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Survival after surgical management of pancreatic adenocarcinoma: does curative and radical surgery truly exist?

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Abstract Surgery for pancreatic cancer offers a low success rate but it provides the only likelihood of cure. Modern series show that, in experienced hands, the standard Whipple procedure is associated with a 5-year survival of 10%–20%, with a perioperative mortality rate of less than 5%. Most patients, however, will develop recurrent disease within 2 years after curative treatment. This occurs, usually, either at the site of resection or in the liver. This suggests the presence of micrometastases at the time of operation. Negative lymph nodes are the strongest predictor for long-term survival. Other predictors for a favourable outcome are tumour size, radical surgery and a histopathologically well-differentiated tumour. Adjuvant therapy has, so far, shown only modest results, with 5FU chemotherapy, to date, the only proven agent able to increase survival. Nowadays, the choice of therapy should be based on histopathological assessment of the tumour. Knowledge of the molecular basis of pancreatic cancer has led to various discoveries concerning its character and type. Well-known examples of genetic mutations in adenocarcinoma of the pancreas are k-ras, p53, p16, DPC4. Use of molecular diagnostics and markers in the assessment of tumour biology may, in future, reveal important subtypes of this type of tumour and may possibly predict the response to adjuvant therapy. Defining the subtypes of pancreatic cancer will, hopefully, lead to target-specific, less toxic and finally more effective therapies. Long-term survival is observed in only a very small group of patients, contradicting the published actuarial survival rates of 10%–45%. Assessment of clinical benefit from surgery and adjuvant therapy should, therefore, not only be based on actuarial survival but also on progression-free survival, actual survival, median survival and quality of life (QOL) indicators. Survival in surgical series is usually calculated by actuarial methods. If there is no information on the total number of patients and the number of actual survivors, and no clear definition of the subset of patients, actuarial survival curves can prove to be misleading. Proper assessment of QOL after surgery and adjuvant therapy is of the utmost importance, as improvements in survival rates have, so far, proved to be disappointing.

Keywords Pancreatic cancer · Adenocarcinoma · Prognostic factors · Survival

Introduction

Adenocarcinoma of the pancreas remains a formidable therapeutic challenge. For the majority of patients this is a systemic disease. Surgical resection offers a low success rate but provides the only chance of cure. Allessandro Codivilla and, later, Walter Kausch, first described the technique of pancreatico-duodenectomy in 1898 and 1912, respectively. Allen Old Father Whipple later popularised the procedure that today bears his name [1, 2]. Since Whipple's time significant advances have been made in the surgical management of pancreatic cancer. In early series published in the late 1960s postoperative morbidity rates exceeding 60% and mortality rates approaching 25% were reported. Most recent series from institutions that specialise in treating pancreatic cancer report mortality rates of less than 5%, with morbidity remaining high at 30%–60%. The majority of perioperative complications are not life threatening, though they are responsible for increased length of hospital stay and cost, readmission for care, and delays in adjuvant therapy. Limited progress has been made at improving the survival of patients with this disease, despite the advances made in surgical technique and perioperative care. The 5-year survival rate is the lowest of all known types of cancer. Low rates of resectable tumours and early recurrence are the main problems facing a surgeon treating pancreatic cancer. The resectability rate for a total of 16,942 patients in the USA was only 13.3%, and 5-year survival was 4% [3].

The incidence of adenocarcinoma of the pancreas has been increasing world-wide in recent years, and it is currently the fourth leading cause of cancer-related mortality in North America [4]. In the Netherlands and in Germany the incidence ranges between nine and 19 patients per 100,000 inhabitants, making it the fourth leading cause of cancer-related death. At the time of diagnosis, more than 85% of tumours have extended beyond the organ's margin, and invasion of the perineural spaces within and beyond the pancreas is present [5–9].

Definitive curative resection is possible in no more than approximately 10% of all cases. The likelihood of a curative resection depends on both location and stage of the tumour. Localisation of the tumour near the papilla is correlated to early detection, due to the presence of obstructive jaundice.

The main challenge is to improve survival rates over the coming years. Since the beginning of the 20th century not much improvement in survival has been achieved, despite extensive trials into adjuvant and neoadjuvant therapy regimes. Improvement in survival has been reached mostly by better surgical skills and improvements in perioperative and postoperative care. Mortality of less than 5% should be achievable in high-volume centres.

An urgent need exists for better insight into both the genetics and the natural behaviour of pancreatic cancer. Molecular biology studies and molecular diagnostics might lead to more sensitive and specific treatment programmes and, hopefully, will improve survival for patients who are diagnosed with pancreatic cancer.

There is hope that, in the new millennium, a multidisciplinary and integrated approach to pancreatic adenocarcinoma will unravel the mystery of this malignancy, making it more amenable to early screening and therapy.

Surgical treatment

The ultimate goal of surgical management of pancreatic neoplasm is total cure. It is preferable that surgical treatment should remove all visible tumours and ensure low mortality and morbidity and short hospitalisation. Surgery ideally includes a radical (R0) resection and re-establishment of gastrointestinal continuity. Although surgical management of pancreatic cancer has so far enjoyed low success rates, it still provides the only hope of cure. Since the introduction of pancreatico-duodenectomy by Walter Kausch in 1912, significant advances have been made. Postoperative morbidity and mortality rates vary in various publications over the decades. Modern series show that, in experienced hands, the standard Whipple procedure is associated with a 5-year survival of 10%–30% in patients who have undergone complete resection, with a perioperative mortality rate of less than 5% [10–19]. This relatively low perioperative mortality rate represents a decline from over 15% in the 1970s, thus making the Whipple operation a much more attractive option. The most important factor in these falling mortality rates appears to be concentration of cases in so-called high-volume institutions. From the Medicare database, a fourfold increase in mortality is found when pancreatico-duodenectomy procedures are performed in hospitals with fewer than one case per year compared with those in hospitals handling more than 16 cases per year. A similar improvement in long-term outcome was noted [20, 21].

The prognosis for pancreatic cancer remains poor, even with surgically negative margins in appropriately selected patients. The most important prognostic factor in radical resections has been shown to be nodal status. Five-year survival after pancreatico-duodenectomy is only approximately 10% for node-positive disease, while it can be 25%–30% for node-negative disease. Other predictors of a favourable outcome include a tumour size of less than 3 cm, negative margins (R0 resections), well-differentiated tumours, and intraoperative blood loss of less than 750 ml [13, 14, 18, 22].

Contraindications for curative resection are the presence of distant metastases, peritoneal seeding, tumour infiltration into mesenteric and portal vessels, and extension of tumour tissue into the small bowel mesentery.

Modifications of the standard Whipple procedure have been developed in an attempt to improve outcome or

minimise the morbidity associated with the operation. Extensive experience has been gained, especially by Japanese centres with ultra-radical surgery. This type of resection includes excision of the portal vein, total or regional pancreatectomy, and extensive retroperitoneal lymphadenectomy. However, for this type of resection, several reports failed to demonstrate improved survival rates. A further problem associated with total pancreatectomy is the development of brittle diabetes [23]. Some groups in Japan routinely complement the Whipple operation with an extensive lymph node dissection (extended lymphadenectomy). The reason for this is that, peri-ampullary malignancies frequently metastasise to lymph nodes that are beyond the confines of the standard pancreatico-duodenectomy [7]. A single prospective trial comparing conventional pancreatico-duodenectomy with a more extended lymphadenectomy was conducted in 81 patients with a potentially curable adenocarcinoma of the pancreatic head [24]. While overall survival was found to be identical for both treatment groups, subgroup analysis indicated better survival rates in those patients with positive nodes who were undergoing extensive lymphadenectomy.

Yeo et al. demonstrated in their study [25] that radical pancreatico-duodenectomy, i.e. addition of a distal gastrectomy and extended retroperitoneal lymphadenectomy to a standard pancreatico-duodenectomy, can be performed with similar morbidity and mortality rates to those of the standard pancreatico-duodenectomy. This, however, could not be shown to benefit survival rates.

Pylorus-preserving pancreatico-duodenectomy (PPPD), a relatively less aggressive operation that preserves the pylorus, was studied in the 1980s. Shorter operation time, less blood loss and shorter hospital stay were found to be advantages, as compared with the standard pancreatico-duodenectomy [26]. The PPPD is increasingly being performed in the USA [27]. Three randomised trials have directly compared a pylorus-preserving operation to standard pancreatico-duodenectomy [28, 29]. The study from Seiler et al. [29] showed no differences in either tumour recurrence or survival rates after a short follow-up. In the small and under-powered study of Lin and Lin [28] no difference was noted in type of recurrence or long-term survival between the two groups.

Unpublished data from our own multi-centre randomised study, [30] which compared PPPD with standard Whipple procedure in 170 consecutive patients, showed a similar incidence of delayed gastric emptying. No significant differences in blood loss, duration of operation, hospital stay and postoperative weight loss could be found. Long-term survival and disease-free survival was also comparable. Thus, both procedures must be considered to be equally effective in the surgical management of pancreatic cancer.

The best predictors of survival after surgery are stage of disease, tumour grade, and resection margins. Nonetheless, even in those patients with potentially resectable disease, 5-year survival following pancreatico-duodenectomy is only approximately 25%–30% for node-negative tumours and 10% for node-positive ones [13, 31, 32].

Standardised surgical technique for the suturing of pancreatico-jejunostomies has led to a decrease in pancreatic fistulas, thus minimising local sepsis complications. The avoidance of the pancreatico-jejunostomy does not lead to fewer complications [33].

More than 95% of the patients undergoing surgical resection are in an advanced stage of cancer. In one-third of the patients undergoing an R0 resection, liver metastasis is the most frequent recurrent disease. Most patients who undergo a curative resection eventually develop recurrence; this usually occurs at the site of primary resection or in the liver. However, little is known about the precise pattern of recurrence of pancreatic carcinoma. From recently published series [34–38], it is known that the majority of patients who undergo macroscopically radical resection develops a tumour recurrence within 2 years of the operation. The most common sites of recurrence were the loco-regional areas, the liver and the peritoneal cavity. The recurrence occurs even more frequently in those with a microscopically irradical resection (R1).

More recent data suggest that outcomes may be improving over time. This is possibly related to the combined effect of an increase in the proportion of patients undergoing surgery at teaching hospitals, lower procedure-related mortality rates, a better selection of surgical candidates, and/or greater use of adjuvant chemotherapy and radiotherapy.

Nevertheless, these patients still have a relatively poor prognosis, and systemic chemotherapy, radiation or a combination of chemotherapy and radiation have all been used either prior to resection (neoadjuvant therapy) or following surgical resection (adjuvant therapy) in an effort to improve the cure rate achieved with surgery alone.

The eventual outcome of surgical treatment appears to be limited by the dissemination pattern of pancreatic cancer. All international classification systems of pancreatic cancer [International Union Against Cancer (UICC); American Joint Cancer Committee (AJCC); Japanese Pancreatic Society (JPS)] rely on tumour size, lymph nodes status, stage of infiltration and presence of distant metastases. Achieving an R0 resection is the prime goal of surgery; macroscopically free resection margins are associated with an increased chance of survival. Birk et al. [5] found that patients without lymph node metastases and a tumour size smaller than 2 cm without distant metastases have significant survival benefit after undergoing an R0 resection (Table 1) [39].

Preoperative staging remains unable to predict reliably the presence of lymph node involvement and the precise extent of this. Kayahara et al. [36] have shown that, even in cancer stages I and II there is extensive cancer cell

Table 1 Survival after radical resection (*R0*) of adenocarcinoma of the pancreas. *NYR* not yet reached, *Pancr* pancreatic *Ampul* (peri)ampullary

References	R0 (*n*)	1 Year (%)	2 Years (%)	3 Years (%)	5 Years (%)	7 Years (%)	Median (months)
[39] *n*=194	122	–	–	–	25.4	12.3	–
[89] *n*=140	81 (pancr)	77	10	–	–	–	21
	34 (ampul)	85	56	–	–	–	NYR
[17] *n*=526	423	69	–	–	23	–	19
[44] *n*=108	108 control arm	–	41	–	22	–	19
[43] *n*=443	443	73	–	37	–	–	21
[18] *n*=118	44	–	–	25	–	–	–

Table 2 Survival rates according to the JPS and UICC stage classification

Kobari 1998 [40]	Stage	3 Years (%)	5 Years (%)
n=1,689 JPS	I	66.2	48.1
	II	37.2	27.7
	III	25.4	22.3
	IV	12.7	8.8
n=1,521 UICC	I	44.3	32.5
	II	22.5	11.5
	III	16.3	12
	IV	9.6	6.6

infiltration in the surrounding tissue of the resected pancreas specimen (Table 2) [40]. Molecular biological methods, such as reverse transcriptase polymerase chain reaction and immunostaining, have given us deeper understanding of micrometastases. A better understanding of the underlying cancer cell dissemination pattern might explain the observed frequency of recurrence rates in patients undergoing a curative surgical resection.

This paper will seek to provide a review of adjuvant and neoadjuvant therapies for pancreatic exocrine cancer. Separately discussed issues are the surgical management of localised disease, treatment of locally advanced disease, and chemotherapy for advanced disease.

Adjuvant therapy

Survival after curative resection is limited for most patients due to the development of local or metastatic tumour recurrence. Several adjuvant regimens, designed to reduce these recurrences, have been evaluated in prospectively randomised trials.

In 1985, the Gastro Intestinal Tumour Study Group (GITSG) [41] studied the efficacy of combined external beam radiation (EBRT) and 5-fluorouracil (5FU). After surgery, patients were randomised to receive either 5FU-EBRT or no further treatment in the control group. Survival in the treatment arm of the study was significantly higher than in the control arm (20 months vs 11 months, *P*=0.03). The trial was terminated before it reached the original accrual goal, and only 43 patients were entered into the trial over a period of 8 years. Both the Norwegian Pancreatic Cancer Trial (NPCT) [42] and a report from Johns Hopkins University [43] supported the GITSG results. The only two large multi-centre randomised trials, the EORTC [44] and ESPAC-1 [32], however, also failed to show the survival benefit suggested by the smaller GITSG study.

In the EORTC study we were also not able to show significant survival benefit from 5FU-EBRT (24.5 months vs 19 months, *P*=0.208). After periampullary tumours had been excluded, median survival time for pancreatic head cancer demonstrated a trend towards better survival after treatment (12.6 months vs 17.1 months, *P*=0.099). The ESPAC-1 study showed a moderate, but nonetheless significant, survival benefit from chemotherapy alone (19.7 months vs 14 months, *P*=0.0005) and no benefit from the combination of 5FU and EBRT (15.5 months vs 16.1 months, *P*=0.24). This provided confirmation for our finding that 5FU-EBRT does not significantly improve survival time.

Treatment failure is found either as local or distant recurrence. In the EORTC study, recurrence patterns for the treatment and control group were very similar. Half of all primary recurrences were local; the other 50% of patients exhibited distant recurrences in addition to the local recurrence. Fifty percent of all progressions showed secondary metasteses in the liver. Beger et al. [45, Link et al. 46] and Lygidakis et al. [47] have published results of prospective trials that assess the effect of intra-arterial chemotherapy on local recurrence and liver metastases. Such chemotherapy has theoretical advantages, since it may increase the drug concentration in both the primary tumour and in the liver. It is believed that overall drug effectiveness is determined by the amount of lymphatic drainage and the absolute drug concentration. Lygidakis et al. [47] showed in their study an improved survival time for combined regional, SMA infusion, and chemoimmunotherapy (gemcitabine, carboplatin, mitomycin, 5FU, leucovorin, interleukin-2) (mean survival 31.07 months, SD 17.315, vs 18.83 months, SD=11.745).

Link et al. [46] achieved a median survival time of 21 months, 10 months more than in their retrospective control group (*P*=0.0003). At the present time a prospective randomised trial (ESPAC-2) is being conducted, to investigate further this promising treatment modality.

Neoadjuvant treatment has not been studied for primarily resectable pancreatic cancer but largely for non-resectable, locally advanced pancreatic cancer. Neoadjuvant therapy has several theoretical advantages. For resectable cancer it reduces the time interval between diagnosis and systemic treatment. The reason for this is that patients cannot be treated directly after surgery, due to wound healing and postoperative complications. Approximately 20% of patients who have undergone resection never undergo adjuvant therapy, because of postoperative problems [44]. Down staging might be able to turn unresectable tumours into resectable ones and make resection feasible in primarily unresectable cases. In patients with rapidly progressive disease a major surgical procedure might be avoided. Preoperative treatment may help to sterilise the tumour field, theoretically reducing the risk of tumour seeding during surgery. Devascularisation of the surgical field, thus minimising tissue oxygenation, is avoided, and this might improve efficacy of chemotherapy and radiotherapy. Several retrospective studies on this subject have been conducted, reporting a benefit in resectability and survival for those patients qualifying for resection [48–52]. This indicates that neoadjuvant therapy might be beneficial in selected patients with primarily unresectable tumours. This finding has not yet been confirmed in large phase III trials.

Current adjuvant therapy is relatively safe, although treatment-related deaths have been reported in several studies. Current chemotherapeutic treatment cannot prevent, but might delay, disease progression. The only adjuvant therapy that can be recommended on the basis of high-level evidence is 5FU chemotherapy [32, 44].

The adjuvant-therapy studies mentioned earlier, except for that by Lygidakis et al. [47], are all 5FU based. Several palliative studies comparing gemcitabine (GEM) with 5FU show better results for GEM [53], noting similar survival times and comparable tolerability but higher response rates and longer progression-free survival. Combinations of GEM (or 5FU) [54] with cisplatin (CIS) seem to be even more effective [55, 56]. Use of GEM–CIS combinations in a (neo-) adjuvant setting deserves further investigation [57].

Current choice of therapy is based on histopathological assessment of the tumour. The molecular basis of pancreatic adenocarcinoma has been studied over recent years and has uncovered various tumour subtypes. Several genetic mutations have been found in adenocarcinoma of the pancreas (K-ras, p53, p16, DPC4), and several hereditary patterns have been uncovered, constituting approximately 5%–10% of all cases [58, 59] (PRSS1, FAMM [60], STK11/LKB1, BRCA-2, HNPCC, Li-Fraumeni{p53}) [61]. Use of molecular diagnostics and markers in the assessment of tumour biology might be able to differentiate subtypes of this tumour in future. There is evidence that specific K-ras mutations (75%–90% are K-ras positive) influence survival [60, 61]. Response to chemoradiation might be influenced by p53 expression. Patients with p53 positive tumours exhibit shorter survival times after chemoradiation than those with p53 negative tumours do [62]. Defining the subtypes of pancreatic cancer in terms of tumour biology and response to treatment will make the choice of therapy more specific [62, 63].

Knowledge of the molecular basis of (pancreatic) cancer has also presented new targets for therapy. Current developments in specific anti-tumour agents are promising.

Imatinib mesylate (Gleevec, Novartis), a specific Bcr-Abl tyrosine kinase inhibitor (TKI), has yielded great results in CML and as a c-kit tyrosine kinase inhibitor in gastrointestinal stromal tumours (GISTs). Although not thought to be effective in pancreatic cancer [64], it shows great potential for target-specific therapy. An example of the consequences of these exciting developments for treatment of gastrointestinal tumours is the production of specific agents targeting the EGF-receptor [65], (tyrosine kinase inhibitors: erlotinib (Tarceva, Genentech/OSI/Roche) gefitinib (Iressa, AstraZeneca), monoclonal antibodies (cetuximab (Erbitux ImClone). These agents are currently under investigation in late-phase trials, hopefully leading to future use in pancreatic cancer treatments.

Recent discoveries have also been made with regard to cyclo-oxygenases (COX). These are key enzymes that mediate the production of prostaglandins from arachidonic acid. Two isoforms of these important enzymes, COX-1 and COX-2, have been described. Data from animal and human studies suggest an important role for COX-2 in gastrointestinal carcinogenesis [66]. Up-regulation of COX-2 has been observed in pancreatic adenocarcinoma [67]. This process is initiated by a number of growth factors and tumour promoters and has been implicated in cancer progression [68]. Furthermore, COX-2 also appears to have a role in the development of resistance to conventional cancer therapy. Increased resistance to apoptosis appear to be an especially important factor in this regard [69, 70]. Enhanced growth inhibition of pancreatic carcinoma cells by COX-2 inhibitors in combination with chemotherapy has also been described [71]. Selective COX-2 inhibitors, such as celecoxib (Celebrex, Pfizer), have recently been approved for the treatment of patients with rheumatoid arthritis and osteoarthritis, and these drugs can be used with minimal side effects. Currently, we are conducting a phase II trial to assess the role of these agents in pancreatic cancer.

In the field of immunotherapy other examples of tumour-specific approaches can be found. Current clinical trials [72] are investigating the induction of anti-tumour response by the body's own immune system by the use of cytokines and vaccines. Mechanistic approaches using targeted therapies, such as the examples mentioned earlier, might help us to find a more effective and less toxic therapy for pancreatic cancer [73]. Unfortunately, such a

Table 3 Randomised prospective trials of adjuvant therapy for pancreatic cancer. AMF: 5FU,doxorubicin,mitomycin; IART: intra-arterial chemotherapy; CHEM: GEM, carboplatin, mitomycin, 5FU; Immuno: CHEM+interleukin-2

References		Methods	Stage (UICC)	*N*	Groups		R0	R1	R0/ R1+0 (%)	*N*+ (%)	Median	Peri-ampullary
[41]	GITSG	5FU-RT	Resectable	43	21	Treatment	21		100	29	20	
					22	Control	22		100	27	11	
[42]	NPCT	AMF	I(22)II(1)III(7)	61	30	Treatment	30		100		23	14/61
			I(19)II(1)III(10)		31	Control	31		100		11	
[44]	EORTC	5FU-RT	T1-2, N0-1a, M0	218	110	Treatment	84	20	81	47/40[a]	24.5	93/114
			T1-3, N0-1a, M0 (peri-ampullary)		108	Control	76	25	75	54/39[a]	19	
[32]	ESPAC-1	5FU-RT	Resectable	541	175	5FU-RT	145	30	83	56	15.5	
					178	Control	146	32	82	55	16.1	
					238	5FU	193	45	81	51	19.7	
					235	Control	193	42	82	55	14.0	
[47]		IART	UICC III	128	40	Control	39	1	98	100	18.83	
					45	CHEM	43	2	96	100	25.02	
					43	CHEM-Immuno	42	1	98	100	31.07	

[a] Periampullary

revolution has, so far, not been witnessed in the treatment of pancreatic cancer.

Survival statistics and definition of endpoints in pancreatic cancer surgery

One must be cautious in drawing direct conclusions based on the survival values presented in most studies when reviewing the results of surgery and/or adjuvant therapy. It is important to be aware of the fact that selected patients for surgery and adjuvant therapy represent only a fraction of all pancreatic cancer cases. They cannot, therefore, be considered to be representative for the survival of the total patient group after first diagnosis for pancreatic cancer. Further long-term survival is observed in only a very small group of pancreatic cancer patients. This finding contradicts the published actuarial 5-year survival rates of 10%–45% among patients who have undergone resection. Gudjonsson did find, after correction for repetition, no more than 300–350 survivors after 65 years of performing resections [74]. He stated that the statistical method used is responsible for misleading survival results. In surgical science, survival is most commonly calculated with the Kaplan–Meier statistical method, instead of the actual method. The difference is that the actual method uses only proven survivors, without lost data, and, therefore, is unlikely to exaggerate results. There is, however, another approach to actuarial methods. This is to take the number of patients alive at the start of a particular period, minus the known deaths over that period. This value is then divided by the number of patients alive, and this value is then multiplied for each period or after each death. So long as there is no loss of patients to follow-up, no difference between the actual and actuarial method will be found. In daily practice, however, clinical trials will always have more or fewer losses to follow-up. Loss of data is completely ignored by the Kaplan–Meier method, the most frequently used method to calculate survival in surgical studies. Loss of data, in other words, censored cases, might influence survival dramatically if the actuarial Kaplan–Meier method is used; this has also been shown clearly by Gudjunsson (Table 3). Therefore, publication of only actuarial survival values should be considered as scientifically unacceptable without information on the total number of patients in the study group, the number of observed (actual) survivors, and a clear definition of the precise subset of patients followed after resection.

Besides actual survival time as an endpoint evaluation, the observed median survival and progression-free survival times have been introduced in surgical series as appropriate primary endpoints from which to measure treatment benefits. Indicators of response, in terms of clinical benefit, have been introduced in recent trials as an additional endpoint to evaluate the effect of chemotherapeutic agents. A combination of improvements in pain perception, performance status, and weight gain is used to objectify clinical benefit. Clinical benefit response, however, can underestimate the effects of chemotherapy because it does not include the assessment of other symptoms. Furthermore, it can overestimate the results of chemotherapy, the reason for this being that it does not properly assess the side effects [75, 76]. Therefore, quality of life (QOL) studies have been introduced in the latest adjuvant clinical trials.

Quality of life

PPPD is gaining acceptance as an appropriate procedure for various malignant and benign diseases of the pancreas and periampullary region [24, 25, 77–82]. As experience with pancreatico-duodenectomy grows, there is an increasing number of survivors who have recovered from the procedure and who live with the resulting altered upper gastrointestinal anatomy. These survivors have been only marginally studied in terms of their post-procedure QOL and as determined by parameters such as pain, stool habits, and activity levels, among other parameters [83–88]. Additional prospective studies incorporating both preoperative and serial postoperative QOL assessment are needed to investigate further the QOL after resection.

The rapidly progressive nature of pancreatic cancer causes deterioration of QOL over time, which leads to reduction of psychological, physical and social functioning. Thus "increased survival time" might, in reality, mean more months of survival with ever decreasing quality of life. This makes QOL a very important tool to measure the clinical benefit of the adjuvant and neoadjuvant treatment protocols.

In advanced pancreatic cancer QOL was found to be significantly greater in patients receiving chemotherapy than in those receiving best supportive care. QOL after resection of pancreatic cancer is mainly determined by the presence or absence of recurrent disease.

QOL assessment in pancreatic disease is currently still in the early stages of data retrieval and evaluation. Additional studies incorporating both preoperative and serial postoperative QOL assessment are needed. Study results are also needed to evaluate QOL in the various non-surgical management strategies. In trials of pancreatic cancer treatment, especially in series with multi-modality treatment, clinical response, as well as QOL measurements, are of utmost importance to evaluate the effect of the treatment given. The primary end points of trials should be actual survival times, median survival times and progression-free survival times.

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