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Status of 5-Year Survivors of the Whipple Procedure for Pancreatic Adenocarcinoma

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Keywords

• Pancreatic cancer • 5-year survivors • Whipple procedures
• Neoadjuvant therapy • Adjuvant therapy

Key points

- 5-year survival among pancreatic cancer patients remains dismal at less than 8%.
- Operative resection continues to offer the best chance for long-term survival, yet fewer than 30% of pancreatic cancer patients present early enough to be deemed resectable at diagnosis.
- Few patients are surgical candidates, and even their 5-year survival rate is only 15% to 20%.
- Factors associated with 5-year survival in multivariate analysis include tumor size, tumor grade, lymph node status (number of nodes and ratio), and negative resection margins.

INTRODUCTION

Incidence and Epidemiology of Disease

Despite advances in other solid tumor cancers, pancreatic cancer remains among the most lethal cancer in the United States, with a 5-year survival that is still less than 8% [1]. Although the incidence of other cancers appears to be decreasing, the incidence of pancreatic cancer appears to be on the rise, with an estimated 88,000 new cases annually. Furthermore, projections suggest it will be the second leading cause of cancer-related deaths by 2030 [2].

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BRIEF HISTORY OF TREATMENT MODALITIES AND EVOLUTION OF THERAPY

Surgical resection and perioperative mortality/morbidity

Operative resection continues to offer the best chance for long-term survival. Although expansion of multimodal therapy has improved survival in certain cohorts, fewer than 30% of pancreatic cancer patients present early enough to be deemed resectable at diagnosis, both because of the asymptomatic nature of early disease and lack of effective screening tests. Few patients are surgical candidates, yet even their 5-year survival rate is only 15% to 20% [3].

Pancreatic resection has evolved since its first appearance in the early twentieth century ,with advances in technique and perioperative care leading to improvements in perioperative morbidity and mortality (Fig. 1).

Substantial decreases in morbidity and mortality for the Whipple procedure (pancreaticoduodenectomy) began in the 1990s with perioperative mortality in the United States now estimated to be less than 5% [4]. Evidence-based efforts at standardization of perioperative care for Whipple patients contributed to centers of excellence [4–7], while improved understanding of the volume outcome relationship for the Whipple procedure [4–7] has led to relatively unanimous consensus that it should be restricted to high-volume centers [8]. Thus improvement in the perioperative mortality is multifactorial and likely because of the standardization of perioperative care, the development of tertiary care centers with multidisciplinary teams, and the increasing specialization of surgeons [9]. Combined, these efforts have led to the pancreaticoduodenectomy becoming the standard of care for all resectable pancreatic adenocarcinomas, with a mortality rate of less than 3% at high-volume centers [10].

Operative techniques for head of pancreas cancer include the standard pancreaticoduodenectomy (Whipple procedure) and pylorus-preserving pancreaticoduodenectomy. Extended retroperitoneal lymphadenectomy and superior

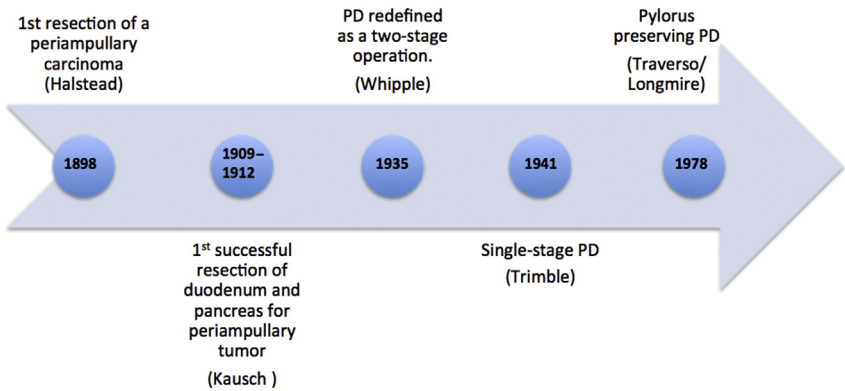

Fig. 1. Evolution of pancreaticoduodenectomy. PD, pancreaticoduodenectomy.

mesenteric vein and/or portal vein resection have recently been evaluated for maximal surgical clearance of disease, yet studies have not reliably confirmed their superiority [11–13].

Leach and colleagues [14] found no survival difference between those patients who require venous resection during pancreaticoduodenectomy for isolated tumor extension to the superior mesenteric vein (SMV) or superior mesenteric portal vein (SMPV) confluence and those who undergo standard pancreaticoduodenectomy.

The type of pancreatic anastomosis has also been examined, including pancreaticojejunostomy versus pancreaticogastrostomy, again without robust evidence supporting one over the other [15–18]. Several institutions have reported their results for laparoscopic or robotic pancreatic resection with comparable results to open resection [19–22]. However, widespread uptake of minimally invasive approaches has still not been achieved because of the complexity of the procedure and the lack of clear benefit.

Although the perioperative mortality for pancreaticoduodenectomy has dropped drastically in recent times, the morbidity rate remains between 30% and 50% [23,24]. Pancreatic fistula continues to be the most serious complication after pancreaticoduodenectomy and occurs in up to 20% of patients, while other major complications include delayed gastric emptying and hemorrhage [23]. A current study using ACS National Surgical Quality Improvement Program (ACS-NSQIP) data found that patients undergoing pancreatic resection are at high risk of complications, Parikh and colleagues [25] found 32% of all resected patients experienced at least 1 complication, and 21% of all complications were considered serious. Using ACS-NSQIP and the National Cancer Data Bank, Merkow and colleagues [26] similarly found that among stage I-III pancreatic adenocarcinoma patients who underwent resection, serious complications were associated with not receiving adjuvant therapy (odds ratio [OR] = 2.20, 95% confidence interval [CI]: 1.73–2.80) and also doubled the likelihood of delaying adjuvant treatment (OR = 2.08, 95% CI: 1.42–3.05). A retrospective institutional study by Ayoma and colleagues also demonstrated that the occurrence of postoperative complications was an independent risk factor for overall survival [27]. The authors anticipate that over the next 2 decades, gains in morbidity will start to mirror those made in mortality, as perioperative care evolves and tertiary care centers with multidisciplinary teams invest more in prevention and early recognition of complications following pancreatic resection.

Neoadjuvant and adjuvant therapy for resectable disease

Both preclinical and clinical data have demonstrated that pancreatic cancer is a systemic disease, and an operation alone will not be a successful strategy for eliminating microscopic disease. Therefore, practice guidelines universally recommend systemic therapy for all stages of pancreatic cancer. This article will limit its summary of therapies to resectable disease, as the focus of this article is on 5-year survivors of the Whipple procedure.

Key adjuvant trials in pancreatic cancer

The survival benefit of adjuvant therapy was established by 3 randomized controlled trials (GITSG [28], RTOG-9704 [29], and CONKO-001 [30]) (Table 1):

- The GITSG trial demonstrated that adjuvant 5-FU-based chemotherapy plus radiotherapy followed by 2 years of 5-FU had a 21-month survival versus 10 months with observation alone ($P = .03$; see Table 1).
- The RTOG-9704 trial compared gemcitabine with fluorouracil before and after fluorouracil-based chemoradiation. In an updated analysis of this trial, the treatment arms did not differ significantly.
- The CONKO-001 trial demonstrated an improvement in survival with 6 months of adjuvant gemcitabine chemotherapy versus observation after surgical resection (median 22.8 months vs 20.2 months; $P = .01$).

Addition of radiation to adjuvant chemotherapy is controversial since it has only demonstrated an improvement in local control, but not overall survival.

- ESPAC-1 trial: 289 patients were randomly (2X2) assigned after resection into 4 different arms: 1) chemoradiotherapy, 2) chemotherapy, 3) chemo-radiotherapy followed by chemotherapy, or 4) observation only
- Improvement in survival with adjuvant 5-FU chemotherapy (chemotherapy only and chemoradiotherapy plus chemotherapy groups combined) compared with the observation plus the chemoradiotherapy only groups (median 20.1 months vs 15.5 months; $P=.009$)
- The use of chemoradiation was detrimental according to this study (median survival of 15.9 months for all patients treated in the chemoradiotherapy groups vs 17.9 months in the observation and chemotherapy only groups combined; $P=.05$)
- Trial had limitations with respect to its design and variability in radiation delivery

Table 1
Survival benefit of adjuvant trials

Trial	Patients (N)	Control Arm	Experimental Arm	Median Survival (months)	*P*-value
GITSG (1985) [28]	43	Observation	5-FU plus XRT, followed by 5-FU maintenance therapy	11 vs 21	.03
RTOG-9704 [29]	551	XRT/5-FU + 5- Gemcitabine	XRT/5-FU + 5- Gemcitabine	20 vs 17	.09
CONKO-001 (2013) [30]	368	Observation	Gemcitabine	20.2 vs 22.8	.005
ESPAC-3 [31]	1088	5-FU	Gemcitabine	23 vs 24	.39
ESPAC-4 [32]	730	Gemcitabine	Gemcitabine + capecitabine	25.5 vs 28.0	.032

- Survival benefit associated with bolus 5-FU chemotherapy compared with observation in patients with resected pancreatic cancer

The median survival duration observed with 5-FU chemotherapy in the meta-analysis of the ESPAC-1 and ESPAC-3 data was similar to the median survival associated with gemcitabine treatment in the CONKO-001 study (median 23.2 months vs 22.8 months; see Table 1).

The combination of gemcitabine and capecitabine represents a potential new standard of care following resection for pancreatic ductal adenocarcinoma from the recent results of the ESPAC-4 trial.

NEOADJUVANT THERAPY IN PANCREATIC CANCER

Neoadjuvant therapy is becoming more common for many cancers as better treatments are developed. For cancers that require large operations associated with significant morbidity and mortality, neoadjuvant therapy is especially attractive. By administering neoadjuvant therapy, the biology of the disease can be better understood, and a potentially futile operation can be avoided [33]. Also, because of the significant morbidity of pancreatic resections, up to one-third of patients will not receive adjuvant therapy [33].

The longest-standing neoadjuvant treatment for patients with PDAC is chemoradiotherapy. Photon therapy with 50.4 Gy is utilized to potentially downsize cancers that are deemed borderline or locally advanced in an attempt to get patients to resection [34]. At MD Anderson, Katz and colleagues [35] reported a median overall survival of 23.9 months in 329 patients with PDAC, of whom 91% received neoadjuvant therapy. Neoadjuvant therapy consisted of chemoradiotherapy and isolated chemotherapy. External-beam radiotherapy usually consisted of 50.4 Gy in 28 fractions or 30 Gy in 10 fractions. Concomitant chemotherapy consisted of 5-fluorouracil, paclitaxel, gemcitabine, or capecitabine at radiosensitizing doses. Chemotherapy, in isolation, consisted of gemcitabine alone or in combination. They found that 27% of these patients survived a minimum of 5 years with a median survival of 11 years [35]. Currently Phase III trials comparing neoadjuvant chemotherapy and chemoradiation to upfront resection for resectable PDAC are underway.

Otherwise, the majority of the literature on neoadjuvant therapy consists of observational studies of patients with locally advanced disease [36–40]. A meta-analysis of the efficacy of neoadjuvant therapy (either chemo- or radiotherapy or both) analyzed 111 prospective studies encompassing 4394 patients. Results were notable for a median survival of 22.4 months in patients who underwent neoadjuvant therapy and resection versus 9.5 months for those who underwent therapy, but did not ultimately undergo resection [41].

Currently multiple neoadjuvant studies are underway in both the United States and Europe to assess the efficacy of neoadjuvant therapy utilizing FOLFIRINOX or gemcitabine/abraxane. Patients with metastatic disease demonstrated a significant overall survival advantage in phase III trials [42–44]. Because of the encouraging results in the metastatic setting, patients with locally

advanced and borderline resectable disease have also been treated with these regimens. At the Massachusetts General Hospital, 141 locally advanced and borderline resectable patients who received neoadjuvant FOFIRINOX followed by chemoradiation were compared with 110 upfront resectable patients who received no neoadjuvant therapy [45]. Although the operations were longer and the blood loss higher in the neoadjuvant group, the morbidity and mortality were not significantly different between the 2 cohorts. Furthermore, the patients who received neoadjuvant therapy had a higher R0 resection rate and a significantly lower rate of lymph node positivity and perineural invasion, despite being diagnosed at a more advanced stage. The median overall survival of the neoadjuvant group was 37.7 months, which was significantly longer than the 25.1 months for the upfront resectable patients [45].

Improved understanding of and experience with neoadjuvant therapy may help to improve the risk stratification of patients with PDAC, with the goal of optimizing the therapeutic regimen for patients.

FIVE-YEAR SURVIVORS – A SUMMARY OF CURRENT EVIDENCE

Early studies failed to demonstrate any survivors 5 years after Whipple [46,47].

Over the last 30 years, long-term survival following an operation has improved, yet remains dismal; median survival ranges from 13 to 27 months, and 5-year survival ranges from 4% to 27% following resection (Table 2). As highlighted previously, the advent of multimodal therapy, advances in preoperative staging, and the importance of an R0 resection have evolved over this same time period, limiting the application of older studies to the current era of treatment for pancreatic cancer.

INDEPENDENT PREDICTORS OF 5-YEAR SURVIVAL

Patient Factors

Patients undergoing the Whipple procedure for pancreatic adenocarcinoma today are older and have more preoperative comorbidities compared with patients 30 years ago. A population-based study using Surveillance, Epidemiology, and End Results (SEER) Medicare data identified 2461 patients with resected pancreatic adenocarcinoma from 1991 to 2005 and found that the mean age of patients undergoing an operation increased over time (for 1991–1996, mean age 72.1 years vs for 2003–2005, mean age 74.0 years; $P<.001$). Furthermore, only 10.4% (n = 59) of patients undergoing a pancreatic operation from 1991 to 1996 had at least 3 preoperative medical comorbidities, compared with 26.0% (n = 222) of patients undergoing an operation between 2003 and 2005 ($P<.001$) [60]. Despite this trend, most 5-year survival studies have not identified patient factors associated with increased survival. Winter and colleagues identified chronic obstructive pulmonary disease (COPD) as the only patient factor negatively associated with survival on multivariate analysis (hazard ratio [HR]: 2.0, $P=.006$), but this has not been reproduced in other studies. The presence of extensive comorbidities or increased patient age has not correlated with decreased long-term survival following the Whipple

Table 2
Studies examining 5-year survivors of pancreatic adenocarcinoma

Study	Period	Patients	Median Survival (months)	5-year Survival Rate (%)	Univariate Factors Associated with Survival	Multivariate Factors Associated with Survival
Conlon et al, [48] 1996	1983–1989	118	14.3	10.2	• N/A	• N/A
Ahmad et al, [49] 2001	1990–1998	116	16.0	19.0	• No lymph node involvement • Adjuvant chemoradiotherapy	• Adjuvant chemoradi-otherapy
Cleary et al, [50] 2004	1988–1996	123	13.6	14.6	• Tumor size • No jaundice at presentation • No lymph node involvement • Tumor grade • AJCC stage	• AJCC stage • Tumor grade
Winter et al, [10] 2006	1970–2006	1175	18.0	18.0	• No history of DM • No history of COPD • Age <65 y • No blood transfusions • Tumor diameter <3 cm • No lymph node involvement • Negative margins • Well/moderately differentiated tumor • No postoperative pneumonia • No postoperative sepsis • No postoperative bile leak • Adjuvant therapy	• Tumor diameter <3 cm • No lymph node involvement • Negative margins • Well/moderately differentiated tumor • No COPD • No postoperative bile leak • Adjuvant therapy

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Table 2
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Study	Period	Patients	Median Survival (months)	5-year Survival Rate (%)	Univariate Factors Associated with Survival	Multivariate Factors Associated with Survival
Han et al, [51] 2006	1985–1999	123	14.8	12.1	• No lymph node involvement • AJCC stage	• AJCC stage • Resection margin
Howard et al, [52] 2006	1990–2002	226	13.0	4.0	• Age • Tumor size • Tumor differentiation • Negative margin	• Tumor size • Tumor differentiation • Negative margin • No postoperative complications
Cameron et al, [53] 2006	1969–2003	405*	33.0*	18.0	• Not applicable (N/A)	• N/A
Ferrone et al, [54] 2008	1983–2001	618	-	12.1	• N/A	• AJCC stage • Negative margin
Schnelldorfer et al, [55] 2008	1981–2001	357	17	17.4	• Tumor diameter • No lymph node involvement • Number of positive nodes • Preoperative serum albumin • Perioperative blood transfusion	• No lymph node involvement
Katz et al, [35] 2009	1990–2002	329	23.9	27.0%	• Negative margins • No lymph node involvement • No prior attempt at resection	• No lymph node involvement • No prior attempt at resection
Robinson et al, [56] 2012	2002–2009	134	N/A	18.6	• No lymph node involvement • Metastatic to resected lymph node ratio	• Metastatic to lymph node ratio (>15%) • Presence of perineural invasion

Kimura et al, [57] 2014	1988–2008	147	14.4	12.2	• <2 LN metastases • Preoperative serum CA 19-9 < 40 U/mL • No intrapancreatic nerve invasion • R0 resection	• <2 LN metastases • preoperative serum CA19-9 < 40 U/mL • R0 resection
Yamamoto et al, [58] 2015	2000–2008	96	27.1	34.5 (A)	• UICC stage • Preoperative CA19-9 $\leq$ 200 U/mL • Preoperative DUPAN-2 $\leq$ 180 U/mL • Tumor size $\leq$20 mm • R0 resection • No lymph node involvement • No extrapancreatic neural invasion • Absence of portal invasion	• Tumor size $\leq$20 mm • Negative surgical margins
Lovecek et al, [59] 2016	2000–2011	90	16.9	18.9	• Absence of perineural invasion • Vascular invasion • Stage • No lymph node involvement • No need for transfusion	• Vascular invasion • Postoperative complications

Data from refs. [10,35,48–54,56–59].

procedure. This may be secondary to selection bias inherent in choosing surgical candidates, as these patients may not have been deemed surgical candidates because of their disease profile or overall functional status.

Tumor pathology (tumor size and tumor grade)

Early studies identified tumor size as a prognostic factor for long-term survival after resection of pancreatic cancer [10,50,51,61]. Small tumors (<2 cm) were found to have improved 5-year survival rate (20%–41%) and median survival time (23–38 months) compared with large tumors, which had a 5-year survival rate of 1% to 20% and median survival time of 10 to 17 months [61]. On a multivariate analysis of factors associated with long-term survival of pancreatic adenocarcinoma patients, Han and colleagues [51] identified tumor-related variables including tumor size (HR 5 1.38, P 5 0.03) and tumor differentiation (HR 5 0.76, P 5 0.02) as covariates affecting long-term survival. A study by the Mayo Clinic examined the histopathological and survival characteristics of small (≤2 cm) pancreatic cancers compared with large pancreatic cancers and found that among patients with localized disease (stages I and II), survival was similar regardless of tumor size. However, survival was significantly better in small pancreatic cancers with regional nodal metastasis (stage III) compared with similar stage large pancreatic cancers (5-year survival 44 vs 7%, median survival 58 vs18 months, $P<.001$). Well-differentiated small and large tumors had similar median survivals (76 vs 74 months, p=NS). In multivariate analysis, tumor differentiation, not tumor size, was the only independent factor predicting survival (risk ratio [RR] for moderate vs well-differentiated: 2.6,95% confidence interval [CI] 1.5–4.5, and RR for poorly differentiated vs well-differentiated: 5.0, 95% CI 2.4–10.1) [62]. After neoadjuvant FOLFIRINOX and chemoradiation, Michelakos and colleagues [45] identified resected PDAC tumors greater than 2.5 cm as an independent predictor of decreased overall survival.

Lymph node status

An increasing body of evidence demonstrates the association between lymph node status and long-term survival in resected pancreatic cancer patients [55–57,63–65]. Konstantinidis and colleagues [65] demonstrated node involvement by metastasis or by direct invasion as an equally significant predictor of reduced survival. Also both the number of positive nodes and the lymph node ratio are prognostic factors, with patients with 1 lymph node positive faring better than those with greater than 1 lymph node positive. Katz and colleagues [35] identified negative lymph node status (odds ratio 1.92, $P=.02$) as significantly associated with 5-year survival on multivariate analysis. Robinson and colleagues examined 134 patients who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma, 78% of whom had T3 disease. For those patients with T3N0 disease, 5-year survival was 71%, whereas those with T3N1 disease had a 5-year survival of 11.5% ($P<.05$). Furthermore, patients with T3N1 disease and a metastatic-to-resected lymph node ratio less than 15% had an overall 5-year survival of 21%, whereas there were no survivors

beyond 40 months in patients with a metastatic-to-resected lymph node ratio greater than 15% ($P<.01$). Other studies have also suggested that the metastatic-to-resected lymph node ratio may be more discriminatory than just the absence or presence of lymph node involvement in determining long-term survival after surgical resection [63,66].

The number of nodes sampled has ramifications for survival. Huebner and colleagues [64] found that patients with less than 11 lymph nodes sampled with pN0 disease had worse survival outcomes compared with those who had greater than 11 nodes sampled, suggesting metastatic nodes were missed because of understaging. The negative survival impact of sampling fewer than 10 to 12 total nodes has also been demonstrated by other population studies [67,68]. Thus, extended lymphadenectomy has been proposed to improve long-term survival. This includes clearance of nodes up to the hepatic hilum and para-aortic nodes from the diaphragmatic hiatus to the level of the inferior mesenteric arteries. However, several studies, including meta-analyses, have failed to demonstrate any convincing survival advantage with this strategy [11,12].

Resection margins

Achieving negative surgical margins (R0) is arguably one of the most consistently reported prognostic factors associated with long-term survival following resection of pancreatic adenocarcinoma [10,51,52,54,69]. Howard and colleagues [52] found that a margin=negative R0 resection (HR = 1.39, $P=.03$) was associated with increased survival. The authors' own examination of 5-year survivors also found that R0 resections were significantly associated with long-term survival [54]. Their recent analysis found that R0 resections have an improved survival compared with R1 resections, but this survival benefit is lost when the tumor is within 1 mm of the resection margin [69]. Prior studies have shown that patients who undergo a resection with a macroscopically positive margin have survival comparable to that of patients who do not undergo an operation [70,71].

The high incidence of positive margins and intra- and extrapancreatic neural invasion has provoked some institutions to explore extended pancreatic resection together with vascular resection and retroperitoneal lymphadenectomy. However, many recent prospective studies have demonstrated that extended operations tend to increase morbidity and mortality rates without a survival benefit. A systematic review showed no differences in the survival rate between standard and extended operations, with a trend toward increased morbidity in patients undergoing extended operations [72]. Similarly, Farnell and colleagues [11] found that an extended operation was not associated with a survival benefit but did increase the rates of postoperative morbidity.

CA 19-19 levels

CA19-9 levels are known to correlate with burden of pancreatic cancer [73,74]. In the authors' own work, preoperative CA19-9 correlated with stage of disease in 424 consecutive patients with pancreatic adenocarcinoma who underwent

resection. A postoperative decrease in CA19-9 and a postoperative CA19-9 value of less than 200 U/mL were strong independent predictors of survival [75]. Kimura and colleagues also found that preoperative CA 19-9 of less than 40 U/mL was associated with increased 5-year survival [57].

SURVEILLANCE OF LONG-TERM SURVIVORS

Similar to short-term survivors, the goal of surveillance is to optimize the detection of local and distant recurrence with the hope of providing patients with therapeutic options that hold the promise of improved quality of life, survival, and/or cure. In addition, surveillance maintains the relationship between providers and patients so that any progression of disease can be more effectively managed through therapy, palliation, or appropriate initiation of hospice [76].

Recommendations by the National Comprehensive Cancer Network include surveillance history and physical examination along with CA19-9 level and an abdominal computed tomography (CT) scan with contrast every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter. For patients who recur, treatment considerations differ depending on the nature of the recurrence. Local recurrence within the pancreas only may be amenable to repeat resection; however, treatment for local recurrence within the pancreatic bed can range from chemoradiation to different chemotherapy regimens or palliation. No specific guidelines address recurrence in long-term survivors.

QUALITY-OF-LIFE ENDPOINTS

Most quality-of-life studies in pancreatic cancer patients have been limited to time periods prior to the 5-year survival endpoint [77–79]. Recently, however, Fong and colleagues [80] surveyed 305 patients who were alive 5 years after undergoing a Whipple using a validated quality-of-life instrument. Although some patients underwent a Whipple for pancreatic adenocarcinoma, many of the patients underwent a Whipple for intraductal papillary mucinous neoplasm, pancreatic neuroendocrine tumor, or pancreatic cystic disease. They found that long-term survivors demonstrated better global quality of life and physical- and role-functioning scores at 5-year when compared with age- and gender-matched controls.

FUTURE DIRECTIONS

As genomics, proteomics, and data science provide a better understanding of the biology of pancreatic adenocarcinoma, the proportion of 5-year survivors will increase. Early detection of pancreatic cancer is key to improving patient survival, and new diagnostic modalities such as screening of microRNA [81,82], liquid biopsies for proteomic analysis [83] and other biomarkers [84] may provide enhanced screening capabilities for at-risk patients in the future.

To better identify patients who need screening for pancreatic cancer, patient registries and other large-scale clinical databases will play an increasing role in providing the big data necessary to identify predictors of pancreatic cancer. Advances in statistical analysis, including machine learning techniques, may

uncover novel genetic or biologic risk factors, elucidate unexpected clinical predictors of pancreatic cancer, or improve the prediction of patient recovery after resection or chemoradiotherapy [85].

The rapid acceleration of technologies across the basic sciences, computer science, and medicine highlights the importance of rigorous academic investigation of pancreatic cancer and its therapies. The continued dedication of patients, clinicians, and scientists in fighting pancreatic cancer will yield important discoveries that can push the 5-year survivor rate to increasing levels.

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