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ABSTRACT

Background: Pancreatic cancer carries a poor prognosis. To date, there has been little research devoted to decision-making regarding treatment options in pancreatic cancer, including the rationale for choosing to withhold tumor targeting treatment (TTT). This study aims to gain insight into the characteristics of patients receiving no TTT, the reasons for this decision and their survival.

Methods: All patients diagnosed in the Netherlands between 1 January 2014 and 30 June 2015 with a proven pancreatic adenocarcinoma or a pathologically unverified pancreatic tumor were identified in the Netherlands Cancer Registry. Information on initial management, patient characteristics, main reasons for no TTT (as reported in medical charts) and survival were analyzed.

Results: A total of 3090 patients was included. Of these patients, 1818 (59%) received no TTT. Median age of no TTT patients was 74 years (range 35–99) versus 66 years (30–87) for TTT patients. In the no TTT group 77% had a clinical stage III/IV versus 57% of patients who received TTT. Main reasons for not starting TTT were patient's choice (27%) and extensive disease (21%). Median survival of patients who did not receive TTT was 1.9 months, ranging from a median survival of 0.8 months (when main reason to withhold TTT was short life expectancy) to 4.4 months (main reason to withhold TTT: old age). In the latter group, a relatively large proportion of clinical stage I tumors was present (37%).

Conclusion: The majority of patients with pancreatic cancer received no TTT and had a very poor median survival. In most patients, patient's choice not to start treatment was the main reason for withholding treatment, suggesting patient's involvement in decision-making.

Introduction

Pancreatic cancer carries a poor prognosis regardless of stage, with a median survival ranging from three months when untreated up to 28 months in case of surgical resection followed by adjuvant chemotherapy [1,2]. The majority of patients are diagnosed with non-resectable locally advanced or metastatic disease. For patients with these advanced stages, unfortunately, just few therapeutic options are available.

Since most cases of pancreatic cancer are diagnosed in the absence of curative treatment options, management primarily focuses on improving survival and quality of life by slowing disease progression and relieving symptom burden. In these cases, the main management options are best supportive care or chemotherapy with palliative intent. For years no substantial progress was made in chemotherapeutic treatment of advanced pancreatic cancer. Since 2011, however, new chemotherapeutic regimens have emerged. The FOLFIRINOX regimen is currently the most effective with an increase in overall survival from 6.8–11 months, compared to gemcitabine [3].

However, this treatment is mainly suitable for younger (<76 years) and relatively fit patients, due to its toxicity. Pancreatic cancer however disproportionately affects elderly individuals; the mean age at diagnosis is 70 years and almost 40% of patients are diagnosed after age 75 years [4]. A recent study that involved more elderly patients (42% ≥65 years and 10% ≥75 years) showed that the addition of nab-paclitaxel to gemcitabine among patients with metastatic pancreatic cancer improved overall survival from 6.6–8.7 months [5]. For patients with advanced pancreatic cancer who are not eligible for an intensive first-line combination chemotherapy regimen, chemotherapeutic treatment with gemcitabine alone may be an option. Despite its very limited response rate (6–11%) [6,7] and marginal survival benefit (5.6 versus 4.4 months in fluorouracil-treated patients), gemcitabine was approved as first-line regimen because of significant improvement in pain, performance status or weight [8]. Overall, the survival benefit of chemotherapeutic regimens for advanced pancreatic cancer unfortunately remains limited.

Clearly, given the limited benefit of therapies, treatment decision-making in pancreatic cancer can be challenging [9].

An ultimate decision regarding treatment for pancreatic cancer could be to withhold tumor targeting treatment (TTT) and to decide for best supportive care only.

In order to decide which treatment plan is appropriate for a patient, it is of utmost importance to weigh patients preferences and clinical circumstances such as life expectancy, potential side effects and potential positive effects of treatment on quality and quantity of life. That decision-making is not a straightforward process and is supported by the influence of individual preferences and experiences of physicians on treatment considerations [10] and inter-hospital variation in the prescription of palliative chemotherapy [11]. Moreover, patients with pancreatic cancer may perceive barriers in the shared decision-making process, such as different clinical opinions of medical experts, a feeling of pressure to accept treatment and a sense that there are no other treatment options [12].

Since most studies focus on tumor targeting treatments for pancreatic cancer, there has been little research devoted to the treatment decision-making process in pancreatic cancer, including the considerations and rationale for choosing to withhold TTT. There is some information available; however, these studies focus on subgroups such as octogenarians [13], patients with early stage [14] or advanced stage disease [15,16]. One Danish population-based study is available, which reports different baseline characteristics of treated and untreated patients with pancreatic cancer (unselected cohort) in the pre-FOLFIRINOX era [17]. In order to better understand the decision-making process regarding treatment for all patients with pancreatic cancer, population-based research can be of additive value. Therefore, this study aims to gain insight into the characteristics of patients not receiving TTT as initial management compared to those receiving TTT, the reasons for this decision and their survival.

Methods

Data collection

Data of all patients diagnosed with pancreatic cancer between 1 January 2014 and 30 June 2015 ($n = 3424$) were obtained from the Netherlands Cancer Registry (NCR). This nationwide registry collects data on all patients newly diagnosed with cancer in the Netherlands and covers nearly 17 million inhabitants. Primary source of notification of the NCR is the automated nationwide pathological archive (PALGA), supplemented by additional sources, such as the national registry of hospital discharge, multidisciplinary team reports and diagnosis therapy combinations (specific codes for reimbursement purposes). Required information on diagnosis, initial treatment, patient- and tumor characteristics are routinely extracted after notification in all hospitals in the Netherlands, by trained registration administrators operating on behalf of the NCR.

Patient selection

For the present study we selected patients diagnosed with a proven adenocarcinoma of the pancreas, a not otherwise specified carcinoma of the pancreas (ICD-O morphology codes 8010, 8012, 8020, 8140, 8141, 8144, 8260, 8310, 8440, 8480, 8481, 8490, 8500and 8560) [18] or a non-microscopic verified neoplasm of the pancreas between 1 January 2014 and 30 June 2015.

Measures

Clinical data were obtained from the NCR and include stage, pathological verification, tumor localization, date of diagnosis, vital status, use of multidisciplinary team consultation and initial treatment received. The number of comorbid conditions, including previous malignancies, was assessed in a subsample of the NCR: the area of the previous Eindhoven Cancer Registry (ECR). Tumors were classified according to the Tumor Lymph Node Metastases (TNM) classification. In the present study, the TNM classification seventh edition was used [19]. Information on vital status of patients was obtained through linkage with civil municipal registries and the central bureau for genealogy, which collects data on all deceased Dutch citizens. Follow-up of vital status was calculated as the time from the date of diagnosis to the date of death or to 1 February 2017. In patients with a proven carcinoma, date of diagnosis was based on the first date of cytological or histological confirmation. For patients with a non-microscopic verified neoplasm of the pancreas, the date of first inpatient or outpatient presentation was used as day 0. The same definition was used for no TTT and TTT patients. Survival was calculated based on all-cause mortality.

Reported initial treatments were classified as either tumor targeting therapy or best supportive care. Tumor targeting therapies included chemotherapy, both palliative and adjuvant, surgical tumor resection and other treatments aimed at primary tumor reduction or destruction, such as radiotherapy, radiofrequency ablation or irreversible electroporation. Best supportive care comprised interventions aimed at symptom burden instead of tumor reduction, including biliary stenting or bypass, enteral stenting or gastroenterostomy, and palliative radiotherapy on bone metastases. Cases with no or incomplete information available on first-line treatment were excluded (not yet completed at time of patient selection).

The main reason for withholding tumor targeting treatment was extracted from the medical records by the trained administrators, allowing them to choose one of nine predefined options: comorbidity, functional status, social context, old age, short life expectancy, patient refusal, extensive disease, other and unknown. Since 'social context' was used only once, this category was recoded into 'other'. Furthermore, additional notes in the registry were screened to identify incomplete information on treatment and main reason for withholding tumor targeting treatment.

In order to ensure the reliability and representativeness of the main reason for withholding tumor targeting treatment, an experienced researcher (NR) and medical oncologist in training (MZ) conducted a sample in one hospital by performing a medical chart review of 26 evaluable cases. In 85% of the cases, the opinion of the researcher and medical

oncologist in training was similar to the opinion of the trained administrator.

Socio-demographic data of the patients were also obtained from the NCR. Socio-demographic variables included age at diagnosis, gender and socio-economic status (SES). SES was based on four-digit postal code of the residence area of the patient, combining aggregated individual fiscal data on the economic value of the home and household incomes and was categorized into low, medium or high [20].

Statistical analyses

Descriptive analyses were used to analyze patient and tumor characteristics, initial treatment characteristics and main reasons for no TTT (as reported in medical charts). Characteristics of patients receiving no TTT or TTT were compared using t-test (continuous variables) and Chi²-test (categorical variables). Two-sided p values of $<.01$ were considered statistically significant. Median survival was calculated and survival curves were constructed by the Kaplan-Meier method, followed by a log rank test. Statistical analyses were performed with STATA Statistical Software (release 14.1, StataCorp, College Station, TX).

Results

Between 1 January 2014 and 30 June 2015, 3424 patients were diagnosed with pancreatic cancer in the Netherlands, of whom 3314 were diagnosed with a proven adenocarcinoma, a not otherwise specified carcinoma or a non-microscopic verified neoplasm of the pancreas. Two hundred twenty-four

(7%) patients were excluded from analysis because no or incomplete information on initial treatment was available, resulting in 3090 selected patients for analysis.

Patient characteristics

The median age at diagnosis was 70 years (range 30–99 years), 51% were male and 56% had metastases at time of diagnosis (Table 1). One thousand eight hundred eighteen patients (59%) received no TTT and 41% received TTT ($n = 1272$), 40% of whom underwent surgical resection, 56% received chemotherapy with palliative intent and 4% received other treatments aimed at primary tumor reduction or destruction. Median age of patients receiving no TTT was 74 years (range 35–99 years) versus 66 years (range 30–87 years) for patients who received TTT ($p < .001$). In the no TTT group, 77% had a clinical stage III/IV, whereas this was the case in 57% of patients who received TTT ($p < .001$). Overall, socioeconomic status differed between the no TTT group in comparison to the TTT group, respectively. Thirty two versus 27% had a low SES ($p = .002$). More patients who did not receive TTT had at least two comorbid conditions compared to the patients who received TTT (52 versus 35%, $p = .002$).

Reasons for deciding to start best supportive care

In 84% of patients, the reason for not starting TTT was recorded. Main reasons for not starting TTT were patient's choice to withhold treatment (27%) and extensive disease (21%; Table 2). Patients who chose to withhold treatment had mainly stage IV disease (65%), median age was 72 years and SES was equally distributed among low (29%), middle

Table 1. Distribution of individual characteristics of patients with pancreatic cancer in the Netherlands across initial treatment decisions ($n = 3090$).

Characteristics	All patients $n = 3090$	No tumor targeting treatment $n = 1818$	Tumor targeting treatment $n = 1272$	p value
Age, median (range)	70 (30–99)	74 (35–99)	66 (30–87)	.000
Sex, n (%)				.024
Male	1584 (51%)	901 (50%)	683 (54%)	
Female	1506 (49%)	917 (50%)	589 (46%)	
Tumor location, n (%)				
Head	1697 (55%)	973 (54%)	724 (57%)	.062
Corpus	390 (13%)	237 (13%)	153 (12%)	.406
Tail	541 (18%)	331 (18%)	210 (17%)	.222
Other/unknown	462 (15%)	277 (15%)	185 (15%)	.595
Pathological verification, n (%)	2320 (75%)	1105 (61%)	1215 (96%)	.000
Socioeconomic status, n (%)				.008
Low	928 (30%)	584 (32%)	343 (27%)	
Medium	1235 (40%)	710 (39%)	525 (41%)	
High	927 (30%)	524 (29%)	404 (32%)	
Multidisciplinary team consultation, n (%)	2062 (67%)	1012 (56%)	1050 (83%)	.000
Surgical exploration not followed by resection, n (%)	230 (7.4%)	127 (7.0%)	103 (8.1%)	.247
Clinical stage, n (%)				
I	381 (12%)	166 (9.1%)	215 (17%)	.000
II	407 (13%)	179 (9.8%)	228 (18%)	.000
III	382 (12%)	206 (11%)	176 (14%)	.037
IV	1744 (56%)	1191 (66%)	553 (43%)	.000
Unknown	176 (5.7%)	76 (4.2%)	100 (7.9%)	.000
Number of comorbid conditions[a]	$n = 454$	$n = 273$	$n = 181$	.002
0	69 (15%)	35 (13%)	34 (19%)	
1	111 (24%)	65 (24%)	46 (25%)	
2 or more	205 (45%)	141 (52%)	64 (35%)	
Unknown	69 (15%)	32 (12%)	37 (20%)	

[a]The number of comorbid conditions was assessed in a subsample of the Netherlands Cancer Registry (NCR): the area of the previous Eindhoven Cancer Registry (ECR).

Table 2. Characteristics of patients with pancreatic cancer in the Netherlands receiving no tumor targeting treatment ($n = 1818$) according to reasons for this decision.

	Patient's choice	Extensive disease	Functional status	Short life expectancy	Comorbidity	Old age	Other	Unknown
	$n = 492$ (27%)	$n = 381$ (21%)	$n = 280$ (15%)	$n = 105$ (5.8%)	$n = 60$ (3.3%)	$n = 41$ (2.3%)	$n = 162$ (8.9%)	$n = 297$ (16%)
Age, median (range)	72 (40–96)	74 (38–99)	74 (39–94)	71 (41–91)	77 (52–91)	86 (77–92)	74 (45 –94)	77 (35–98)
Socioeconomic status								
Low	29%	31%	37%	25%	37%	37%	29%	36%
Medium	41%	41%	36%	46%	45%	24%	43%	33%
High	30%	28%	27%	29%	18%	39%	28%	30%
MDT consultation	64%	50%	54%	48%	52%	37%	61%	55%
Clinical stage								
I	9.6%	1.1%	13%	1.0%	20%	37%	8.0%	13%
II	8.7%	5.5%	7.9%	10%	18%	15%	10%	16%
III	13%	14%	6.4%	4.8%	8.3%	9.8%	9.9%	14%
IV	65%	78%	67%	84%	42%	29%	70%	49%
Unknown	3.7%	1.3%	5.7%	0%	12%	9.8%	1.2%	8.1%

MDT: multidisciplinary team.
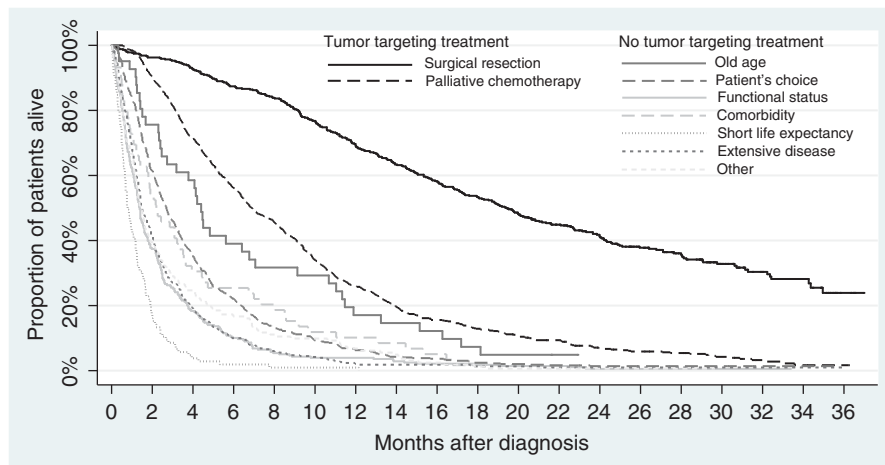
Figure 1. Overall survival of patients with pancreatic cancer, subdivided by tumor targeting treatment versus no tumor targeting treatment and reasons to withhold treatment.

(41%) and high (30%) scores. In 8.9% of patients, "other than the predefined reasons' was indicated. Additional notes in the registry showed that in these cases, the following other reasons were mainly reported: more than one reason applicable, early or premature death which made it impossible to have started initial treatment at all and the physician's assessment that treatment had no or too little benefit on quality and quantity of life. In patients with old age as main reason to withhold TTT ($n = 41$, 2.3%, median age 86, range 77–92 years), 37% of the patients had a clinical stage I tumor, compared with 1–20% in patients with other reasons for no TTT. These patients were less often discussed in a multidisciplinary team consultation, 37 versus 56% in patients with other reasons for no TTT ($p = .013$).

Survival of patients with pancreatic cancer

Median survival of patients who received no TTT was 1.9 months, ranging from a median survival of 0.8 months (when the main reason to withhold TTT was short life expectancy) to 4.4 months (main reason to withhold TTT: old age; Figure 1). In the TTT group, median overall survival was 10.6 months. Patients who underwent surgical resection had a median survival of 19.4 months; patients treated with palliative chemotherapy had a median survival of 6.9 months (all stages). Survival curves of patients receiving TTT or no TTT

for different reasons differed significantly ($p < .001$). The superior median survival of patients who received TTT was similar in both younger and older patients; 10.2 months in patients up to 70 years and 11 months in patients in patients aged 70 years and above ($p = .533$) versus 1.8 and 2 months, respectively in patients who received no TTT (although survival curves of patients with no TTT appeared similar, they differed significantly, $p = .006$; Figure 2). This was also observed in a subgroup analysis among only stage IV patients (data not shown).

Discussion

This population-based study among 3090 patients with pancreatic adenocarcinoma or a pathologically unverified pancreatic tumor in the Netherlands showed that the majority (59%) of patients received no tumor targeting treatment, whereas 41% received tumor targeting treatment. The most prevalent reasons for choosing no TTT were patient's choice to withhold treatment and extensive disease. Median survival of patients who received no TTT was very poor, 1.9 versus 10.6 months in patients receiving TTT.

Little information is known regarding the tumor targeting treatment rate in the pancreatic cancer population. Population-based data from Ireland from 1994 to 2003 showed that 80% of patients received no TTT. During the
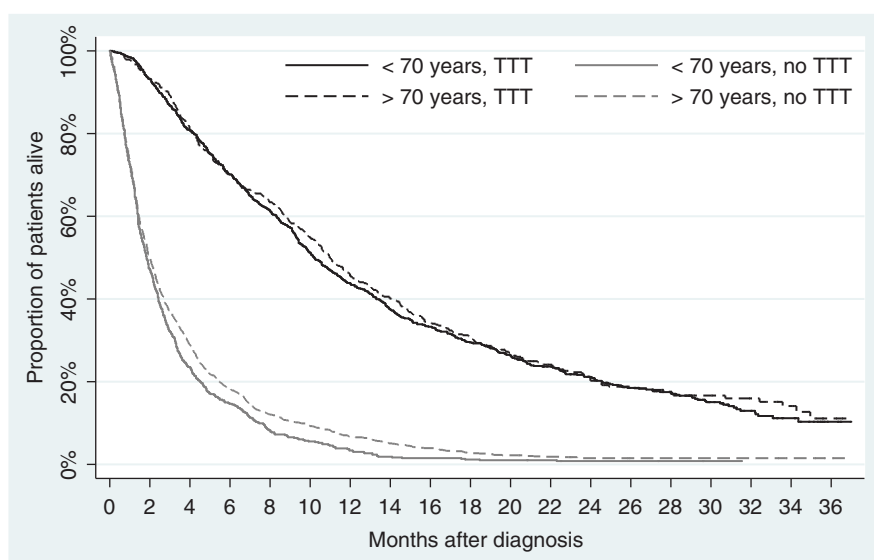
Figure 2. Overall survival of patients with pancreatic cancer, subdivided by tumor targeting treatment versus no tumor targeting treatment and age.

course of this time period, the proportion of patients receiving no TTT decreased considerably [21]. A more recent Danish population-based study from 2007 to 2009 showed that 56% of the patients with pancreatic cancer did not receive TTT, which is similar to our data [17]. However, US data from 2008 to 2012 based on three large integrated claim databases showed an even lower proportion of patients with pancreatic cancer receiving no treatment (35–55%) [22]. This may be an underestimation of the proportion of untreated patients as claim databases only reflect the insured (cancer) population or could be related to cultural differences when it comes to deciding not to treat the tumor. The reported median overall survival of patients with pancreatic cancer who did not receive TTT in our study was 1.9 months, slightly longer than population-based data from Denmark (1.1 months) [17]. In comparison, the median survival of selected patients from the first randomized trials that received best supportive care only was 2–4 months [23–25].

Our analyses demonstrated various reasons for withholding tumor targeting treatment. Patient's choice was the most prevalent reason (27%). Although older age appears to increase the preference for a more passive role in the decision-making process [26], our results are in line with the previously reported percentage of octogenarians who chose to withhold treatment (29%) [13]. The fact that a large proportion of patients decided to withhold treatment could indicate that they play a role in the decision-making process. The value of shared decision-making is widely embraced as it is considered essential for appropriate care and may have a beneficial impact on quality of life [27]. Results of a German qualitative interview study demonstrate that the involvement of patients in the decision-making process may even increase further during the course of their illness, due to increasing experience with the disease and treatment [28]. However, overall the involvement of patients in the decision-making process remains limited [29,30].

Some previous studies, assessing different pancreatic cancer populations (non-metastatic pancreatic cancer, stage I pancreatic adenocarcinoma and advanced pancreatic cancer),

have also investigated reasons and predictors for withholding tumor targeting treatment. Reasons to withhold treatment found in these studies are similar to the reasons demonstrated in our study and include comorbidity [14], unfavorable prognosis [31], limited survival gain [31] and old age [14,32]. However, since these studies focus on subgroups of patients with pancreatic cancer, comparison with our results is difficult.

Furthermore, SES may play a role in the decision-making process, as our data suggest that patients with a higher SES may be more likely to receive tumor targeting treatment, which is consistent with several prior studies [11,33]. Patients with a higher SES are more likely to prefer an active role in the decision-making process [26] and moreover, a lower SES is associated with a higher prevalence of comorbidity [34], which may be a reason for withholding TTT. However, assessment of SES is challenging. In our study SES has been based on the four-digit postal code of the residence area of the patient, combining aggregated individual fiscal data on the economic value of the home and household incomes. This is a widely used method, although it is a rather crude proxy of SES and should be interpreted with care. In line, our results showed that patients who received no TTT, more often had two or more comorbid conditions.

In patients with old age as main reason to withhold tumor targeting treatment (2.3%), survival was relatively favorable compared to patients for whom other main reasons to withhold tumor targeting treatment were identified. A rather large proportion of low stage tumors in this group most likely explains this. Furthermore, among this group, a large proportion concerned a pathologically unverified tumor (76%), what may have led to longer survival due to misclassification [35]. In addition, older patients receiving tumor targeting treatment seem to have similar survival benefit as younger patients. This supports current international guidelines in which the general consensus states that, advanced age per se should not be a contraindication for any treatment modality in pancreatic cancer [36]. It remains interesting however, that age has been indicated as the main reason

to withhold tumor targeting treatment, especially in light of ageism. Nevertheless, one can imagine that there is some restraint regarding the treatment of older patients due to their increased frailty. Furthermore, evidence-based data regarding treatments of these older patients are scarce, due to under-representation of older adults in cancer registration trials.

Although there is a general trend towards more aggressive cancer care near the end of life [37], there appears to be restraint regarding tumor targeting treatment in pancreatic cancer. This may be related to the pessimistic attitude of both doctors and patients towards diagnosis and prognosis. The awareness of the extremely poor prognosis is high among clinicians [38] and this awareness of the often palliative nature of the diagnosis is also reflected in the fact that patients with pancreatic cancer have a higher probability to be admitted to specialized palliative care units, compared to other cancer diagnoses, regardless of symptom burden [39].

Strengths and limitations

An important strength of the current study is that we included a large nationwide population-based sample of pancreatic cancer patients. At this population-based level we were able to investigate characteristics of patients receiving no tumor targeting treatment and reasons for this decision, providing valuable information to improve insight into the decision-making process.

A limitation of our analysis may lie in the assessment of the reason to withhold treatment. First, this assessment may be susceptible to interpretation due to interrelatedness of several reasons to start or withhold treatment. However, the item was registered by experienced and trained administrators and subject to strict quality control. Furthermore, the performed medical chart review of a sample in one hospital suggests that it is a reliable measure. The 15% differences in reasons for withholding treatment was mainly related to interrelatedness of reasons, such as short life expectancy and extensive disease. Finally, in our database, only one main reason to withhold TTT was registered, while in real life often a combination of various reasons may play a role in the decision-making process. Moreover, medical records often contain a limited reflection (from a doctors perspective only) of what is actually considered and discussed in consulting rooms or multidisciplinary team consultations. In addition, information regarding certain clinical parameters that may be valuable in the decision-making process is missing, such as performance status, surgical resectability and partly, comorbidity.

The proportion of patients not receiving TTT in particular could be underestimated in the NCR, since among unregistered patients pathological confirmation is lower and survival is significantly poorer, as was demonstrated in a recent Dutch study [40]. It is plausible that in these patients it was decided to abstain from pathological confirmation and TTT, because of poor clinical condition or poor prognosis.

Practical implications

Our results show that there is restraint regarding tumor targeting treatment of pancreatic cancer, a decision that may be understandable when in view of quality of life, disadvantages of treatment may outweigh its benefits. Our study, however, is not focused on the quality of life of patients who do not receive tumor targeting treatment versus patients who receive tumor targeting treatment. Assessing quality of life by using patient reported outcome measures (PROMs) is seen as an increasingly important aspect in determining appropriate oncological care [41]. Hence, PROMs are now recorded in three comprehensive nationwide cohorts of pancreatic, esophageal/gastric and colorectal cancer patients in the Netherlands [42]. Our study provides scope for future research into quality of life to further improve decision-making processes regarding treatment of patients with pancreatic cancer.

Conclusion

The majority of patients with pancreatic cancer received no TTT and had a very poor median survival. In most patients, patient's choice not to start treatment was the main documented reason for withholding treatment, suggesting patient's involvement in decision-making.

Disclosure statement

No potential conflict of interest was reported by the authors.

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