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The relevance of pathological verification in suspected pancreatic cancer

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ABSTRACT

Objectives: This population-based study assessed which factors were associated with pathological verification of pancreatic cancer.
Methods: All patients diagnosed with a malignancy of the pancreas between 1993 and 2010 in the South of the Netherlands ($N = 3321$) were included.
Results: Pancreatic cancer was pathologically verified in 59% of patients. The proportion of verification increased over time from 56% in 1993–1996 to 69% in 2009–2010 ($p < 0.0001$). High rates of verification were found among young patients (<50 years vs. 60–69 yrs: adjusted odds ratio (OR_{adj}) 3.2 (95% CI: 1.9–5.4)), patients with a high socioeconomic status (high vs. low: OR_{adj} 1.3 (95% CI: 1.1–1.7)), patients with metastatic disease (metastatic vs locoregional: OR_{adj} 3.2 (95% CI: 2.7–3.8)) and patients treated with chemotherapy (yes vs. no: OR_{adj} 2.4 (95% CI: 1.8–3.2)). The most favorable prognosis was found in patients with verified locoregional disease (median overall survival (mOS) 7.6 months, 95% CI: 7.1–8.6). Patients with unverified metastatic disease carried the worst prognosis (mOS 1.7 months, 95% CI: 1.4–2.0).
Conclusion: Verification by pathology remains preferable and desirable whenever possible. However, the median survival rate exhibited by patients without verification suggests that the vast majority of patients suffered from true invasive pancreatic cancer. This may justify treatment decisions even in the absence of pathologic verification in selected patients.

1. Introduction

According to the current guidelines, suspected malignancies of the pancreas should be pathologically confirmed whenever possible. For patients with a resectable pancreatic tumor a preoperative biopsy is not always necessary as pathological verification will automatically follow after resection. For patients with locally advanced or metastatic pancreatic cancer, the guidelines recommend fine needle aspiration [1,2].

Obtaining tissue to establish diagnosis can be notoriously difficult in patients with suspected pancreatic cancer. It often requires invasive investigations, such as ultrasound guided punctures. These procedures are more complicated in patients with a poor performance status. A German survey revealed that not all physicians treated their patients according to the international recommendations. Of the respondents only 61% agreed with the guideline and stated that pathological verification is mandatory. In addition, for 37% of the respondents an elevation of the tumor

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marker CA19-9 plus a tumor in the pancreas on imaging was sufficient for the diagnosis [3].

In the EUROCARE-4 study, a study that collected data from 93 European cancer registries between 1995 and 2002 a microscopic verification of 63% (range 30–91%) was found for pancreatic cancer [4].

Although patients without pathological verification constitute a significant proportion of the patients with pancreatic cancer, no previous studies described this group of patients in detail. Therefore we assessed which factors were associated with pathological verification, and the clinical relevance.

2. Methods

2.1. Data collection

For the present study we used data from the Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Centre Netherlands. The registry collects data on all patients newly diagnosed with cancer in the southern part of the Netherlands. The area comprises about 2.4 million inhabitants (~15% of the Dutch population) and encompasses ten community hospitals, two radiotherapy institutions and six pathology departments.

In case of histological or cytological verification of a tumor the ECR is notified by the national automated pathological archive PALGA. If this verification is lacking, notification occurs by additional sources as the national registry of hospital discharge (LMR), multidisciplinary team reports and diagnosis–therapy combinations (specific codes used for reimbursement purposes). Completeness is estimated to be at least 95% [5].

Our study included all patients who were diagnosed with a neoplasm of the pancreas (International classification of Disease for Oncology (ICD-O), second edition, topography code 157 and third edition, code C25), between 1 January 1993 and 31 December 2010. Trained registrars, operating on behalf of the ECR, extracted patient characteristics such as gender, date of birth, comorbidity and socioeconomic status, as well as tumor characteristics, such as date of diagnosis, anatomic location, histology, stage, and primary treatment from the medical records.

Tumors were categorized as verified whenever there was histological or cytological verification from the primary tumor or one of the metastatic sites. There was no additional information on the timing of verification.

Carcinomas were classified according to the Tumor Lymph Node Metastasis (TNM) classification and staged following the recommendations of the International Union against Cancer in the respective period. For staging of other neoplasms especially those without pathological verification the clinical extent of disease (cEOD) was used. From a practical perspective we classified the tumors as locoregional (confined to the pancreas with or without extension to the surrounding organs) or metastatic disease.

Vital status of all patients on 1st of January 2014 was assessed through linkage with civil municipal registries and the Central bureau for genealogy, which collects data on all citizens who die.

2.2. Statistical analyses

We performed all statistical analyses using SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA). The percentage of cases for which the diagnosis was based upon pathological verification was described for different subgroups. Differences between those groups were tested by means of a χ^2 test and trends across the five periods (1993–1996, 1997–2000, 2001–2004, 2005–2008 and 2009–2010) were analyzed by means of a Cochran–Armitage trend test. Independent influences on the rate of pathological verification were evaluated by means of a logistic regression analysis.

Survival time was defined as the time from diagnosis to death or 1 January 2014, for patients who were still alive. The median follow-up time (from initial diagnosis to 1 January 2014) of patients alive ($N = 134$) was 64 months (range 37–250 months). The crude survival was calculated with the life test and differences between survival curves were evaluated by means of a log rank test. The independent prognostic effect of pathological verification was estimated using Cox regression analyses, the hazard rates for death were adjusted for gender, age, socioeconomic status, comorbidity, extend of disease and period of diagnosis. Surgery and chemotherapy were added separately to the model to investigate the effect of treatment on the hazard ratio of death.

3. Results

Between January 1, 1993 and December 31, 2010, a total of 3321 patients were diagnosed with a neoplasm of the pancreas in the southern part of the Netherlands. The median age at time of diagnosis was 70 years (range 29–100). Fifty-two percent of the patients were male and 49% of the patients presented with metastatic disease. Table 1 displays the general characteristics by the presence of pathological verification and disease extension (locoregional or metastatic disease).

In 1960 patients (59%) the diagnosis was confirmed by pathological examination. In 83% of the cases pathological verification was achieved by histopathology, in the remaining patients cytological sampling was used. The percentage of verification increased over time from 56% in 1993–1996 to 69% in 2009–2010 ($p < 0.0001$). Fig. 1 shows that pathological verification was obtained more often in patients with metastatic disease compared to patients with non-metastatic disease. In patients with non-metastatic disease the verification rate increased significantly over time, from 45% in the first period to 57% in the last period ($p < 0.0001$) and in patients with metastatic pancreatic cancer the verification rate remained stable between 74% and 77% ($p = 0.10$).

The results of the logistic regression analysis are shown in Table 2. Younger patients and patients with a higher socioeconomic status were more likely to have their diagnosis confirmed by cytology or histology. After adding the treatment variables surgery and chemotherapy to the model these differences persisted. In contrast, differences between the periods of diagnosis disappeared after adding surgery and chemotherapy to the model. Overtime the resection rate in patients with non-metastatic pancreatic cancer increased from 11% in 1993–1996 to 24% in 2009–2010 ($p < 0.0001$). The prescription of chemotherapy increased from 6% to 27% ($p < 0.0001$). In patients with non-metastatic disease, tumors located in the tail were more often pathologically verified (tail 71%, head 45%). In metastatic disease, high verification rates were found, especially if metastases were limited to the peritoneum (90%) or to extra regional lymph nodes (85%). Low rates of verification were found in patients with pulmonary metastases only (50%). In 73% of the patients with histologically verified metastatic disease, tissue was obtained from one of the metastatic sites. In the remaining patients tissue was sampled from the primary tumor.

Adenocarcinoma was the histological subtype found in 90% of the pathologically verified cases, another 3% was represented by large cell carcinomas. Tumors of neuroendocrine origin accounted for 4% of the verified cases.

The median overall survival for all patients was 3.5 months with a 2-year survival rate of 7%. Fig. 2 shows the crude survival curves for patients with and without pathologically verified pancreatic cancer, stratified according to disease extension (locoregional or metastatic disease). Patients with pathologically verified locoregional disease had the most favorable prognosis with a median survival of 7.6 months and a 2-year survival rate of 18%. Patients