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REVIEW

Borderline Resectable Pancreatic Cancer: Challenges for Clinical Management

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains a significant worldwide health problem with a poor prognosis. A borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) is a tumor with limited vascular involvement that is technically resectable but with a high risk of positive margins (R1 resection).

Objective: To identify the current challenges that exist in the management of BR-PDAC.

Methods: A review of the literature was conducted to identify articles discussing the definitions and management of BR-PDAC.

Key Findings: Several anatomic definitions of BR-PDAC exist, and there is significant heterogeneity in their utilization across published trials. To improve the odds of a margin negative (R0) resection, a neoadjuvant treatment approach involving chemotherapy with or without radiation is currently preferred. While supporting the efficacy of a neoadjuvant approach in BR-PDAC, the largest published randomized trials have utilized older gemcitabine-based regimens. Recently published Phase II evidence and meta-analyses have supported the use of modern multi-agent regimens such as FOLFIRINOX. The utility of adding radiation to a chemotherapy backbone remains in question. Due to remnant fibrosis and edema following neoadjuvant therapy, accurately selecting patients for resection based on a restaging CT scan is challenging. Furthermore, the role of adjuvant therapy in BR-PDAC patients receiving neoadjuvant therapy needs to be defined.

Conclusion: Though progress has been made, the optimal management of BR-PDAC is uncertain. Phase III trials utilizing modern chemotherapeutic regimens are needed to establish a standard of care.

Keywords: pancreatic cancer, borderline resectable disease, surgery, neoadjuvant chemotherapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a significant worldwide health challenge, being the 7th leading cause of cancer-related death despite having only the 14th highest incidence.[1] It is projected that PDAC will surpass breast cancer as the third leading cause of cancer death by 2025. Although notable advancements have been made in managing this highly lethal malignancy, 5-year survival rates remain low at 10%.[2]

Several factors contribute to the poor prognosis of PDAC. For one, due to its aggressive biology and tendency to grow subclinically, most patients present with metastatic (50%) or locally advanced or borderline resectable disease (30%).[3] Only 20% have resectable disease, and therefore the potential for upfront curative-intent therapy in the form of surgery. The 5-year overall survival (OS) rates in patients with resectable, locally advanced, and metastatic PDAC are 32%, 12%, and 3% in the United States, respectively.[4] Preclinical work has suggested that pancreatic cancer cells may tend to metastasize early, even before the clinical appearance of the primary tumor.[5] This early systemic involvement of disease likely explains why most patients with a tumor resection will recur within 4 years, and, therefore why cures remain so elusive in this population.[6]

Non-metastatic PDAC occurs on a spectrum that includes tumors that are considered resectable (R-PDAC), borderline resectable (BR-PDAC), or locally advanced (LA-PDAC). LA-PDAC generally encompasses tumors not amenable to upfront resection due to extensive local vascular invasion. While there are ongoing efforts to investigate novel treatment

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strategies in this population, most commonly, they are managed like those with metastatic disease.[7,8] Historically, the reference regimen for the treatment of PDAC was gemcitabine as monotherapy. However, the treatment landscape across all stages of the disease has changed in the last 12 years. The most effective regimen identified for treating metastatic PDAC (M-PDAC) is a combination of 5-fluorouracil/Irinotecan/Oxaliplatin (FOLFIRINOX). In a phase III trial of patients with metastatic pancreatic adenocarcinoma (M-PDAC), when compared to gemcitabine monotherapy, FOLFIRINOX improved median OS to 11.1 months vs 6.8 months with an objective response rate of 31.6%.[9] In another phase III trial, the combination of gemcitabine/nab-paclitaxel improved median OS to 8.5 months vs 6.7 months with gemcitabine alone in patients with M-PDAC, with an objective response rate of 23%.[10] In patients with R-PDAC, surgical resection followed by adjuvant chemotherapy has become the standard of care. The PRODIGE-24 phase III clinical trial demonstrated that in PDAC patients with an Eastern Cooperative Oncology Group (ECOG) performance status 0–1, who had undergone an R0/R1 resection, modified FOLFIRINOX given on an adjuvant basis for 6 months improved median OS to 54.4 months vs 34.8 months with gemcitabine.[11] The ESPAC-4 phase III trial showed that in a similar population, a combination of gemcitabine/capecitabine given for 6 months improved OS to 27.7 months vs 26.0 months with gemcitabine alone.[12]

The BR-PDAC is a more recently defined entity with unique considerations for management. Its definition was initially conceived to describe a locally invasive tumor, where resection is potentially feasible but with a higher risk of positive margins (ie, R1 resection). Pre-operative therapies are considered for these patients to best facilitate a margin negative (R0) resection. While there is agreement on the importance of a neoadjuvant treatment strategy in BR-PDAC, several key challenges in managing this patient population remain inadequately addressed. This review will aim to discuss the critical literature and outstanding questions that remain in identifying the optimal management of this significant patient population.

Defining Borderline Resectability

Among the critical predictors of improved outcomes in resected PDAC is a negative post-operative resection margin (R0).[13–15] The initial goal in defining BR-PDAC has been to identify individuals at higher risk of R1 resection and who might benefit from additional treatments pre-operatively to improve the odds of an R0 resection. To date, significant differences exist amongst the numerous published definitions of BR-PDAC, and this lack of uniformity has negatively impacted the broad applicability of completed trials.

The first formal definition of BR-PDAC was published by the National Comprehensive Cancer Network (NCCN) in 2006. Since then, that definition by the NCCN has been updated, and several alternative definitions have been published by the MD Anderson Cancer Center (MDACC), Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT), and the Intergroup Alliance.[7,16–18] These early definitions were similar in that they were based on anatomic criteria, considering the pancreatic lesion's interface with the portal vein (PV), superior mesenteric vein (SMV), celiac artery (CA), common hepatic artery (CHA), and superior mesenteric artery (SMA). Differences exist in the degree of involvement that was permissible, however. For example, the Intergroup Alliance definition of BR-PDAC allows an interface between the tumor and the CA of less than 180° of the circumference of the vessel wall, compared to the AHPBA/SSAT/SSO definition that stipulates the cancer should be uninvolved with the CA. Criticism has also been levied at the ambiguity of terms such as "abutment" or "reconstructable" commonly used across definitions.[19]

In 2016, at the 20th meeting of the International Association of Pancreatology (IAP) in Japan, a consensus definition of BR-PDAC was sought.[19] The goal was to achieve a uniform definition with unambiguous terms and, in addition to anatomic considerations, to consider "biological" and "conditional" factors in defining BR-PDAC. The biological definition is based on factors that might raise the possibility of extra-pancreatic metastatic disease. Biological factors considered part of this consensus definition were pre-operative CA19-9 levels and lymph node metastases. Hartwig et al found that resectability inversely correlated with CA19-9 levels, with resection rates dropping below 70% for CA19-9 levels above 500 IU/mL compared to as high as 83% in patients with levels between 37 and 100 IU/mL.[20] According to data from the Japanese pancreatic cancer registry, an increasing number of positive lymph nodes identified pre-operatively was associated with poorer survival in patients with T1-T3 tumors. For example, median survival in patients

with T2 lesions having 0, 1–3, and >4 lymph nodes were 32.6 months, 21.3 months, and 14.6 months, respectively.[21] The conditional definition includes patient factors that introduce a high risk for morbidity or mortality after surgery and includes performance status (PS) and co-morbidities. Tas et al reported that performance status was the prognostic factor that best predicted survival across all stages of PDAC.[22] For example, in patients with Stage I/II disease with an ECOG PS of 0–1, median survival was 23.5 months, compared to 12.4 months in patients with PS ≥2. Ultimately, a consensus definition including anatomic, biological, and conditional factors was published in 2017.[19] According to this definition, R-PDAC, BR-PDAC, and LA-PDAC are first defined anatomically and then modified based on biological and conditional factors. Recent retrospective series in European and Asian populations have supported the validity of this consensus definition.[23–25]

The published literature consists of studies defining BR-PDAC in a heterogeneous fashion based on the previously mentioned definitions. In a meta-analysis of patient-level outcomes when using neoadjuvant FOLFIRINOX in BR-PDAC, 21 studies reported their definition of BR-PDAC. Eight of those studies used the NCCN definition, 7 used the AHPBA/SSO/SSAT definition, 2 used the Alliance, and 4 used other criteria. It remains to be seen whether the IAP consensus definition will become widely adopted. None of the major consensus guidelines have been updated to include this definition.[7,26,27] Utilization of an internationally agreed upon consensus in clinical practice and amongst future trials will be vital in arriving at a universal standard of care in this population.

Treatment

To facilitate an optimal surgical resection, a neoadjuvant therapeutic approach has emerged as the preferred strategy in treating BR-PDAC. A neoadjuvant treatment strategy offers several key benefits in this setting. This includes potential downstaging of disease, increased likelihood of an R0-resection, early treatment of micrometastatic disease, and an opportunity to identify individuals who quickly progress while on treatment and therefore have more aggressive tumors, for which surgery may be futile. Van Dam et al conducted a meta-analysis of randomized controlled trials comparing Neoadjuvant Therapy (NAT) vs upfront surgery in patients with R-PDAC and BR-PDAC.[28] Five out of the seven analyzed trials included BR-PDAC patients. Only one trial had an arm that included neoadjuvant FOLFIRINOX, the remainder utilizing gemcitabine-based chemotherapy or chemoradiotherapy (CRT). None of the studies used adjuvant FOLFIRINOX. They found that NAT improved the R0 resection rate to 42% vs 29%, N0 resection rate to 36% vs 17%, and median OS to 29 months vs 19 months. There was no difference in major surgical complications. Most of these trials were published before more active multi-agent regimens such as FOLFIRINOX were established as effective adjuvant therapy in R-PDAC. The focus in the literature has shifted towards investigating FOLFIRINOX and other multi-agent regimens with or without radiation, as NAT in BR-PDAC.

Neoadjuvant Chemotherapy

To date, the highest quality of evidence supporting a neoadjuvant chemotherapy approach in BR-PDAC using modern regimens comes from two phase II trials and a meta-analysis of neoadjuvant FOLFIRINOX based predominantly on retrospective evidence.

The first phase II trial by Yoo et al was a single-center trial conducted in Seoul, Korea. It investigated neoadjuvant mFOLFIRINOX followed by adjuvant gemcitabine in 44 patients with BR-PDAC, as defined by NCCN criteria.[29] Patients received eight cycles of mFOLFIRINOX and up to 6 cycles of adjuvant gemcitabine. The objective response rate was 34.1%, and 27 out of 44 (61.4%) patients received curative-intent surgery. Of the 17 patients who did not undergo surgery, 11 failed to do so due to inadequate tumor response, 5 had progressive disease, and 1 refused surgery despite conversion to resectable disease. An R0 resection was achieved in 22 out of 27 (81.5%), and N0 disease was observed in 17 (63%). The median Progression-free Survival (PFS) and OS were 12.2 and 24.7 months, respectively. Some notable weaknesses in this trial included that 20% of the patients on radiologic blinded central review were found to have LA-PDAC rather than BR-PDAC, suggesting some inter-observer variability among radiologists. Furthermore, the use of adjuvant gemcitabine is no longer in keeping with the current standard of care, which would instead support adjuvant mFOLFIRINOX or Gemcitabine/Capecitabine as more preferred regimens. Nevertheless, this study does suggest that neoadjuvant mFOLFIRINOX is tolerable and can yield impressive rates of R0 resectability in patients with BR-PDAC.

Kondo et al investigated the use of gemcitabine/nab-paclitaxel/S-1 (GAS) in a phase II trial in patients with BR-PDAC with arterial contact defined by modified NCCN criteria.[30] Previously, neoadjuvant gemcitabine/S-1 followed by adjuvant S-1 was found to improve median OS compared to upfront surgery in R-PDAC.[31] Patients in the study by Kondo et al were recruited from 3 centers in Hiroshima, Japan. They were treated with Gemcitabine/nab-paclitaxel on the first day of a 14-day cycle, with S-1 given twice daily on days 1–7, for a planned total of 6 cycles. The objective response rate was 43%, and two patients had progressive disease identified after completing chemotherapy. Surgical resection was achieved in 45 out of 47 (95.7%), and 40 out of 45 (89%) underwent an R0 resection. Median PFS and OS were 24.2 months and 41 months, respectively. This study ultimately yielded impressive results that in part, may be attributed to the aggressiveness of the surgeons in pursuing arterial resections. The international availability of S-1 may ultimately limit the utility of these results in some countries.

The ESPAC-5F prospective phase II trial also bears mentioning in this context, although only preliminary data is available from a report presented at the 2020 ASCO meeting.[32] In this trial, 90 patients with BR-PDAC as defined by NCCN criteria were randomized to receive immediate surgery, neoadjuvant gemcitabine and capecitabine for 2 cycles, FOLFIRINOX for 4 cycles or 50.4Gy of capecitabine-based chemoradiotherapy. Patients who had a surgical resection received adjuvant therapy. There was no difference in resection rate between the immediate surgery arm and NAT arms (62% vs 55%, p=0.668). The R0 resection rate was numerically higher in the NAT groups but not statistically significant (23% vs 15%, p =0.721). However, those patients receiving NAT did have an improved 1-year survival rate (77% vs 40%, p<0.001). Ultimately, these results support the efficacy of a neoadjuvant approach in BR-PDAC. However, given the small sample size in each arm, it is unlikely that much insight into the optimal neoadjuvant regimen will be gained from this trial. Also notable is the dramatically lower R0 resection rate across all arms in the study when compared to the other trials discussed previously.

Janssen et al published a patient-level meta-analysis of outcomes with neoadjuvant FOLFIRINOX.[33] Twenty-four studies were ultimately included in their review, 16 of which were retrospective analyses, 3 prospective cohorts, 4 Phase I, and 1 Phase 2. Only eight studies were exclusive to BR-PDAC patients, the remainder containing a mix that included LA-PDAC and metastatic patients. Eleven studies reported the median number of FOLFIRINOX cycles between 4 and 9 cycles. Overall patient-level median OS was 22.2 months, which was not different when comparing OS in retrospective vs prospective studies. Median PFS was 18 months. The pooled resection rate was 67.8%, with an R0 resection rate of 83.9%. Some studies included BR-PDAC patients who also received radiotherapy as part of their neoadjuvant protocol, though the percentage of patients receiving radiotherapy did not correlate with median OS.

Combined Modality Approaches

There has been greater interest in investigating combined chemotherapy and radiotherapy protocols for managing BR-PDAC. The addition of radiotherapy has been hypothesized to assist in sterilizing resection margins, thereby improving R0-resection rates and reducing the risk of locoregional recurrence.[34] The highest level of evidence comes from two phase III trials, the largest of which will be discussed below.[35–37]

The Dutch phase III PREOPANC trial, was a months trial that randomly assigned 246 patients with either R-PDAC or BR-PDAC to receive either preoperative gemcitabine-based chemoradiotherapy followed by surgery and adjuvant gemcitabine or upfront surgery followed by adjuvant gemcitabine. Staging laparoscopy was mandated for all patients to rule out occult metastases, and the preoperative group received three cycles of gemcitabine, with the second cycle being combined with 15 fractions of radiotherapy. In the initial analysis of the intention to treat population, there was no statistically significant difference in the median OS (16.0 months vs 14.3 months, p=0.0960) or resection rate (61% vs 72%, p = 0.0580). However, there was a significant improvement in the R0 resection rate (71% vs 40%, p < 0.0010). In analyzing only the patients with BR-PDAC (n = 113), there was an improvement in median OS (17.6 months vs 13.2 months, p = 0.029) and R0-resection rate (79% vs 13%, p < 0.001). Patients with an R0 resection had a better OS than patients with a non-R0 resection (HR 0.47, p < 0.001). Long-term follow-up results did demonstrate an advantage in median OS in the CRT group of 15.7 months vs 14.3 months. To date, this trial is the largest phase III trial of NAT in BR-PDAC. Its major limitation is the use of gemcitabine-based treatment protocols that are no longer the standard of care in the face of more recent data supporting the efficacy of multi-drug regimens such as FOLFIRINOX.

More recently, some phase II evidence supports the use of neoadjuvant chemoradiotherapy following FOLFIRINOX.[38] In this study by Murphy et al, 48 patients with BR-PDAC were planned to receive eight cycles of FOLFIRINOX followed by either short-course capecitabine-based chemoradiotherapy or long-course fluorouracil/capecitabine-based chemoradiotherapy. The latter was chosen only if there was persistent vascular involvement on restaging imaging. No postoperative chemotherapy was planned. Ultimately, 27 patients (56%) had short-course chemoradiotherapy, and 17 (35%) had long-course chemoradiotherapy, and among 32 patients who underwent resection, the R0 resection rate was 97%. Median OS and PFS were 37.7 monhs and 14.7 months, respectively among all eligible patients. Among patients who underwent resection, median PFS was 48.6 months, and median OS had not been reached. In this study, intraoperative RT (IORT) was allowed at the surgeon's discretion, though the rates at which patients received this modality were not offered. The benefits of IORT in a previous review were modest at best in patients with localized PDAC.[39]

Many of the earliest trials exploring NAT in BR-PDAC used a combined modality approach; however, the extent to which radiation provides an additional benefit on top of chemotherapy is uncertain. The A021501 phase 2 randomized trial aimed to address this question by randomizing 126 patients with BR-PDAC to receive preoperative mFOLFIRINOX (8 cycles) vs mFOLFIRINOX (7 cycles) followed by radiotherapy, preferably stereotactic body radiation therapy.[40] Four cycles of FOLFOX6 were considered on an adjuvant basis for patients that did not have evidence of residual or recurrent disease on a postoperative CT/MRI. At an interim analysis of the first 30 patients in each arm, 17 (57%) in arm 1 and 10 (33%) in arm 2 underwent an R0 resection. On this basis, the second arm was closed to accrual. The 18-month OS rate in arm 1 was 66.1%, with a median OS of 29.8 months. In the second arm, statistical requirements to conclude efficacy were not met due to early closure. Median OS was 17.1-month with an 18-month OS rate of 47.3%. One of the major criticisms of this trial is that it was not powered to detect a difference in outcomes between the two arms. Instead, each arm was powered to compare to a historical reference of 50% survival at 18 months. As a result, while this trial supports the efficacy of FOLFIRINOX in BR-PDAC, it does not conclusively discredit the utility of RT in this population.

In a systematic review and meta-analysis of the added value of radiotherapy following neoadjuvant FOLFIRINOX, Janssen et al compared outcomes from 8 studies (351 patients) investigating the efficacy of FOLFIRINOX alone vs 7 (161 patients) investigating FOLFIRINOX with radiotherapy.[34] Three studies in the FOLFIRINOX alone and 4 studies in the FOLFIRINOX with radiotherapy groups were prospective, with the remaining being retrospective. The pooled estimated median OS was 21.6 months for FOLFIRINOX alone vs 22.4 months for FOLFIRINOX with radiotherapy. The pooled R0 resection rate was higher for FOLFIRINOX with radiotherapy (97.6% vs 88.0%, p=0.045). N0, pathologic complete response and perineural invasion were comparable between the two groups.

Overall, there is promising data to support the efficacy of modern multi-agent chemotherapeutic regimens in the neoadjuvant treatment of BR-PDAC. However, the additional value of radiation cannot be recommended as part of the standard of care based on the available evidence. Phase III trials are ultimately needed to determine the optimal regimen, including its duration, before establishing a standard of care.

Restaging

The optimal way of selecting patients who can safely and effectively undergo surgical resection following NAT remains an area of active inquiry. Guidelines from both the NCCN and ASCO recommend restaging following NAT with a pancreatic protocol CT[7,27] The accuracy of a restaging CT after NAT has been questioned, however, with the concern that patients who are deemed to have unresectable disease based on a CT scan may have resectable disease when taken to the operating room. Before the initiation of NAT, CT has been shown to have a sensitivity and specificity to detect vascular invasion ranging from 70% to 96% and 82% to 100%, respectively, with a false-positive determination of vascular invasion being rare[41] Following NAT, however, though the cancer cells within the tumor may decrease, the pre-existing associated fibrous tissue often persists and results in high attenuation of the perivascular fat that may be interpreted as persistent vascular invasion. Radiation therapy might also induce regional edema that further obscures an accurate determination of vascular involvement.

The consequences of a higher false-positive rate of identifying vascular invasion following NAT were demonstrated in a study by Katz et al.[42] Of the 122 patients identified in their retrospective review, 84 (69%) were radiographically

determined to have stable disease, 15 (12%) had a partial response, and 23 (19%) had progressive disease. Only a single patient had radiographic evidence of a reduced vascular involvement sufficient to improve their anatomic stage. Despite this, 85 out of 101 (85%) patients who did not have metastatic progression on restaging underwent a successful pancreatectomy, with an R0 resection rate of 80%. Those that underwent pancreatectomy had a median OS of 33 months, compared to 22 months among the entire cohort. Though a radiographic regression was not evident for the vast majority of included patients, histopathologic evidence of treatment response was clear, with a grade IIA or greater treatment effect score in 81 out of 85 resected patients. Notably, vessel reconstruction was required in 60% of the patients who underwent resection, supporting the idea that these resections should occur in high volume, expert centers.

The concerns above underscore the need to consider additional strategies in determining resectability following NAT. For one, devising alternative definitions of anatomic resectability seems important. One retrospective study by Cassinotto et al found that even partial regression of tumor contact with any peripancreatic vessel was associated with an R0 resection rate of 91%.[43] Furthermore, the persistence of SMV/portal vein stenosis after NAT was not predictive of R1 resection. These findings suggest that the CT-based anatomic criteria intended to define resectability at diagnosis would be unreliable in the post-NAT setting. Alternative criteria are required if CT imaging continues being used for re-staging in this setting. To that end, Noda et al devised a resectability scoring system based on the extent of arterial involvement and resectability status as determined by NCCN criteria before and after neoadjuvant CRT.[44] On a retrospective basis, 112 patients were assigned a 5-point arterial involvement score (A score; 1 = no involvement, 2 = haziness, 3 = abutment, 4 = encasement, 5 = deformity) and a 4-point resectability score (R score; 1 = resectable, 2 = borderline resectable, 3 = BR with arterial involvement, 4 = locally advanced). A composite AR_{total} score was derived through summation of the A score and R score before and after CRT. This composite score was associated with R0 resection, and patients with an AR_{total} >9 had a significantly lower median OS and DFS. This study shows how more nuanced radiographic criteria can be useful in predicting the likelihood of effective surgery post CRT.

Other strategies that have proven potentially helpful in assessing resectability post-NAT are PET/CT and biomarkers such as CA19-9 and the neutrophil-to-lymphocyte ratio (NLR). Lee et al demonstrated that decreased parameters on PET/CT following neoadjuvant chemotherapy such as SUV_{max}, $SUV_{peak,}$ and MTV were associated with positive impacts on survival and recurrence.[45] An SUV_{max} <3 compared to SUV_{max} ≥3 post-NAT showed an improved tumor regression grade and lower R1 resection rate (17.9% vs 31.1%), though these were not statistically significant changes. Lee et al also demonstrated that a reduction in CA19-9 post-NAT is associated with better survival and reduced risk of recurrence.[46] Murakami et al, in a single-center retrospective analysis, found that a pre-NAT NLR > 2.78 predicted inoperability following NAT.[47]

Overall, while work is being done to identify more robust metrics of resectability, there is insufficient data to arrive at a uniform standard. To avoid depriving patients of potentially life-prolonging surgery based on imperfect metrics, it might be most reasonable to consider at the very least a re-staging laparoscopic assessment in patients who have no evidence of metastatic progression. This strategy has been assessed in the phase II NEOLAP trial of LA-PDAC patients.[48] In this trial, laparotomy was mandatory for patients with stable or responding disease following NAT. Though most patients had radiographically stable disease, the macroscopically complete resection rate of those that underwent surgical exploration was 57.5%.

Adjuvant Chemotherapy

Another element of management that currently lacks clarity is the role of adjuvant therapy in BR-PDAC patients who received NAT. The ASCO guidelines recommend that adjuvant therapy be offered for 6 months, including the preoperative course.[27] The NCCN suggests that adjuvant chemotherapy can be considered in this context.[7] In a retrospective review, Ivey et al found that postoperative chemotherapy was associated with an improved median OS, specifically in those with node-positive disease.[49] The majority (69.3%) of patients received neoadjuvant FOLFIRINOX, though the regimen, duration, and the number of cycles of NAT did not predict OS. Ultimately, there is no randomized controlled data to advise on this topic. However, it would seem reasonable to consider adjuvant chemotherapy in BR-PDAC patients post NAT, particularly if they had node-positive disease.

Future Perspectives

While the evidence informing optimal management of BR-PDAC is growing, there remain several challenges that have not been adequately addressed. The most pressing need is phase III clinical trial evidence to guide the optimal neoadjuvant regimen for this population. Perhaps the most notable of the ongoing phase III trials is the PREOPANC-2 trial which is targeting the recruitment of 368 R/BR-PDAC patients to compare the efficacy of neoadjuvant FOLFIRINOX to neoadjuvant gemcitabine-based chemoradiotherapy followed by adjuvant gemcitabine.[50] Additionally, there are ongoing phase III trials investigating neoadjuvant nab-paclitaxel/gemcitabine vs FOLFIRINOX (NCT04617821) and a novel immunotherapy-based strategy comparing neoadjuvant FOLFIRINOX ± anti-PD-1 blockade (NCT03983057). Concerning the latter trial, the demonstrated efficacy of immunotherapy in PDAC with intact mismatch repair has been limited, in part owing to its low tumor mutational burden and immunosuppressive tumor microenvironment.[51] However, there appears to be a synergistic effect of immunotherapy in combination with cytotoxic agents.[52] Interestingly, the cancer vaccine, algenpantucel-L did not improve survival when added to chemotherapy plus chemoradiotherapy in a phase III trial.[53]

PDAC is known to be an inherently chemoresistant tumor, and therefore efforts to investigate novel therapeutic agents will become increasingly important. The PIONEER-Panc platform trial exemplifies how multiple treatment arms can simultaneously and efficiently be tested against a common control.[54] In its initial conception, six cohorts including treatment naïve or previously treated patients with either R-PDAC, BR-PDAC, or LA-PDAC have been devised, each with one or multiple concurrent treatment arms. While its initial design is intended to test different chemotherapeutic regimens, it could conceivably be used to test non-cytotoxic agents. Platform trials have successfully been employed to investigate treatments in several other solid tumor groups, perhaps most notably with the STAMPEDE platform that has published several practice-changing results in the management of prostate cancer.[55]

It is thought that one of the contributors to the poor prognosis of PDAC is its heterogeneity at a molecular level. Recent genomic, transcriptomic, and metabolomic analyses have highlighted the heterogeneity between individuals and within the tumor of a single individual.[56] Certain somatic mutations such as KRAS or CDKN2A mutations have been shown to impact prognosis, likely related partly to a patient's response or lack thereof to standard therapies.[57] In the POLO trial, the efficacy of maintaining olaparib in M-PDAC patients with germline BRCA pathogenic variants following platinum-based chemotherapy was investigated and olaparib use was associated with improved progression-free survival.[58] Reddy et al demonstrated the potential impact of molecular diagnostics in BR-PDAC.[59] In their retrospective analysis, they found that patients with KRAS G12V mutations showed better pathologic tumor regression grade to NAT than patients with other KRAS mutations. Furthermore, NOTCH1/2 mutations were associated with worse OS, PFS, and distant metastasis-free survival. As our understanding of the molecular underpinnings of PDAC grows, so too should our ability to optimally select patients for both NAT and surgical resection.

Conclusion

BR-PDAC is a recently defined clinical entity with unique considerations for management. Only recently has a consensus definition considering anatomic, biologic, and conditional factors been conceived. It remains to be seen whether such a definition will be adopted broadly in future trials. NAT offers several advantages and has emerged as the preferred method of treatment administration. Uncertainty remains regarding the additional benefit of radiation therapy when added to chemotherapy, and phase III trials are ultimately needed to define the optimal regimen. Restaging following NAT is also an ongoing challenge due to how NAT obscures our ability to define resectability based on CT imaging. Liberalized criteria for taking patients to the operating room post-NAT may be necessary until more reliable restaging metrics can be developed. As has been seen in the management of many other cancers, an increasing emphasis on understanding the molecular underpinnings of PDAC will be essential in taking the next leap towards better care for these patients.

Disclosure

Dr Omar Abdel-Rahman is part of the advisory board for Amgen, Eisai, Ipsen, Roche, Lilly, and Bayer, outside the submitted work. The authors report no other conflicts of interest in this work.

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