequently recommend no adjuvant treatment after R0 tumor resection (fig. 4a), and they seem to prefer adjuvant chemoradiotherapy after R1 resection (fig. 4b). In patients with metastatic disease, the frequency of single-agent therapy is higher in low-volume centers (fig. 5a). Figure 5b summarizes the treatment regimens offered to patients with metastatic disease and a good performance status, divided into subgroups by number of patients treated per year.

Discussion

The progress in the treatment of patients with PC during the last 10 years has been steady but slow. However, several new treatment options are available now for PC patients, including an improvement in surgical techniques, the use of newer chemotherapeutic agents (gemcitabine) in the adjuvant and palliative setting and recently the new oral anti-EGFR tyrosine kinase inhibitor erlotinib has been approved in the EU for the treatment of patients with metastatic disease [2, 3]. Nevertheless, it still remains unclear how many PC patients in Germany actually do have access to treatment protocols according to the current S3 guidelines published in 2007 [3].

For this AIO/CAO national survey, 181 German centers (university hospitals, community hospitals and medical practices) returned a completed questionnaire on their local standards for PC diagnosis and treatment. For 37% of the participants, a histological confirmation of the diagnosis of a suspected (advanced) adenocarcinoma of

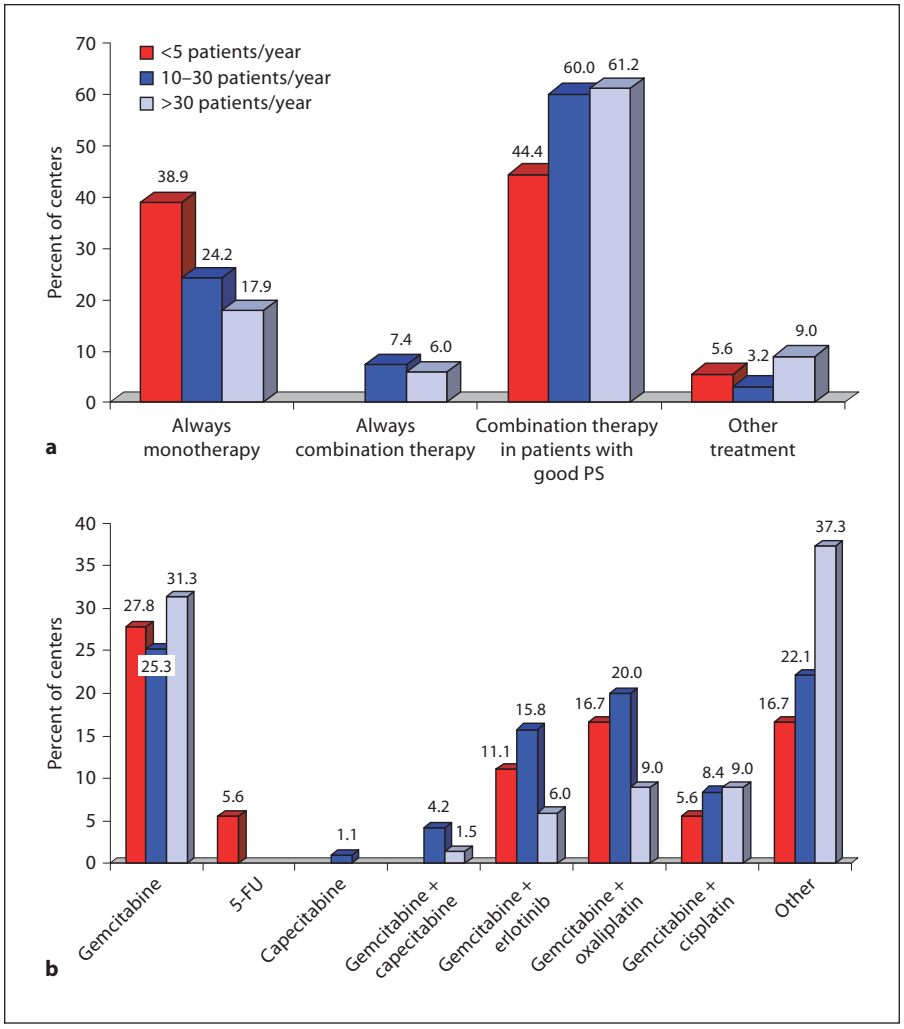

Fig. 5. Palliative treatment of PC patients with distant metastasis, by number of patients (pts)/year. **a** Monotherapy vs. combination therapy. **b** Treatment regimens in patients with good performance status.

the pancreas was not regarded as necessary. These physicians treat their patients based on imaging (e.g. CT scan) and laboratory (e.g. CA 19-9 elevation) findings. This approach is contrary to the recommendation of the S3 guideline and contains a significant risk of treating patients with, for example, an endocrine tumor of the pancreas with ineffective gemcitabine chemotherapy [3]. The serum tumor marker CA 19-9 has no diagnostic utility in PC, and several confounders may lead to a false-positive elevation of CA 19-9 levels [22]. Also in the neoadjuvant setting, a significant proportion (21%) of German oncological centers treat their patients without an evidence-based rationale for this therapy. To date, no scientific evidence exists that a neoadjuvant treatment (chemotherapy and chemoradiotherapy) provides a survival benefit for patients with (potentially) resectable disease [20]. Phase II data showed the feasibility of such an approach, but randomized studies are still lacking and thus neoadjuvant therapy should currently have no place – outside controlled clinical trials – in daily clinical practice [21].

Significant progress in the treatment of resectable PC was the introduction of adjuvant chemotherapy as a new standard of care [20]. Two large European randomized phase III trials recently showed that adjuvant chemotherapy may provide a statistically significant (and clinically meaningful) benefit for disease-free and overall survival in PC [15–17]. Interestingly, in Germany, the vast majority of centers already offers their patients adjuvant gemcitabine chemotherapy (according to the CONKO-001 trial [16, 17]), and nearly no doctors recommend adjuvant chemotherapy according to the 'Mayo regimen' (bolus 5-FU plus folinic acid, ESPAC-1 study [15]) to their PC pa-

tients (table 1). However, from a scientific point of view, an evidence-based recommendation for the preferred chemotherapy regimen will not be possible until the results of the ESPAC-3 study (gemcitabine vs. 5-FU/FA) become available. It is noteworthy that there are still centers not offering adjuvant therapies at all (about 18%), and after R1 resection about 14% of the survey centers recommend chemoradiotherapy as their treatment of choice [18, 19].

For palliative treatment of advanced disease, single-agent gemcitabine is still regarded as a standard of care, especially in patients with a poor performance status (table 2). The combination of gemcitabine plus erlotinib (approved in Germany in January 2007) was selected as their treatment of choice by only 12% (for patients with good performance status) and 4% (for patients with poor performance status) of the survey doctors. Perhaps this low selection rate for gemcitabine plus erlotinib was also influenced by the fact that our survey was initiated in February 2007, a time point when erlotinib had just received regulatory approval in Germany. The combination of gemcitabine with a platinum compound (e.g. cisplatin or oxaliplatin) is mainly restricted to patients with a good performance status (table 2). However, such a treatment decision is only based on post-hoc subgroup analyses from randomized phase III trials that suggest a survival benefit for combination chemotherapy in good performance status patients [23]. Prospective trials for an evidence-based recommendation of this treatment decision are lacking. Second-line therapy was not regarded as an international standard of care for all patients with PC at the time this survey was conducted [24]. This is also reflected by the survey results, with most doctors regarding salvage chemotherapy as an individual treatment decision. A randomized study, presented as an abstract at the ASCO meeting in 2008, was the first to provide preliminary evidence for a survival benefit with the use of second-line therapy after failure of first-line gemcitabine [25].

The role of follow-up investigations after curative-intent surgery is discussed controversially for different types of malignant tumors. In Germany, most centers offer their patients regular follow-up investigations after PC surgery, with imaging and also tumor marker monitoring [26–28]. To date, it remains unclear if a survival benefit could be obtained for PC patients with the use of such (expensive) follow-up methods. The pre-defined subgroup analyses of this national AIO/CAO survey (fig. 1–5) suggest that treatment decisions are influenced by both the number of patients treated in an institution per year and by the professional site of the responding physician. However, these results should rather be regarded hypothesis-generating than definitive. The main limitations for interpretation of the data derived from this national multicenter survey arise from the fact that an unexpectedly low number of questionnaires were returned (16%) and that there may be a possible selection bias with the invitation to members of the AIO and CAO. Thus, when interpreting the presented data, one should be aware of these possible confounders, which also apply to the above named subgroup analyses from this survey.

In conclusion, this national AIO/CAO survey provides evidence that there is still room for an improvement in the treatment of patients with PC in Germany. The current S3 guidelines are not applied in each hospital/practice in Germany, and a combined effort of each participant in the public health system seems necessary to offer each of our patients the current international standard of care for his/her disease.

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