Improving Survival of Pancreatic Cancer. What Have We Learnt?

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Abstract Pancreatic adenocarcinoma still ranks high among cancer-related deaths worldwide. In spite of substantial strides in preoperative staging, surgery, perioperative care, and adjuvant treatment, the survival still remains dismal. A number of patient-, disease-, and surgeon-related factors play a role in deciding the eventual outcome of the patient. The aim of this commentary is to review the current knowledge of various factors and the recent advances that impact the survival of patients with pancreatic adenocarcinoma. A search of scientific literature using Embase and MEDLINE, for the years 1985–2015, was carried out for search terms “pancreatic cancer” and “survival.” Further search was based on the various specific prognostic factors that contribute towards survival of patients with pancreatic cancer found in the literature. Most of the studies used for this review include those that deal with pancreatic head cancers, some include patients with pancreatic cancers in all locations while very few included patients with tumors of body and tail only. In spite of significant developments in pre- and perioperative management, increased rates of margin-negative resections, and use of adjuvant treatment, the survival rates of pancreatic cancer patients remains poor. A paradigm shift with more effective adjuvant regimen and genetic interventions may help change the outcomes of patients with pancreatic cancer.

Keywords Pancreatic cancer · Survival · Complications · Borderline resectable · Neoadjuvant therapy

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Introduction

Pancreatic cancer is the 11th most common cancer and the fourth leading cause of cancer-related death in the west. Cumulative 5-year survivals of these patients range from 7 to 13.6 % [1–4]. In other words, approximately merely one in eight patients will survive more than 5 years. Dismal though the long-term outcomes may be, surgery offers the only chance of cure. Unfortunately, however, only 15 to 20% cases are potentially resectable at presentation. Moreover, prognosis is poor even for this minority that undergoes a timely and complete resection. Reported 5-year survival rates following pancreaticoduodenectomy for node-negative and node-positive disease are 25 and 10 %, respectively [5–7]. The actual survival is so poor that surgeons have questioned and reviewed the histopathology of their long-term survivors to make sure they actually were suffering from pancreatic cancer to begin with. Nitecki et al. [8] reviewed their results in Mayo clinic and found that 12 of the 31 cases (more than one third) re-reviewed among the total 186 patients did not have ductal adenocarcinoma, but other tumors known to carry a much better.

Given the increase in popularity of the concept of high-volume centers, improved perioperative care, and increased use of adjuvant treatment, it was assumed (and probably logically so) that outcomes of pancreatic cancer patients would improve over time. However, there are conflicting reports in the literature regarding the progress in terms of long-term survival of patients with resected pancreatic cancer:

Some of the publications in recent times have provided a reason for optimism. Most of these studies have examined the role of adjuvant treatment which has been shown to improve survival of these patients [9–11]. Additionally, there are reports that suggest that progress in surgical technique and perioperative care, in conjunction with the emergence of high-

volume centers of excellence, has reduced the early mortality and morbidity rates after pancreatic resection [12–14]. The long-term survival figures however have only shown modest improvements at best.

A SEER database review of patients who underwent resection for pancreatic cancer between 1991 and 1996 showed a 3-year survival rate of 34%, which compares favorably with published reports from the earlier literature [15]. In this report, on multivariate analysis, one of the strongest predictors for improved survival was the use of adjuvant chemoradiotherapy.

There are other studies that do not share the same optimism. Winter et al. reviewed data from Memorial Sloan-Kettering Cancer Center and compared early and late survival over three decades [9]. They concluded that patients who underwent resection for pancreatic cancer between 2000 and 2009 experienced improved operative mortality and 1-year survival compared to those who underwent resection in the 1980s. However the long-term survival was similar over all three decades. These data underscore the need for earlier detection and more effective multimodal therapies for better survival.

Furthermore, it has been seen that many patients who died more than 5 years after surgery did so from recurrent disease [1]. These patterns have also been confirmed in multiple studies [16, 17]. Thus it may be naïve to assume that 5-year survival is synonymous with cure. The causes of these late recurrences are not yet clear.

The characteristics of long-term survivors are very heterogeneous and not well defined. Perrisynakis et al. [1] reviewed several reports dealing with this issue and evaluated the heterogeneity of clinicopathologic characteristics found in long-term survivors in various studies [9, 18, 19]. Over time, however, we have come to realize that there are some established factors that impact the prognosis and survival of pancreatic cancer patients. Riall [20] et al. suggested that nodal status, tumor size, and differentiation are factors that should be taken into account when predicting long-term survival. We also know that disease stage and adjuvant treatment impact survival. These and other factors that may have an impact on survival are reviewed in detail below.

Neoadjuvant Treatment

For Potentially Resectable Tumors

The advent of neoadjuvant and adjuvant therapy and its success in other cancers prompted its evaluation in pancreatic cancer. Since majority of tumors are upfront unresectable and also patients with complete resection do not do too well in terms of tumor recurrence, it seemed only logical to try preoperative therapy with or without adjuvant treatment.

Besides, as with other cancers, neoadjuvant therapy is a good *in vivo* tool to check for sensitivity and aggressiveness of the tumor thereby improving patient selection. The disadvantage of preoperative therapy for an aggressive disease like pancreatic cancer is that it may take away a lot of precious time during which the patient may have benefited from upfront surgery. This may also be true in cases where the preoperative treatment could not be completed because of side effects. Though the practice is not prevalent, some reputed centers (M D Anderson, Texas) have believed in the concept of neoadjuvant treatment even for resectable disease.

Gemcitabine and 5-fluorouracil are two of the most commonly used agents that have been evaluated by various investigators as potential neoadjuvant agents [21–24]. These agents have been tried alone or in conjunction with radiotherapy. The experience with chemotherapy alone for patients with pancreatic cancer is limited.

Three meta-analyses [25–27] have been published comprising a heterogeneous mix of various types of trials addressing the impact of neoadjuvant treatment in potentially resectable disease. The resectability rates varied in these studies from 66 to 89 % after neoadjuvant treatment. In one of these, it was shown that 35 % patients had an objective response to neoadjuvant treatment while 21 % had progressive disease.

Though these studies may show promise, most were uncontrolled and did not have a surgery alone arm for comparison. Hence, drawing a definite conclusion about the role of neoadjuvant treatment in resectable tumors is not possible. Thus, at present, this cannot be considered a standard approach.

Borderline Resectable Pancreatic Cancer

After it was first described by Varadhachary [28] et al. in 2006, there has been extensive research focusing on the best treatment for a subcategory of pancreatic cancer patients that sits on the distinction between resectable and locally advanced disease. The entity has been variously defined by various groups and surgical associations, but a consensus is lacking even to date and we are still in the process of defining an entity that was identified almost a decade ago [29].

To add to the complexity, Katz [30] and colleagues in 2008 studied 160 patients with borderline resectable disease (using the Varadhachary definition) treated at MD Anderson Cancer Center and introduced three subtypes of borderline resectable disease, now often referred to as Katz types A, B, and C which took into account radiological and biochemical findings as well as the performance status of the patient.

A consensus statement from a joint conference of the American Hepato-Pancreato-Biliary Association and the Society of Surgical Oncology and the Society for Surgery of the

Alimentary tract defined the following criteria for borderline resectable tumors [31]:

- No distant metastases
- Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct tumor abutment of the hepatic artery, without extension to the celiac axis
- Tumor abutment of the SMA not to exceed $>180^\circ$ of the circumference of the vessel wall

These criteria have also been adopted as definitions of borderline resectable disease in the consensus-based guidelines of the National Comprehensive Cancer Network (NCCN) [32].

As is well known, survival rate is particularly poor for patients who undergo an incomplete (margin-positive) resection. There is evidence to suggest that the survival of patients who undergo a margin-positive resection is similar to those with advanced disease treated with chemoradiation only [33, 34]. Hence, the optimum treatment of this subgroup of patients in whom the chances of achieving a margin-negative resection are low, assumes immense importance. What was still not clear for a long time (and is still debatable) was how best to treat patients with borderline resectable pancreatic cancer prior to consideration of surgery.

Some centers will subject these patients to upfront exploration and resection, if technically possible. Others, however, in an attempt to increase the likelihood of a margin-negative resection (and especially in the presence of arterial involvement/ abutment), will initially treat these patients with chemotherapy, chemoradiotherapy, or both followed by reassessment and operative decision made accordingly based on reassessment.

There are no randomized trials that have tried to investigate the best treatment for borderline resectable disease. Most of the data to date comes in the form of single institution experiences [30, 35–39], and some uncontrolled trials in which a case mix of patients with resectable, unresectable, and borderline disease were included.

Two meta-analyses suggested that approximately one third of unresectable/borderline resectable tumors could be downstaged and, on reassessment, deemed resectable using neoadjuvant treatment [26, 27]. However, as mentioned above, the patient population in these studies, like in most other such studies, is heterogenous and data needs to be

interpreted with caution. Also, some of the studies in these meta-analyses used chemotherapy, some chemoradiotherapy, and others both.

In the abovementioned study by Katz et al [30], out of 160 patients with borderline resectable disease, 125 (78.1 %) were able to complete neoadjuvant therapy. These 125 were then restaged and 82 (51 %) were found to have resectable disease. Seventy-nine were eventually taken up for surgery and 66 (41.2 %) had resectable disease on exploration. Sixty-two of them (37.5 % of the initial 160 patients) had a margin-negative resection. Median survival was significantly better for patients who had resection.

Assifi [25] et al. reviewed a number of phase II trials of patients undergoing neoadjuvant therapy. They found out that among the subset of patients with borderline tumors, it was possible to perform a margin-negative resection in approximately one third of the patients.

These studies suggest that in patients with borderline resectable pancreatic cancer, neoadjuvant treatment may be feasible and effective. We still do not have level I evidence to prove that this approach is superior to upfront surgery followed by adjuvant therapy. We also do not have consensus over what constitutes ideal neoadjuvant treatment (chemotherapy or chemoradiation) and what chemotherapeutic agent to use (gemcitabine with albumin-bound paclitaxel or FOLFIRINOX).

Adjuvant Treatment

Pancreatic cancer is now thought of as a systemic disease considering the fact that R0 resection does not ensure good long-term outcome and there is early propensity for distant spread, hence the need for some kind of locoregional and systemic therapy that can take care of local and distant recurrence. Multiple studies have shown that one of the strongest predictors for survival has been the use of adjuvant chemoradiotherapy. Three-year survival rate was significantly higher among those who received it compared to those who did not (45 versus 30 %, respectively) [15]. Unfortunately, however, pancreatic cancer has relatively poor sensitivity to radiation therapy and cytotoxic agents. Though the benefits of adjuvant treatment may have become apparent in recent years, there is still ambiguity about optimal choice of treatment modality (chemotherapy with or without RT). Various agents and combinations have been tried and suggested.

Multiple randomized trials [10, 11, 40–43] have compared surgery with adjuvant therapy to surgery alone. A statistically significant difference in survival could be demonstrated in two trials and nearly achieved in a third trial. CONKO-001 trial [11] evaluated the impact of gemcitabine in adjuvant setting. Gemcitabine almost doubled median disease-free survival and 5-year overall survival. It was also well tolerated. However,

the survival advantage mentioned above was not statistically significant. There have been other trials that have examined the role of other agents like 5FU-leucovorin combination [44] and S-1 [45]. While both these agents/ combination have been found to be effective, multiple other factors determine their utilization like side effect profiles and availability.

There are other studies that have looked into the role of chemoradiotherapy as an adjuvant treatment [40] while others have compared the impact of chemotherapy, chemoradiotherapy, and chemoradiotherapy followed by chemotherapy to observation alone [46]. In some of these studies that have compared various combinations of chemotherapy and radiotherapy, patients receiving chemoradiotherapy have not been shown to have benefitted. On the other hand, there are studies [47] that have shown gemcitabine-based chemoradiotherapy to be beneficial compared to control arm. The survival benefit with adjuvant chemotherapy has been consistent across many trials. There are no randomized trials that have evaluated the role of radiation alone in the adjuvant setting compared to chemotherapy or chemoradiotherapy. Experience with intra-operative radiotherapy or targeted chemotherapy, though encouraging, is sparse, preliminary, and non-randomized [48–50].

Summary of all the evidence regarding adjuvant treatment for pancreatic cancer patients points towards the fact that gemcitabine-based chemotherapy may be the best among the currently available adjuvant treatment options and chemoradiotherapy may not have a significant advantage over chemotherapy alone.

There are divergent views in Europe and the USA with respect to adjuvant treatment for pancreatic cancer. European groups emphasize the lack of significant benefit with chemoradiotherapy and hence recommend chemotherapy alone in the adjuvant setting and chemoradiotherapy is to be given only in the setting of a trial as per ESMO (European Society of Medical Oncology) [51]. The Americans on the other hand relying on the findings of GITSG study [47] advocate chemoradiotherapy. They also allude to the fact that there is a high risk of local failure for which radiation may be beneficial.

Surgery-Related Factors

Total Pancreatectomy

Total pancreatectomy has been used sparingly for treatment of pancreatic cancer in recent times. One of the rationales for performing this more radical albeit morbid procedure is to remove more tissue and potentially minimize the chances of recurrence. The procedure may be indicated at times to achieve a microscopic negative margin especially in cases of IPMN. The other reason to perform a total pancreatectomy is to avoid a pancreaticojejunal anastomosis. Avoidance of

pancreaticojejunal anastomosis eliminates the biggest source of morbidity and mortality in patients undergoing pancreaticoduodenectomy, viz. pancreatic fistula. However, total pancreatectomy comes with its own set of complications in the form of permanent exocrine insufficiency and poorly controlled diabetes [52, 53].

High-quality data comparing perioperative outcomes of total and partial pancreatectomy is lacking. Most of the available evidence which is in the form of single-institution studies points towards higher operative morbidity and mortality as compared to pancreaticoduodenectomy [52, 54]. A review of NSQIP database [55] evaluated 166 patients who underwent total pancreatectomy, 4317 who underwent pancreaticoduodenectomy, and 2364 who underwent distal pancreatectomy. The mortality was 5.4, 2.9, and 1.7 %, respectively, for the three procedures. The incidence of complications however was similar.

There is also paucity of data for long-term outcomes. Some studies claim that the long-term survivals of total pancreatectomy are comparable with partial pancreatectomy [56, 57]. In a retrospective study of over 4000 patients who had a pancreatectomy [57], the perioperative mortality rates at 1 and 3 months were similar between patients who underwent total or partial pancreatectomy. The long-term survival was also similar.

While routine use of total pancreatectomy is not recommended, it may be performed in certain select situations, especially where the anatomy of the tumor so demands, in order to achieve a negative margin. This is typically encountered when dealing with a bulky tumor of the pancreatic head extending into the body of the pancreas. The other common indication of total pancreatectomy is IPMN which may diffusely involve the whole gland.

Extended Lymphadenectomy

A high proportion of patients with pancreatic head cancer have lymph node involvement [58, 59]. The prognostic value of lymph nodes in pancreatic cancer cannot be overemphasized. Spread to the lymph nodes is associated with a median survival of <17 months compared with 5-year survival rates of up to 38 % in patients without lymph node involvement [58]. Not only lymph node positivity but also the number and the ratio of metastatic/examined nodes has been found to have bearing on the outcome of pancreatic cancer patients [16, 60]. As has been seen in colon and gastric cancer, the number of negative nodes examined also impacts prognosis [61, 62]. At least, some data support the view that pathologic examination of a minimum of 15 nodes in the pancreatectomy specimen is necessary to declare a node-negative adenocarcinoma [62].

Some centers routinely perform extended lymphadenectomy along with the Whipple's operation. The argument in favor

of doing such extended nodal dissections is that the tumor frequently metastasizes to lymph node stations that may be outside the boundaries of the conventional Whipple's procedure [63, 64]. Not only is consensus lacking to support such practices, operative times, blood loss, and morbidity may increase with addition of extended lymphadenectomy [65].

There have been a number of studies from Japan addressing the role and value of extended lymphadenectomy in pancreatic cancer [66–68]. Many of these have hinted at improved survival in patients who underwent extended lymphadenectomy compared with conventional pancreaticoduodenectomy. The shortcoming of these studies however is that most of these are non-randomized and retrospective, often comparing survival from their own institution or historical cohorts. So there are doubts about the validity and relevance of these studies, however significant their outcomes may appear.

Contrary to these, some Japanese authors have also questioned the role of radical resection. Nagakawa and Hanyu [69, 70] showed that the 5-year survival after radical pancreaticoduodenectomy was less than 10 %. Pedrazzoli [71] et al. compared conventional pancreaticoduodenectomy with extended lymphadenectomy and found that overall survival was identical for both treatment groups. Subgroup analysis however showed better survival in patients with positive nodes who had undergone an extensive lymphadenectomy.

Other randomized trials have also compared conventional and radical pancreaticoduodenectomy. Not only did they not find any survival difference between the two cohorts, but also the quality of life, especially early after surgery, was worse in patients undergoing extended lymphadenectomy [72, 73].

Thus, as per the existing data, extended lymphadenectomy appears to confer no survival benefit and may be associated with a poorer quality of life, particularly in the early postoperative period. Pancreaticoduodenectomy with standard lymphadenectomy remains the operation of choice. More evidence from centers outside Japan will be required before this can be considered more frequently.

Vascular Resection

One of the deterrents for a margin-negative resection for patients with locally advanced tumors is the presence of vascular involvement, most commonly the superior mesenteric vein and artery. The definition of unresectability because of vascular involvement is debatable though consensus is desirable with the emergence of the entity “borderline resectable pancreatic cancer.” Moreover, the treatment may have to be individualized based on the nature of disease, the age and performance status of the patient, and the vascular surgery skills of the operating surgeon [74].

Adherence/ abutment of vessels on preoperative imaging may not necessarily imply vascular invasion. It is not easy to determine the relation of the tumor to the vessels based on

imaging. Even at exploration, it may not be possible to certainly decipher involvement. Desmoplasia and peritumoral inflammation may lead to changes that may mimic tumor.

The concept of regional pancreatectomy as first promulgated by Fortner [75] involved subtotal or total pancreatectomy, resection and reconstruction of the superior mesenteric vein-portal vein confluence, and extensive en bloc regional lymph node dissection with or without arterial reconstruction. The idea was to improve results by following a more radical approach. Vascular resection as part of regional pancreatectomy remains controversial due to the technical complexity and morbidity imposed on the patient. That too, in a disease that is associated with poor long-term survival. There is a paucity of randomized evidence to demonstrate its efficacy. However, some high-volume centers perform resection and reconstruction of a short segment of the portal vein or superior mesenteric vein (SMV) for limited tumor involvement of the SMV, portal vein, or the confluence [73]. Studies have also shown that tumors with portal vein involvement have similar frequency of positive lymph nodes or aneuploidy compared to those without portal vein involvement [76–78]. These findings suggest that venous involvement is a function of tumor location rather than an indicator of aggressive tumor biology.

Studies from high-volume centers, containing selected patients have shown similar morbidity, mortality, and survival rates if a margin-negative resection was performed [79–81]. A systematic review concluded that venous resection is a safe and feasible procedure that increases the number of patients who can undergo curative resection and, therefore, may provide important survival benefits to selected groups of patients [82].

Chua et al. reviewed [74] 28 retrospective studies and found that the median mortality rate was 4 % for extended pancreaticoduodenectomy with vascular resection. Even the complication rates were similar. The median length of hospital stay was 17 days. The authors thus concluded that the perioperative outcome was similar to that of a standard pancreaticoduodenectomy. Same study also looked at the survival rates which were also comparable to patients undergoing standard pancreaticoduodenectomy. Among these 28 studies, the ones that analyzed prognostic factors suggested that vascular resection was not associated with a poorer survival. The rate of margin negative resection was 75 %, which supports this radical procedure when an R0 resection is achievable.

In contrast to these studies that suggest good outcomes, NSQIP data [83] of 3582 patients undergoing pancreatectomy suggests higher rates of morbidity (39.9 versus 33.3 %) and mortality (5.7 versus 2.9 %) in patients who underwent vascular resection. However, this data set was heterogenous and included institutions with different levels of expertise.

There is also some evidence that in patients where the tumor is seen to involve the vein on histopathology, the outcome is poor as compared to those in whom the tumor is abutting or

adherent [84]. Thus, in patients in whom the preoperative investigation is suggestive of infiltration of tumor into the vein, the survival may not improve with venous resection.

So although still a controversial procedure and requiring technical expertise, venous resection and reconstruction should be considered a standard approach in a selected group of patients for tumors focally involving the portal vein or SMV. The prerequisites include adequate inflow and outflow veins, absence of superior mesenteric artery (SMA) or hepatic artery involvement, and high chance of an R0/R1 resection [85].

As compared to venous resection, the status of arterial resection and reconstruction is even more controversial. High-volume centers, with expertise in en bloc resection of the hepatic artery, superior mesenteric artery, or even the celiac trunk itself [86–88] have shown good survival outcomes.

On the other hand, a review of 26 studies of patients undergoing pancreatectomy with arterial resection showed significantly increased morbidity and mortality [89]. The authors also demonstrated that long-term survival rates were significantly worse in patients who underwent arterial resection as compared to those who did not. If the outcome of these patients were compared to those patients who did not undergo any surgery at all on an intention to treat basis, survival benefit could be demonstrated.

Another reason for most surgeons to avoid an arterial resection along with pancreatectomy is the fact that a tumor that has involved the artery has also probably infiltrated the neural plexus around the artery and hence, it will be associated with poor prognosis anyways. In most centers, arterial resection is performed infrequently, and therefore, there is scanty data supporting its use.

The Hospital Volume Effect

Since the survival of pancreatic cancer patients remains dismal, short-term clinical outcomes and economic impact are important as the life expectancy is short. There is considerable interest among hospitals, health care providers, and insurance companies concerning the referral of patients to hospitals that have special expertise in a given procedure [90–93].

Several reasons have been attributed to the success of high-volume centers. These include but are not limited to the development of a systematic approach and protocols for handling patients by developing critical care and enhanced recovery pathways. Such recovery protocols may enhance the performance of all participants in the health care delivery team. It is not just the total volume of patients per se that is associated with improved performance [94], but volume of similar types of patients that makes the difference. Data also suggest that combined “experience effect” of the whole team may be more important than the number of operations performed by a particular surgeon.

There is evidence from some centers that short-term outcomes of pancreaticoduodenectomy are better at hospitals where a higher volume of these procedures is performed [95, 96]. Sosa [90] et al. showed that unadjusted mortality rates for all pancreatic cancer procedures increased as hospital volume decreased, even when the data were stratified by individual surgeon volume. They were also able to show a markedly decreased mortality rate even for palliative procedures in patients with pancreatic cancer. One study showed that mortality rates following a Whipple procedure for a low-volume (fewer than two procedures per year), intermediate-volume (two to four per year), or high-volume (greater than four a year) surgeon in the late 1990s were 14.7, 8.5, and 4.6 %, respectively [97]. In this study, hospital volume was also an independent predictor of mortality. A meta-analysis of 14 studies has addressed the relationship between surgeon and hospital volume, and postoperative mortality and survival after pancreatic cancer surgery [98]. There was a significant association between hospital volume and postoperative mortality as well as overall survival.

Extrapolating from such studies, some experts have recommended that patients requiring complex procedures such as the Whipple operation be referred to high-volume centers whenever possible [91].

While there seems to be ambiguity about what constitutes a high-volume center (and the definition keeps changing with time), there is little doubt about the benefits of high-volume centers for surgery in general and pancreatic surgery in particular. Also, there are concerns about developing a new high-volume center or transforming low-volume to a high-volume center if all the patients are referred to an established high-volume center.

The Role of Genetics

The completion of pancreatic cancer exome is a giant step towards understanding of the genetics of pancreatic cancer [99–101]. Pancreatic cancer may contain upto 63 genomic alterations. Most if not all of these are point mutations. Though most of these genetic aberrations represent somatic mutations, some are present in the germline of kindreds who carry a familial predisposition to pancreatic cancer.

The genes most commonly involved in the carcinogenesis of pancreatic cancer are KRAS, CDKN2A (p16), TP53, and SMAD4 (DPC4) [102, 103] and are thus classified as “driver” genes for this tumor. Among these, KRAS is a proto oncogene while the other three are tumor suppressor genes.

Over 90 % of pancreatic cancers harbor a KRAS gene mutation [101, 104, 105]. Furthermore, KRAS mutations appear to occur very early in pancreatic carcinogenesis followed by mutations in CDKN2A. The mutations in other two genes, i.e., TP53 and SMAD4, occur relatively late in the sequence.

This classical sequence of genetic mutations is followed in less than half of the patients of pancreatic cancer. This suggests a great degree of heterogeneity in the genetic mechanism of pancreatic cancer. KRAS gene mutations have been identified in noninvasive intraductal papillary mucinous neoplasms (IPMNs), pancreatic intraepithelial neoplasia (PanIN), and noninvasive mucinous cystic neoplasms (MCNs). The prevalence of mutations increases with increasing degrees of dysplasia in these noninvasive precursor lesions [106, 107].

Besides these four, various other genes have been identified that may be altered, though at lower frequency. These include BRCA2, PALB2, STK11, MLL3, and ARID1A and DNA mismatch repair genes [101, 102]. It is important to emphasize that these other genes also play an important role in the pathogenesis and determination of prognosis of pancreatic cancer. For example, some of these mutations may confer susceptibility to cisplatin or other drugs.

Mutations associated with particular cancers can provide new targets for the development of sensitive screening tests for that disease. Given the frequency of genetic events in the carcinogenesis of pancreatic cancer and the fact that advanced cancers carry a poor prognosis even if surgically amenable to resection, an accurate and sensitive test for diagnosing curable noninvasive pancreatic neoplasia is needed of the hour. Several techniques can detect rare mutant genes even when they are admixed with thousands of normal copies of the gene. KRAS mutations can be detected in duodenal juice and stool of patients with pancreatic cancer [108–110]. However, questions exist about the ability of a detected KRAS mutation in a particular patient to differentiate cancer from chronic pancreatitis.

The clinical implications of these mutations though limited at present may have far-reaching effects in the near future. Yachida et al. [111] demonstrated that among patients with stage I/II disease who had two driver gene alterations, the median disease-free and median overall survival was longer. Also, these patients were significantly more likely to develop oligometastatic failure. This suggests that the presence of these genetic features in pancreatic cancer patients may be a harbinger of long-term survival.

The same authors also showed that SMAD4 status correlates with patterns of failure in pancreatic cancer [112]. Also, mutations that abolish TP53 gene expression promote widespread metastatic failure independently of SMAD4 loss in some patients. Thus, both SMAD4 and TP53 status may have value in identifying patients at high risk for widespread metastatic failure.

Blankin et al. [113] also demonstrated the relationship between DPC4/SMAD4 expression and outcomes of patients in terms of survival and concluded that DPC4/SMAD4 expression may be a potentially important indicator of response to resection of patients with pancreatic cancer. Aberrant expression of p53, p21WAF1/CIP1, p16INK4A, or cyclin D1 was not associated with differences in outcome.

The significance of exomic sequencing can only be realized by translational studies. It also remains to be seen how we can use this extensive knowledge of genetics of carcinogenesis to diagnose, prognosticate, and possibly treat pancreatic cancer. There may be a scope for genetic screening, manipulation, and intervention in the years to come.

Conclusion

In spite of giant strides in operative and oncological management, the lack of improvement in long-term survival observed in patients with resected pancreatic cancer points towards the fact that the disease may be more complex and heterogeneous than what it is thought to be. This also underscores the need for improved early detection and novel multimodal treatment strategies for this aggressive disease. Probably, an even more in-depth and thorough knowledge of biology and nature of pancreatic cancer is needed to “cure” patients with pancreatic cancer. A truly curative approach must embrace adjuvant therapy, molecular biology, and genetic manipulations.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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