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Hyperprogression under treatment with immune-checkpoint inhibitors in patients with gastrointestinal cancer: A natural process of advanced tumor progression?

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Abstract

Immunotherapy has shown great promise in treating various types of malignant tumors. However, some patients with gastrointestinal cancer have been known to experience rapid disease progression after treatment, a situation referred to as hyperprogressive disease (HPD). This minireview focuses on the definitions and potential mechanisms of HPD, natural disease progression in gastrointestinal malignancies, and tumor immunological microenvironment.

Key Words: Hyperprogressive; Immunotherapy; Natural process; Gastric cancer; Colorectal cancer

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Core Tip: There have been several literature reviews on the definition, incidence, predictors, potential biomarkers, and prognosis of hyperprogressive disease. However, this is a minireview of two conflicting concepts: HPD is a new form of immunological response *vs* a natural process of advanced tumor progression. It also takes a look at cellular and molecular mechanisms of the pathways of the tumor microenvironment and recent clinical trials exploring the risk factors and mechanisms of HPD in gastrointestinal cancer.

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INTRODUCTION

A minority group of patients with gastrointestinal cancer during the treatment of checkpoint inhibitors (ICIs) show paradoxical acceleration in tumor growth. Patients with hyperprogressive disease (HPD) show a shortened progression-free survival or overall survival as compared to patients with natural progressive disease (PD)[1]. According to a recent meta-analysis, the overall incidence of HPD was 13.4% (95% confidence interval [CI], 10.2%-16.6%), with a range of 5.9% to 43.1%[2]. However, this might be an underestimation and the true incidence could be higher, as a certain number of patients might not be diagnosed due to clinical disease progression. Colonic and gastric cancers are the fifth and sixth most common types of cancer, ranking second and fourth worldwide in terms of mortality, respectively[3]. The survival benefits of ICIs such as nivolumab and pembrolizumab in gastrointestinal cancer vary in clinical studies due to different molecular targets and cytotoxicity[4]. To make ICIs safer and more effective in treating gastrointestinal cancer, there is an immense need to explore the molecular mechanism of HPD. This minireview will discuss two contradicting viewpoints in this regard: Is the development of HPD unique to immunotherapy in gastrointestinal cancer patients or is it a natural process of progression of advanced cancers?

DEFINITION

The most widely used indexes for HPD diagnosis include tumor growth kinetics (TGK), time to treatment failure (TTF), response evaluation criteria in solid tumors (RECIST), and tumor growth rate (TGR) or their combinations. However, there has been no consensus on the medical diagnosis criteria for HPD so far.

Kato *et al*[5] suggested three criteria to define HPD in patients with non-small cell lung cancer (NSCLC): Progression increase (TGR) of at least two times, a tumor burden increase of 50%, and TTF < 2 mo. Kim *et al*[6] defined HPD as a progressive disease (PD) based on TGK or TGR, *i.e.*, an increase of more than two folds of TGR or TGK during the treatment time interval as compared to that of the reference times in sicker populations already diagnosed with PD by RECIST 1.1 at the first response assessment after PD-1/PD-L1 inhibitors. Ten Berge *et al*[7], Petrioli *et al*[8], and Refae *et al*[9] adopted the same definition for HPD by using RECIST 1.1 at first assessment and TGRPOST/TGRPRE ≥ 2.

In a retrospective analysis of 270 patients with pan-cancer, three criteria were used in defining HPD: (1) 40% increase in sum of target lesions (STL) *vs* baseline or/and; (2) 20% increase in STL *vs* baseline plus the appearance of new lesions in at least two different organs; and (3) Minimum increase in the measurable lesions of > 10 mm and PD by RECIST at first 8 wk after treatment initiation[10]. In the other two retrospective studies about advanced gastric cancer (AGC), HPD was similar for Aoki *et al*[2] and Lu *et al*[11], who defined it as TGKPOST/TGKPRE ≥ 2. There are a few retrospective AGC studies evaluating the incidence of HPD, which are summarized in Table 1.

In a recent meta-analysis, subgroup analysis of varied underlying malignancies suggested that the overall incidence of HPD was 19.4% (95% CI: 9.7%-29.1%) in patients with AGC[2]. An optimal definition of HPD should be comprehensive and contain few variables (early tumor burden increase, TGR, TGK, new lesions, TTF, and clinically associated criteria, *etc.*). There is a need to establish quantifiable criteria based on Eastern Cooperative Oncology Group (ECOG) performance status or Karnofsky Performance Scale score, a systematic measure of tumor growth acceleration, and alternative diagnostic criteria.

Table 1 Incidence and definition of hyperprogressive disease in advanced gastric cancer patients receiving immunotherapy

Study agent	Tumor	HPD definition	Number of patients	Incidence of HPD, %	Ref.
Nivolumab	AGC	(1) An increase of $\geq 50\%$ in the sum of longest diameter (SLD) of target lesions at 8 wk post baseline; (2) An increase of $\geq 20\%$ in the sum of longest diameter of target lesions at 8 wk post baseline; and (3) An increase of $\geq 100\%$ in the sum of longest diameter of target lesions at 8 wk post baseline	243; 243; 243	5.4; 27.6; 1.2	Feng <i>et al</i> [75], 2018
PD-1 inhibitor monotherapy	AGC	$TGK_{POST}/TGK_{PRE} \geq 2$	9	55.6	Sugimoto <i>et al</i> [76], 2018
PD-1 inhibitor monotherapy	AGC	$TGR_{POST}/TGR_{PRE} \geq 2$	105	24.8	Sunakawa <i>et al</i> [77], 2019
PD-1 inhibitor monotherapy	AGC	$TGR_{POST}/TGR_{PRE} \geq 2$	218	17.4	Suzuki <i>et al</i> [78], 2020

HPD: Hyperprogressive disease; AGC: Advanced gastric cancer; TGK: Tumor growth kinetics; TGR: Tumor growth rate.

MAIN VIEWPOINTS

Natural process

First, HPD is not caused by immunotherapy alone. A *post hoc* analysis from the OAK study (a randomized phase 3 study to describe results of atezolizumab therapy in NSCLC) suggested that fast progression is a universal phenomenon that coexists with ICIs and chemotherapy. The proportion of patients encountering fast progression criteria was analogous between the docetaxel and atezolizumab cohorts ($n = 41$ [9.6%] *vs* $n = 44$ [10.4%], respectively)[12]. However, a retrospective study by Aoki *et al* found that HPD incidence was slightly higher with nivolumab (29.4%) than irinotecan (13.5%) ($P = 0.0656$)[13], suggesting that hyperprogression after baseline is not unique to PD-L1 blockade therapy in NSCLC and AGC. There are also unbalances in the arms that may affect the therapeutic response. For instance, the irinotecan group had fewer patients with recurrent disease in contrast with the ICI group (18 of 66 [28.8%] *vs* 19 of 34 [52.9%]; $P = 0.028 < 0.05$). A higher proportion of patients treated with ICIs had posterior line therapy (13 of 34 [38.2%]) compared with those in the chemotherapy (20 of 66 [30.3%]; $P = 0.502$)[13]. After immunotherapy, it is possible that therapeutic resistance in patients who do not respond to ICIs developed secondarily to past chemotherapy. The large real-world data regarding gastric tumor treated with nivolumab had showed an insignificant difference in median overall survival (2.40 *vs* 2.79 mo; $P = 0.8$)[14] in patients with PD with or without HPD.

HPD is not unique to immunotherapy as it is also present in chemotherapy, but the incidence is higher in the former. This phenomenon also applies to NSCLC under treatment of Sorafenib (a multi-target tyrosine kinase inhibitor) and in metastatic renal cell carcinoma[15,16]. According to published data, HPD incidence is correlated to the type of tumor[17]. The incidence of immunotherapy-related HPD in AGC cases ranges from a few percent to about 21% (13 of 62)[18], according to a recent study, while the incidence stands at 6% in colorectal cases[19].

There is increasing evidence demonstrating that the predictive factors for HPD include age > 65 years, metastasis burden (number of sites of metastatic disease), local and regional relapse ($TGKR \geq 2$: 90% *vs* $TGKR < 2$: 37%; $P = 0.008 < 0.01$), but do not include distant or local recrudescence, liver metastases, a large tumor at baseline, and ECOG performance status of 1 or 2[12,18-23].

A recent study suggested that hyperprogression is usually associated with high risk genetic alternations (*i.e.*, MDM2/4, epidermal growth factor receptor [EGFR], DNMT3A, AKT1 E17K, KRAS, and FBXW7) [18,23,24], which correlate with a shorter time to TTF. For instance, MDM2/4 is an oncogenic gene which functions through inactivation of p53, a tumor suppressing transcription factor. Experiments have demonstrated that MDM2 mediates resistance to immunotherapy by reducing T cell activation in malignancies[18]. However, the relationship between MDM2/4 amplification and hyperprogression remains unclear, although some scholars hypothesize about the involvement of a genomic site on the MDM2 amplicon[25,26]. Another study reported that one of 36 patients with AGC under nivolumab treatment had MDM2 gene amplification[27]. There is also evidence showing that two of 47 patients with AGC had MDM2 gene amplification, where one patient developed HPD under nivolumab treatment[18]. Data from a few studies investigating MDM2 inhibitors suggested that the combination of MDM2 inhibitors and immunotherapy could be an alternative strategy for patients with MDM2 AMP tumor and hyperprogression.

The EGFR signaling cascade is a key regulator in cancer development, survival, differentiation, and cell proliferation. It belongs to the ERBB family of tyrosine kinase receptors[28]. During nivolumab administration as anti-PD1 treatment in patients with AGC, three patients with ERBB2 mutation or amplification showed HPD ($P = 0.48$ or 1)[18]. Despite that all patients with FBXW7 mutation or KRAS amplification developed HPD in this study, the association between these genetic alterations and

hyperprogression needs to be further explored. There is evidence supporting the presence of EGFR mutated tumors (EGFR E746-A750 del and T790M mutation or EGFR exon 20 insertion mutation and MYC amplification) in patients with non-gastrointestinal (non-GI) cancer such as NSCLC who showed a less satisfactory response to ICIs and rapid progression[29]. According to a case report, the subtype of EGFR Kinase Domain Duplication, somatic alteration EGFR exon 2-28 duplication is present in a patient with esophageal squamous cell carcinoma who developed hyperprogression under camrelizumab treatment, existed[30]. A retrospective study on pan-cancer reported that the mutated type of KRAS mutation was associated with HPD in colorectal cancer (23.5% in non-HPD *vs* 80.0% in HPD; $P = 0.039 < 0.05$)[31].

A case report presented that a 64-year-old man with stage IIIA colon tumor remained disease-free for 10 years during the treatment with adjuvant chemotherapy. After recurrence in the liver, lymph nodes, and ureters, the patient was treated with FOLFIRI and bevacizumab, followed by cetuximab and irinotecan. In 2016, he was started on compassionate use of pembrolizumab for 9 mo until his CEA progressively increased and PET-CT imaging displayed progression in the liver and ureters. Atezolizumab was given for his urothelial tumor; however, the CEA rapidly increased 3 mo later. After discontinuing pembrolizumab and atezolizumab and following treatment with nivolumab and ipilimumab combination for four cycles, his CEA decreased to a stable level, and PET-CT imaging revealed a lower uptake in his original cancer as well as other metastases[32]. If hyperprogression is strongly correlated with immunotherapy, immunotherapy should be terminated after the occurrence of disease progression, although in this case, the patient was treated effectively with sequential PD-1/PD-L1 blockades as well as dual checkpoint inhibitors with good control of tumor burden. In the non-GI tumors, a patient with metastatic breast tumor developed HPD during the treatment of pembrolizumab, then the patient switched to the chemotherapy plus the PD-L1 inhibitor atezolizumab[33]. The patient maintained a partial response to rechallenge with atezolizumab for more than 8 mo. Repeated exposure to different ICIs after failure of initial ICI treatment existed in the other types of tumors, such as NSCLC [34-36].

These phenomena may indicate that PD-L1 blockade relieves B7.1 sequestration *in cis* through PD-L1 in dendritic cells[37], which leads to a B7.1/CD28 reaction to increase T cell priming, and rechallenging with other PD-L1/PD-1 inhibitors might synchronously revive immune response in the tumor microenvironment (TME)[38,39]. Further research is needed to explore what patient population are most likely to benefit from successive ICIs and the basic molecular and cellular mechanisms of different ICIs by analyzing gene expression and genetic mutations, and molecular dynamics simulations of the cancer microenvironment.

Most importantly, large-scale randomized controlled trials are urgently warranted to clarify the correlation among predictive factors for HPD, the molecular mechanisms of hyperprogression, and the natural progression of advanced malignant neoplasms in GI tumors. Prospective observational studies are also essential to compare treatment courses after each treatment.

This minireview has several limitations. Most of the referenced studies were not randomized controlled trials and instead were mostly retrospective. The incidence of HPD is lower in GI tumors than in lung cancers. The future perspective on HPD in GI tumor patients should be focused on the predictive biomarkers of response to immunotherapy, immuno-oncology mechanism, and the murine model of HPD.

Clear effect of immunotherapy

Tumor infiltrating lymphocytes in patients with HPD are rich in regulatory T (Treg) cells, a subset of CD4⁺ T cells with immunosuppressive function. They highly express PD-1 or CTLA-4 and thus can be targeted by ICIs[40,41]. PD-1 blockade or deficiency in T cells enhances T cell receptor and CD28 signaling, which leads to the activation of Treg and conventional T cells. The former suppresses and the latter promotes antitumor immunity[42,43]. Anti-PD-1 antibody in Treg cells highly augments their proliferation and inhibition of antitumor immunity[44] in AGC patients[45,46]. Up-regulation of the EGFR pathway suppresses immune responses by activating Tregs after using ICIs[23]. Moreover, high Treg ratio is associated with poorer survival in patients with colorectal carcinoma and gastric cancer[47, 48].

INF- γ hypothesis

When utilizing ICIs, the CD8⁺ T cells release INF- γ and up-regulate PD-L1 expression in tumor cells to make NLRP3 induce immunosuppressive myeloid-derived suppressor cells into the TME, which results in suppression of P53 and tumor growth[49].

Indoleamine 2,3-dioxygenase, an immunosuppressive enzyme, contributes to immune tolerance, inhibition of inflammation, and autoimmunity[50]. Up-regulation of indoleamine 2,3-dioxygenase inhibitors (IDO) promotes the release of the immunosuppressive cytokines IL-10, angiopoietin 2, and INF- γ into the TME. It enhances the infiltration and proliferation of effector T cells and hyperactivates the JNK pathway, resulting in P53 suppression and activation-induced cell death (AICD), which leads to T-cell depletion[50-53]. IFN- γ also induces overexpression of interferon regulatory factor 8 by activating JAK-STAT signaling, which might stimulate mouse double minute 2 homolog (MDM2) expression[54-56]. Mechanistically, MDM2 negatively regulates T-cell activation through degradation of the

transcription factor NFATc2[57] or inhibits P53 activity by its direct interaction[58-60], suggesting a potential role of MDM2 in immune evasion.

CD38 hypothesis

CD38, a multifunctional ectoenzyme, modulates adenosine receptor signaling in the TME, leading to the inhibition of T-cell proliferation and function[49]. Adenosine in the TME has two dominating aspects: It increases the number of T-regulatory cells and the polarization of M2 macrophages; active adenosine A2A receptor in tumor cells induces treatment resistance and under-regulation of P53[61,62]. CD38 leads to the expression of AICD and FasL on T-cells[63] and angiopoietin 2 that promotes angiogenesis and triggers more invasive M2 macrophages expressing PD-L1. CD38 also makes tumor cells express HIF-1 α to release insulin-like growth factor and vascular endothelial growth factor[64], which recruit Treg cells or promote tumor growth by initiating paracrine or autocrine signaling.

Other mechanisms

ICIs may stimulate tumor-infiltrating dendritic cells to secrete IL-10. It impedes antigen presentation and co-stimulation, which inhibits antigen-specific T cell responses. Alternative immune checkpoints increasing T cell depletion, such as LAG-3, T2M-3, and CTLA-4, might result in HPD[65]. TH1 and TH17 recruit neutrophil populations, causing inflammation that contributes to proliferation and survival of malignant cells, angiogenesis, metastasis, and subversion of adaptive immunity[66]. Group 3 innate lymphoid cells produce IL-22 to promote tumor growth through STAT3 activation[67]. Fc receptor promotes functional reprogramming by ICIs to make related immune cells, such as tumor-associated macrophages or M2-like CD163⁺CD33⁺PD-L1⁺ epithelioid macrophages, more aggressively cause HPD [68,69]. CD74-MIF was found absent in HPD, thus we speculated that it potentially impairs proliferation of effector T cells, resulting in HPD[54]. Radiotherapy can lead to changes in the TME by inhibiting TGF expression[70]. Studies have confirmed that TGF-derived epithelial-mesenchymal transition increases mesenchymal cells, leads to tissue fibrosis, and restricts T cell movement and anti-tumor responses[71-73]. By limiting the infiltration of inflammatory/immune cells, it suppresses CD8⁺ T cells and NK cell-mediated anti-tumor response[74]. HPD is associated with flared expansion of FoxP3 T-regulatory cells in gastric cancer patients[25].

CONCLUSION

The scientific community does not have a consensus on HPD definition, and different criteria are used for different cancer types. Whether ICIs are used or not, what appears to be HPD could be the natural progression of advanced cancer associated with MDM2/4 or EGFR signaling. The INF- γ and CD38 hypotheses have been studied in depth in the development of HPD. In the setting of immunotherapy, a large number of immunosuppressive and inflammatory factors affect the TME, resulting in decreased P53 expression or inducing oncogenic signaling, which are all potential mechanisms of HPD.

FOOTNOTES

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Retrospective Study

Whipple's pancreaticoduodenectomy at a resource-poor, low-volume center in Trinidad and Tobago

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Abstract

BACKGROUND

Many authorities advocate for Whipple's procedures to be performed in high-volume centers, but many patients in poor developing nations cannot access these centers. We sought to determine whether clinical outcomes were acceptable when Whipple's procedures were performed in a low-volume, resource-poor setting in the West Indies.

AIM

To study outcomes of Whipple's procedures in a pancreatic unit in the West Indies over an eight-year period from June 1, 2013 to June 30, 2021.

METHODS

This was a retrospective study of all patients undergoing Whipple's procedures in a pancreatic unit in the West Indies over an eight-year period from June 1, 2013 to June 30, 2021.

RESULTS

This center performed an average of 11.25 procedures per annum. There were 72 patients in the final study population at a mean age of 60.2 years, with 52.7% having American Society of Anesthesiologists scores \geq III and 54.1% with Eastern Cooperative Oncology Group scores \geq 2. Open Whipple's procedures were performed in 70 patients and laparoscopic assisted procedures in 2. Portal vein resection/reconstruction was performed in 19 (26.4%) patients. In patients undergoing open procedures there was 367 ± 54.1 min mean operating time, 1394 ± 656.8 mL mean blood loss, 5.24 ± 7.22 d mean intensive care unit stay and 15.1 ± 9.53 d hospitalization. Six (8.3%) patients experienced minor morbidity, 10 (14%) major morbidity and there were 4 (5.5%) deaths.

CONCLUSION

This paper adds to the growing body of evidence that volume alone should not be used as a marker of quality for patients requiring Whipple's procedures. Low volume centers in resource poor nations can achieve good short-term outcomes. This is largely due to the process of continuous, adaptive learning by the entire hospital.

Key Words: Pancreas; Surgery; Pancreatectomy; Whipple's; Pancreaticoduodenectomy

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Core Tip: Although conventional recommendations suggest that Whipple's procedures should only be performed in high-volume centers, this is not practical in many nations. This paper adds to the growing body of evidence that volume alone should not be used as a marker of quality for patients requiring Whipple's procedures. Low volume centers in resource poor nations can achieve good short-term outcomes. This is largely due to the process of continuous, adaptive learning by the entire hospital.

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INTRODUCTION

Whipple's procedure is a major operation designed to treat malignant peri-ampullary lesions[1,2]. Many Whipple's procedures tend to be concentrated in high-volume hospitals, usually found in high income nations[3,4,5].

Pancreatic surgeons in the West Indies work in limited-resource environments and perform small numbers of resections annually[5]. There are no centers that qualify as high-volume centers in this setting. Traditional teaching suggests that this scenario is not ideal. In this paper, we examine outcomes of Whipple's procedures at a low volume/resource environment in a West Indian nation.

MATERIALS AND METHODS

The country of Trinidad and Tobago is comprised of two small islands with a cumulative population of 1.35 million persons. A pancreatic surgery unit was established in the main referral hospital in 2013. This unit was led by a single fellowship-trained pancreatic surgeon, one dedicated senior resident and two junior residents. We received permission from the institutional review board to collect and examine data from all consecutive patients who underwent Whipple's procedures in this setting over an eight-year period from June 1, 2013 to June 30, 2021.

We identified patients by reviewing the hospital records and operating room log books. The hospital records for all patients who underwent Whipple's operations were retrieved for detailed review. The data extracted included diagnoses, performance scores, estimated operative blood loss, duration of operation (from incision to closure), therapeutic outcomes, post-operative morbidity and mortality. Complications were classified according to the modified Clavien-Dindo system[6]. Pancreatic leak was categorized according to the International Study Group on Pancreatic Fistula criteria. Cardiopulmonary complications included myocardial infarction, arrhythmia, congestive heart failure, pneumonia, pulmonary embolus, and respiratory failure. Statistical analyses were performed using SPSS ver 16.0.

RESULTS

There were 90 patients with operable peri-ampullary neoplasms who had Whipple's procedures attempted (mean annual case volume of 11.25). The detailed paper-based hospital record could not be retrieved in 14 cases. A search of the intensive care unit (ICU) and hospital registers indicated that these 14 patients were discharged from hospital alive, but they were excluded from the final analysis since their clinical details were not available. We also excluded 4 patients who were deemed irresectable at the time of operation and had palliative bypasses. The final study population included 72 patients who underwent Whipple's procedures.

There were 32 men and 40 women at a median age of 61 years (range 46-77; mean 60.2; SD \pm 9.28). There were 62 (86%) patients with > 1 comorbid condition, 38 (52.7%) with American Society of Anesthesiologists (ASA) scores $> II$ and 39 (54.1%) with performance scores > 1 (Tables 1 and 2). Pancreatic ductal adenocarcinoma was the commonest pathology, as outlined in Figure 1.

The operation was anticipated to be technically difficult in 26 (36.1%) persons due to: vein involvement requiring resection and reconstruction (19 patients), prior open surgery for abdominal sepsis (5 patients) and planned laparoscopic approach (2 patients).

Operative details

Four patients had palliative bypasses as they were deemed irresectable at the time of operation due to: invasion of common hepatic artery (1 patient), metastatic disease (2 patients) and portal vein encasement (1 patient). Data on these patients were excluded from further analysis.

In 70 cases, the operation was planned *via* the open approach using a modified Makuuchi incision, aided by an Omnitract® retractor (Integra Life Sciences, Princeton, NJ). This was our preferred incision as it afforded us good access to the pancreatoduodenal complex in the retro-peritoneum.

Two patients underwent laparoscopic-assisted Whipple's procedures. In these cases, Kocherization of the duodenum, dissection of the pancreatic neck tunnel, dissection of the gallbladder and structures in the hepatoduodenal ligament, transection of the stomach and full mobilization of the duodenum were completed laparoscopically. A 7 cm midline incision was used to create a pancreatogastrostomy, hepatico-jejunostomy and for specimen removal. Both of these patients had ampullary lesions and none required vein resection or reconstruction.

Clinical outcomes

The median operating time for open Whipple's procedures was 350 min (range 260-485; SD \pm 54.1; mean 367). The median blood loss was 1.2 L (range 0.6-4.0; SD \pm 0.7; mean 1.4) and 2 packed red cell units was the median transfusion rate (range 0-5; SD \pm 1.4; mean 1.88).

Nineteen (26.4%) patients underwent planned vein resections and reconstruction. Reconstruction was performed with primary anastomoses in 13 cases, vein patches in 4 cases and interposition grafts in 2 cases.

In the patients with technically difficult operations, the duration of operation was 374 ± 57.34 minutes (mean \pm standard deviation), estimated blood loss was 1494 ± 815 mL (mean \pm standard deviation) and 2 ± 1.6 packed red cell units (mean \pm standard deviation) were transfused per patient.

We insisted on a policy of mandatory admission to intensive care (ICU) after Whipple's resection since institutional limitations prevented the expected level of supportive care to be delivered in other areas. Our patients stayed in the ICU for 3 ± 7.22 d (mean \pm standard deviation), with 29 (40.3%) needing extended stay > 72 h for ventilator and/or inotropic support. The median hospital stay for all patients was 12 ± 9.6 d (mean \pm standard deviation).

Morbidity/mortality analysis

There were no complications in 56 patients within this series. Patients without complications remained in ICU for 3.5 ± 1.5 (mean \pm standard deviation) d and remained hospitalized for 14 ± 7.9 (mean \pm standard deviation) d. Patients who experienced a complication remained in ICU for 9.8 ± 11.3 (mean \pm standard deviation) d and remained hospitalized for 15.3 ± 8.4 (mean \pm standard deviation) d.

There were 16 (22.2%) patients with overall morbidity - 6 (8.3%) minor and 10 (14.0%) major (Table 3). There were 4 (5.5%) in-patient deaths: (1) A man at 53 years of age with pancreatic head adenocarcinoma who developed massive bleeding from a pseudoaneurysm that could not be controlled at re-operation; (2) A 59-year-old man who did not receive pre-operative stenting and had frank pus in the biliary system at operation. He developed bacteremia and septic shock; (3) A 48-year-old man who developed a leak from the jejuno-jejunal anastomosis, leading to intra-abdominal sepsis and multiple organ failure; and (4) A 70-year-old man with no prior cardiac history who succumbed to a massive myocardial infarction on day 5 post-operation.

In an attempt to analyze the outcomes chronologically, we tabulated the case volume by year (Table 4). The case volume remained relatively stable with time, although there was a notable reduction in the case volume for the last period (June 2020 to June 2021) due to effects of the coronavirus disease 2019 pandemic. We also analyzed complications and mortality chronologically as outlined in Figure 2. Although minor morbidity reduced over time, there was no statistically significant change in outcomes over time.

We also analyzed clinical outcomes according to patient risk as stratified by their performance scores and ASA scores (Table 5). Although there were trends toward greater morbidity and mortality in high-risk patients, none of these parameters attained statistical significance.

Table 1 American society of anesthesiologists scores for patients undergoing Whipple's procedures in a low volume caribbean centre

Score	American Society of Anesthesiologists Descriptor	No (%)
I	Completely healthy	10 (13.9)
II	Mild systemic disease	24 (33.3)
III	Severe systemic disease that is not incapacitating	30 (41.7)
IV	Incapacitating disease that is a threat to life	8 (11.1)
V	Moribund and not expected to survive > 24 h	0

Table 2 Performance scores for patients undergoing Whipple's procedures in a low volume caribbean centre

Grade	Eastern Cooperative Oncology Group performance status	No (%)
0	Fully active, able to carry out all activities without restriction	13 (18.1)
1	Restricted in physically strenuous activity, but ambulatory and able to carry out light work	20 (27.8)
2	Ambulatory and capable of self care, but unable to carry out work activities. Up and about > 50% of waking hours	34 (47.2)
3	Capable of limited self care and confined to bed or chair for more than 50% of waking hours	4 (5.6)
4	Completely disabled and cannot carry on self care. Confined to bed or chair	1 (1.4)
5	Dead	0

Table 3 Complications after Whipple's procedures in a low volume caribbean centre

Morbidity	Description	No	%
Overall	Number of patients with any complication	16	22.2
Minor	Clavien-Dindo I or II	6	8.3
	Pneumonia	2	
	Deep vein thrombosis	1	
	Delayed gastric emptying	1	
	Gastrointestinal bleeding	2	
Major	Clavien-Dindo III or IV	10	13.9
	Anastomotic dehiscence	1	
	Massive upper gastrointestinal bleeding	1	
	Myocardial infarction	3	
	Pseudoaneurysm	2	
	Biliary sepsis as a source of septicemia	2	
	Post-operative pancreatic fistula/intra-abdominal collection	1	
Mortality	30-d mortality: All causes: (1) Massive bleeding from a pseudoaneurysm; (2) Generalized sepsis secondary to cholangitis; (3) Jejunio-jejunal anastomotic leak leading to multiple organ failure; and (4) Myocardial infarction	4	5.6

DISCUSSION

Although it is a high-risk operation, Whipple's procedure is the only existing treatment with the potential to cure peri-ampullary malignancies[7,8]. Early series in the late 1960s reported 60% post-operative morbidity and mortality rates approaching 25%[9-11], but with better surgical equipment and supportive care, the safety profile has improved. Modern reports document 30-d mortality rates between 4%-6%[7,8,12-14].

Much of the recent progress in surgical treatment has been aimed at minimizing peri-operative morbidity with a multidisciplinary approach to care[1,2], advanced cross-sectional imaging[1,15], specialized surgical equipment[5], appropriate support services[16,17], full-time intensive care, interventional radiology and gastroenterology services[1,14-17] and quaternary surgical training. In our

Table 4 Chronologic analysis of clinical outcomes after Whipple's procedures in a low volume caribbean centre

Year	Case volume	Minor morbidity	Major morbidity	Mortality
2013-2014	9	0	1	1
2014-2015	10	1	2	0
2015-2016	11	1	3	0
2016-2017	8	1	1	1
2017-2018	10	1	2	1
2018-2019	8	0	0	0
2019-2020	11	1	1	1
2020-2021	5	1	0	0
Total	72	6 (8.3%)	10 (13.9)	4 (5.6%)

Table 5 Clinical outcomes stratified according to patient risk

American Society of Anesthesiologists scores			
Parameter	ASA I-II (34)	ASA III-IV (38)	P
Overall morbidity	7 (20.6%)	9 (23.7%)	0.7843
Overall mortality	2 (5.9%)	2 (5.3%)	1.000
Eastern Cooperative Oncology Group performance status			
Parameter	ECOG 0-2 (67)	ECOG 3-4 (5)	P
Overall morbidity	14 (20.9%)	2 (40%)	0.307
Overall mortality	3 (4.5%)	1 (20%)	0.255

ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group.

center, we have been able to achieve many of these goals.

Another change was the centralization concept, that was popularized in the early 21st century[3,4,11-13]. Published data showed reductions in morbidity[1,2,18], cost[19], mortality[1,2,18,10,20-22] and hospitalization[1,18] in high-volume hospitals. However, the high-volume definition remained elusive. Some have designated centers performing as few as 3 Whipple's procedures per annum as high-volume centers[12,14,19], while others reserve this designation for facilities performing ≥ 30 per annum[18,23,24]. Most researchers quote numbers ≥ 18 Whipple's procedures per annum as high volume[2,7,11,18,22-26]. Using this definition, our facility did not qualify as high-volume. Although our center has documented the largest volume of Whipple's procedures per annum in the region[5], we still only performed an average 11.25 cases per annum.

Centralization remains controversial. Even in developed countries, most Whipple's procedures are still performed in low-volume centers[7,20,27]. In Texas, Riall *et al*[27] reported that $\geq 25\%$ of Whipple's procedures were performed in hospitals doing < 5 cases per annum and 35% were done in hospitals performing < 10 cases per annum. Similarly, McPhee *et al*[22] reported that 61% of Whipple's procedures across the United States in the year 2007 were done outside of high-volume centers. Furthermore, it has been documented that centralization contributes to health care inequity, with significantly fewer females[27], non-caucasians[18,27-31], persons from low socio-economic brackets [32], persons from low-income zip codes and persons without private health insurers[18,27-30] being able to access care in these centers. We do not believe that the traditional centralization concept is practical for the West Indies due to travel restrictions, low health insurance rates, financial limitations and absent social support pathways.

Despite the fact that these surgeons performed small numbers of operations in a setting with scarce blood products, limited operating time and restricted intensive care support, short-term outcomes were still reasonable. The 30-d mortality in high-volume centers ranged widely, but most high-volume centers maintained 30-d mortality rates between 4%-6% [2-4,7,11-14,18,22,26,27]. At 5.5%, our 30-d mortality compared favorably. Similarly, our major morbidity rates compared favorably with high-volume centers reporting figures that ranged from 16%[33] to 26%[1]. Several authors have advocated documentation of procedure-related complications that include pancreatic fistula, delayed gastric emptying, intra-abdominal sepsis and intra-abdominal haemorrhage[34]. In our series the incidence of

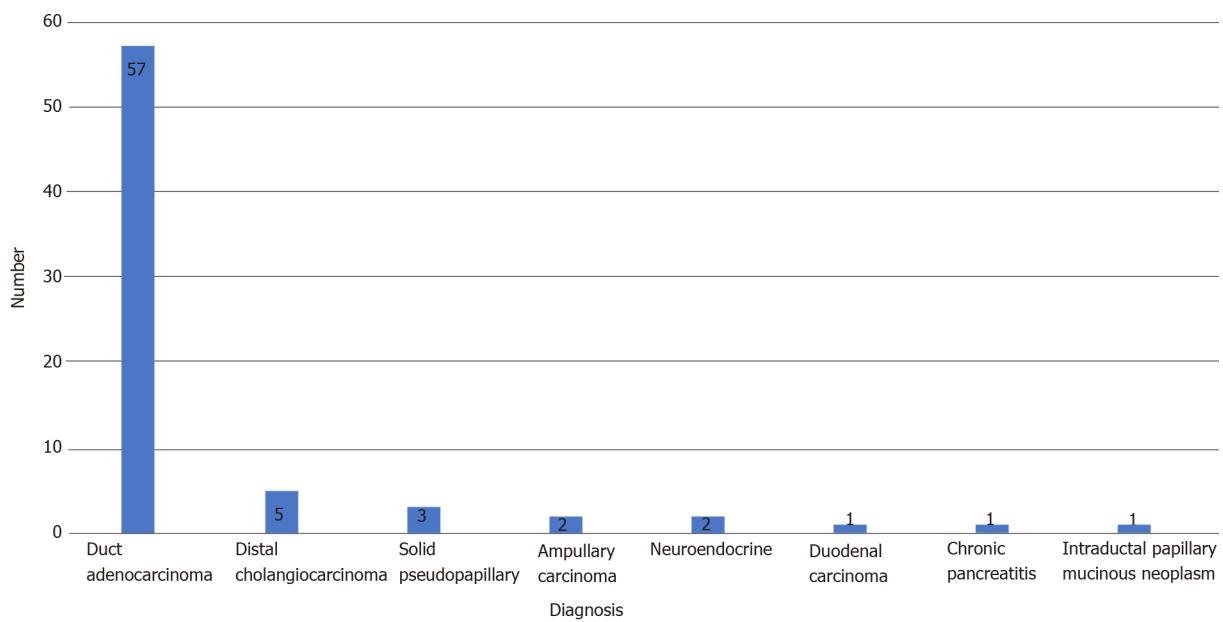


Figure 1 Histologic diagnoses of patients undergoing Whipple's procedure.

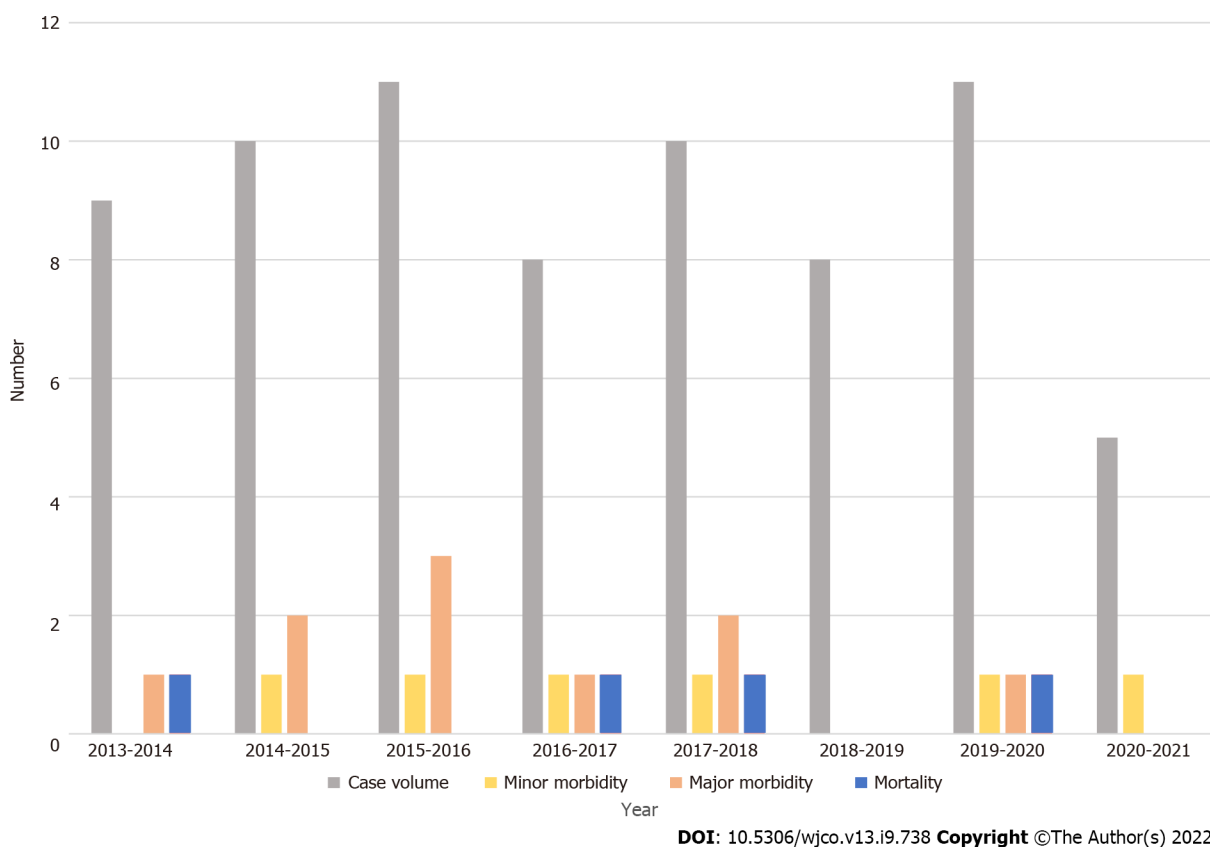


Figure 2 Chronologic analysis of clinical outcomes.

these procedure-specific complications was acceptable (1.4%, 1.4%, 2.8% and 2.8% of cases respectively).

It has been demonstrated in the medical literature that procedure-related complications are similar between low- and high-volume hospitals, but there is a significant difference in medical complications such as aspirations, pneumonia, pulmonary failure, renal failure and septicemia[33,34]. This reinforces the thinking that, while surgical expertise is necessary, it alone is not sufficient to guarantee good post-operative outcomes[2,33,34]. Medical complications occurred in 8.3% of our cases, suggesting that there may still be room for us to optimize support care/medical services.

Schmidt *et al*[2] introduced the concept of the “experienced surgeon” as being distinct from a “high-volume surgeon.” They defined the “experienced surgeon” as one who performed ≥ 50 Whipple’s procedures in their career, regardless of the interval[2]. They also made the point that experienced surgeons may not be high volume surgeons (which was time dependent) and demonstrated that experienced surgeons with low annual volumes had equivalent outcomes to high-volume surgeons[2]. The pancreatic surgeon in this setting was experienced, having performed ≥ 100 Whipple’s procedures. We believe that this contributed to the outcomes reported in this paper, and gives support to Schmidt’s concept of the experienced surgeon.

In their paper, Schmidt *et al*[2] counted the number of procedures in which a vein resection was performed as a surrogate marker of technical complexity and surgeon experience. In our series, 26.4% of patients had portal vein resection and reconstruction. It should be noted, however, that while these were experienced surgeons, they would have accrued much of their experience in high volume centers in developed countries during fellowship training. These facilities operate under different circumstances. Upon repatriation to the West Indies, these surgeons would have to adapt to challenging, new working environments. These surgeons adapted their practices to the new environment, focusing on peri-operative management and inter-disciplinary cooperation that evolved with time and were hospital-specific. This interaction and continuous institutional learning are difficult to measure and would evolve specific to each surgeon’s health care environment. Several authors have alluded to the concept of continuous, adaptive learning by the institution[1,2,7,18,35-37]. This is not limited to the surgeons alone, but includes pre-operative evaluation, multidisciplinary team interaction, intra-operative anaesthesia care, surgeon training, post-operative care pathways, post-procedure nursing care, ICU care, availability of emergency medical doctors and experienced subspecialty supportive care [1,2,7,18,35-37].

We agree that Whipple’s procedure is a complex operation that depends heavily on surgeon experience. At the same time, we believe that there is more to experience than technical facility. For example, the experienced surgeon would know how to resect and reconstruct the portal vein when required to achieve negative margins[2], when not to operate on patients[2], to recognize aberrant anatomy[2], how to get out of trouble when complications occur intra-operatively[7]. These can only be learned with experience and proper mentorship[2].

Recently, there has been focus on learning curves as a part of the concept of surgeon volume and surgeon experience. Tseng *et al*[38] suggested that after 60 Whipple’s procedures, surgeons improved on peri-operative outcomes such as blood loss, operation time, hospital stay and margin status. However, the most senior author in our paper performed over 300 Whipple’s and felt that he was still improving well beyond 200 cases, although the steepest part of the curve was the first 50. Similarly, the first author who performed all Whipple’s procedures in this series felt that he continued to improve during this series. It seems reasonable to conclude that the learning curve lies somewhere between 50 and 70 cases.

We believe that multiple factors contributed to the outcomes in our setting: (1) Population-based data [5]; (2) Training of unit staff; (3) Developing an intimate knowledge of the hospital; (4) Fostering teamwork; (5) Diligent administration of care; and (6) Regular audits. We also advocate two experienced surgeons operating to maximize experience. Also, if one surgeon is more experienced it speeds up the learning curve for the second surgeon. The key is overall team experience because, in addition to reducing intraoperative complications, effectively managing post-operative complications is important.

LIMITATIONS

It is tempting to think that the outcomes reported here may be biased due to case selection. However, we do not believe that this was the case in our setting because this was a government funded hospital and we were required to provide care for all patients who presented to this unit. In addition, many of our patients were physiologically challenging, with 52.7% having ASA scores \geq III and 54.1% with ECOG scores \geq 2.

The retrospective study design did limit our ability to collect detailed clinical information, such as accurate blood loss, adherence to post-care pathways and, as previously noted, we were unable to locate paper-based records for 14 patients who underwent Whipple’s procedures.

CONCLUSION

This paper adds to the growing body of evidence that volume alone should not be used as a marker of quality for patients requiring Whipple’s procedures. Low volume centers in resource poor nations can achieve good short-term outcomes. This is largely due to the process of continuous, adaptive learning by the entire hospital and includes: Population-based data, good teamwork, effective staff training, regular audit and due diligence in care administration.

ARTICLE HIGHLIGHTS

Research background

Whipple's operations are high-risk operations that should be done in high-volume centers for optimal outcomes. This is supported by data from several high-volume hospitals.

Research motivation

High-volume centers are usually in developed nations. There are no high-volume centers in the West Indies. In this setting, pancreatic surgeons have to perform Whipple's operations in resource-poor, low-volume settings. This scenario is not ideal, but it is the reality on the ground.

Research objectives

We sought to document the clinical outcomes when Whipple's operations were performed in resource-poor, low-volume centers in the West Indies. If the outcomes are poor, this would be impetus not to perform these operations in this setting or to develop service centralization with high-volume centers.

Research methods

A retrospective audit of all Whipple's operation performed at a referral center over an eight-year period was performed. Data collected from hospital records included: diagnoses, performance scores, estimated operative blood loss, duration of operation, therapeutic outcomes, post-operative morbidity and mortality. Statistical analyses were performed using SPSS version 16.0.

Research results

This facility performed 11.25 Whipples procedures per annum. There were 72 patients in the final study population at a mean age of 60.2 years. Open Whipple's procedures were performed in 70 patients and laparoscopic assisted procedures in 2. Portal vein resection/reconstruction was performed in 19 (26.4%) patients. In patients undergoing open procedures there was 367 ± 54.1 min mean operating time, 1394 ± 656.8 mL mean blood loss, 5.24 ± 7.22 d mean intensive care unit stay and 15.1 ± 9.53 d hospitalization. Six (8.3%) patients experienced minor morbidity, 10 (14%) major morbidity and there were 4 (5.5%) deaths.

Research conclusions

Low volume centers in resource poor nations can achieve good short-term outcomes once they pay attention to continuous, adaptive learning. Volume alone should not be used as a marker of quality for patients requiring Whipple's procedures.

Research perspectives

The direction of future research is to identify specific hospital-based pathways and/or team-focused processes that improve clinical outcomes in low-volume facilities.

FOOTNOTES

Author contributions: Cawich SO, Naraynsingh V, Thomas D and Pearce NW designed and coordinated the study; Pearce NW, Thomas D and Naraynsingh V acquired and analyzed data; Cawich SO, Naraynsingh V, Thomas D and Pearce NW interpreted the data; Cawich SO, Naraynsingh V, Thomas D and Pearce NW wrote the manuscript; all authors approved the final version of the article.

Institutional review board statement: The study was reviewed and approved by the University of the West Indies Institutional Review Board (CREC-SA.1623/06/2022).

Informed consent statement: This was a retrospective audit of written hospital records and so informed consent was waived by the institutional review board.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: All data are available from the corresponding author upon reasonable request at tt.liver.surgery@gmail.com.

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Observational Study

Factors predicting upstaging from clinical N0 to pN2a/N3a in breast cancer patients

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Abstract

BACKGROUND

With sentinel node metastasis in breast cancer (BC) patients, axillary lymph node (ALN) dissection is often omitted from cases with breast-conserving surgery. Omission of lymph node dissection reduces the invasiveness of surgery to the patient, but it also obscures the number of metastases to non-sentinel nodes. The possibility of finding ≥ 4 lymph nodes (pN2a/pN3a) preoperatively is important given the ramifications for postoperative treatment.

AIM

To search for clinicopathological factors that predicts upstaging from N0 to pN2a/pN3a.

METHODS

Patients who were sentinel lymph node (SLN)-positive and underwent ALN

dissection between September 2007 and August 2018 were selected by retrospective chart review. All patients had BC diagnosed preoperatively as N0 with axillary evaluation by fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and ultrasound (US) examination. When suspicious FDG accumulation was found in ALN, the presence of metastasis was reevaluated by second US. We examined predictors of upstaging from N0 to pN2a/pN3a.

RESULTS

Among 135 patients, we identified 1-3 ALNs (pN1) in 113 patients and ≥ 4 ALNs (pN2a/pN3a) in 22 patients. Multivariate analysis identified the total number of SLN metastasis, the maximal diameter of metastasis in the SLN (SLNDmax), and FDG accumulation of ALN as predictors of upstaging to pN2a/pN3a.

CONCLUSION

We identified factors involved in upstaging from N0 to pN2a/pN3a. The SLNDmax and number of SLN metastasis are predictors of ≥ 4 ALNs (pN2a/pN3a) and predictors of metastasis to non-sentinel nodes, which have been reported in the past. Attention should be given to axillary accumulations of FDG, even when faint.

Key Words: Breast cancer; Axillary lymph node metastasis; Positron emission tomography/computed tomography; Sentinel lymph node; Predictive factors of lymphnode metastasis; Standardized uptake value max; Diameter of sentinel lymphnode metastasis

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Core Tip: This is the first report to include the results of preoperative positron emission tomography/computed tomography (PET/CT) and to examine results related to the upstaging of pN2a/pN3a (more than 4 axillary lymph node metastases) in breast cancer (BC) patients. Specifically, 135 patients who were sentinel lymph node (SLN)-positive and underwent ALN dissection were selected by retrospective chart review, all of whom had BC diagnosed preoperatively as N0 with axillary evaluation by fluorodeoxyglucose (FDG) PET/CT and ultrasound. Our results suggest that the size and number of SLN metastases were still important factors. And, attention should be given to axillary accumulations of FDG, even when faint.

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INTRODUCTION

Sentinel lymph node (SLN) biopsy is usually performed in N0 cases. If SLN biopsy yields a positive result, an axillary lymph node (ALN) dissection is performed. However, since the publication of findings from the American College of Surgeons Oncology Group (ACOSOG) Z-0011 trial, many cancer centers have been omitting ALN dissection from breast-conserving surgeries[1]. The problem with omitting axillary dissection is that the number of non-SLN metastases cannot be ascertained, which may lead to over or under-treatment with adjuvant chemotherapy and radiation therapy. For example, patients with pN2a [4-9 ALN metastases (ALNMs)] or pN3a (≥ 10 ALNMs) need to be irradiated to not only the residual breast, but also the supraclavicular region after breast-conserving surgery. However, without knowing the number of metastases, no accurate decision on the need for irradiation can be made. Post-mastectomy radiation (PMRT) is also required for pN2a/N3a patients. Some reports have noted that PMRT after reconstruction impairs conformity[2-4]. Further analyses have shown that direct implants and autologous tissue reconstruction have fewer complications from PMRT[5,6]. The ability to predict the necessity of postoperative irradiation before surgery would affect surgical planning, including reconstructive surgery. A variety of factors and nomograms have been reported to allow preoperative prediction of the presence or absence of ALNMs[7-9], but few reports have examined factors predicting the presence of ≥ 4 ALNMs. Preoperative fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is reportedly excellent for predicting metastasis preoperatively and may have influenced the prediction of ALNMs in the present study. Although many

papers have described predictors of non-SLN metastasis, few have rigorously assessed ALNM preoperatively using PET/CT. In this study, all patients were evaluated preoperatively by PET/CT, and cases with false-negative results on other imaging modalities were excluded. This is the first report to include the results of preoperative PET/CT and to examine results related to the upstaging of pN2a/pN3a.

MATERIALS AND METHODS

Patients

A retrospective chart review was conducted for patients who were SLN-positive and underwent ALND between September 2007 and August 2018. All patients had breast cancer (BC) diagnosed preoperatively as N0 with axillary evaluation by PET/CT and ultrasound (US) examination. This study was conducted with approval from the institutional review board and with the informed consent of each patient. Axillary dissection was performed in all patients with SLN metastasis > 2 mm in diameter. In the case of total mastectomy, axillary dissection was performed for metastases > 0.2 mm in diameter. A flow chart of the eligible/included patients is shown in [Figure 1](#).

About ultrasound examination

A EUB-7500 scanner with a EUP-L54MA 9.75-MHz linear probe (Hitachi Medical Systems, Tokyo, Japan) or Aplio XG scanner with a PLT-805AT 8.0-MHz linear probe (Toshiba Medical Systems, Tochigi, Japan) was used for US examinations. If ultrasound or PET/CT findings were suspicious for metastatic lymph nodes, cytology was performed.

Protocol for FDG-PET/CT

All patients were intravenously administered ^{18}F -FDG (3.7 MBq/kg; 0.1 mCi/kg) after a minimum 4-h fasting period. Next, whole-body images were routinely obtained using a PET/CT system (Aquiduo; Toshiba Medical Systems, Tokyo, Japan). In addition, CT was performed using the following parameters: pitch factor, 0.938; gantry rotation time, 0.5 s; table time, 30 mm/s; auto-exposure control (SD20), 120 kVp; and slice thickness, 2.0 mm. Notably, contrast media were not used for CT examinations. Approximately 60 min after ^{18}F -FDG administration, whole-body PET was performed using the following parameters: emission time per bed, 2 min; bed positions, 7-8; slice thickness, 3.375 mm; and matrix, 128×128 .

Data analysis of FDG-PET/CT

In the present study, ^{18}F -FDG-PET/CT findings at each examination were assessed using a consensus reading by two breast radiologists (T.F. with 14 years of experience in breast imaging; M.M. with 10 years of experience in breast imaging). We performed visual analysis of primary lesions and ALNs without defining a cut-off value. Of note, lesions with an ^{18}F -FDG uptake value higher than that of the background tissue were defined as FDG-positive.

Immunohistochemical examination

All specimens were analyzed by pathologists from our institution, and specimens were considered estrogen receptor (ER) positive on immunohistochemistry (IHC) for staining rates higher than 10%. For human epidermal growth factor receptor 2 (HER2) values, and IHC result of 3+ was defined as BC with strong, complete membrane staining observed in at least 10% of tumor cells. For HER2 overexpression of 2+, gene amplification with fluorescence in situ hybridization was performed in this study.

Statistical analysis

Differences in proportions of categorical data were tested using Fisher's exact probability test. Unless otherwise indicated, significant differences among mean values of numerical data were analyzed using Mann-Whitney test. Relationships between the size of SLN metastases and the number of ALNMs were measured using Spearman rank correlation analysis, which can have a magnitude ranging from 0 to 1, with 0 denoting no correlation at all and 1 denoting complete correlation. Predictors of upstaging to pN2a/pN3a were determined by univariate and multivariate logistic regression analyses. Values of $P < 0.05$ were regarded as statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interfaces for R (The R Foundation for Statistical Computing, Vienna, Austria)[10]. More precisely, EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.

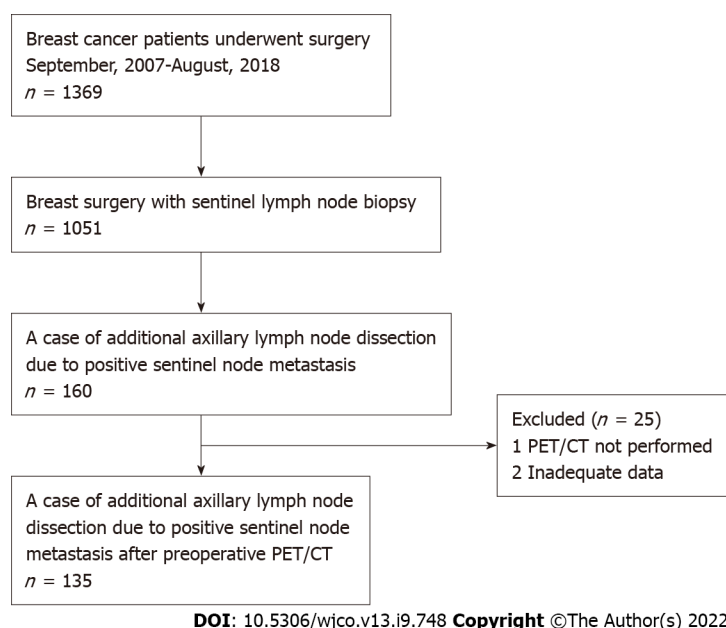


Figure 1 A flowchart of eligible patients. PET/CT: Positron emission tomography/computed tomography.

RESULTS

Demographic and clinical characteristics of study subjects

We retrospectively analyzed 135 BC patients who were SLN-positive and had undergone ALN dissection. FDG-PET/CT was performed in all cases preoperatively. The detailed clinicopathological characteristics of subjects are summarized in [Table 1](#). Among these, 113 patients showed 1-3 ALNMs (pN1) and 22 patients had ³⁴ ALNMs (pN2a/pN3a). FDG accumulation in ALNs was found on PET/CT in 19 cases (14.1%). The mean standardized uptake value (SUV) max was 1.48 (range, 0.8-2.0). Preoperative PET/CT showed accumulation in the ALNs, and second-look US was performed in cases where metastasis could not be ruled out. The mean number of excised SLNs was 1.6 (range, 1-5) and the mean number of SLN metastasis was 1.2 (range, 1-3). The median maximal diameter of metastasis in the SLN (SLNDmax) was 3 mm. The correlation between the SLNDmax and the number of ALNMs is shown in [Figure 2](#). A strong correlation was identified between SLNDmax and the number of ALNMs ($P < 0.001$). We measured the cut-off value for the SLNDmax from the receiver operating characteristic (ROC) curve and the cut-off value for upstaging from N0 to pN2a/pN3a was set at 5 mm (area under the curve: 0.873; 95% CI: 0.808-0.931) ([Figure 3](#)). [Table 2](#) shows a comparison between pN1 and pN2a/pN3a.

Univariate logistic regression analysis of risk factors associated with upstaging

To search for risk factors for upstaging to pN2a/N3a, univariate and multivariate analyses were performed for associations with clinicopathological factors in two groups of pN1 and pN2a/N3a cases. Invasive diameter at the primary site, number of SLN metastasis, FDG accumulation in ALNs, and SLNDmax were associated with upstaging to pN2a/pN3a, but age, ER status, HER 2 status, tumor grade, and SUVmax at the primary site were not ([Table 3](#)).

Multivariate logistic regression analysis of risk factors associated with upstaging

Multivariate logistic regression analysis of clinicopathologic factors was used to examine risk factors for upstaging to pN2a/pN3a. The number of SLN metastasis, SLNDmax, and FDG accumulation in ALNs were associated with upstaging ([Table 3](#)).

DISCUSSION

The ACOSOG Z-0011 trial concluded that ALN dissection is not always necessary for women undergoing breast-conserving surgery with 1-2 positive SLNs[1]. However, the overall number of ALNMs represents crucial clinical information. Although avoidance of ALN dissection reduces the degree of surgical invasiveness of a procedure, the number of ALNMs cannot be ascertained. If more than 4 metastatic lymph nodes are present, radiation to the breast or chest wall as well as to the supraclavicular area is necessary[11]. Thus, not knowing the number of ALNMs may lead to over- or under-

Table 1 Background characteristics of all patients

Background characteristics (n = 135)	
Age (yr)	56 (35-84)
SUVmax of primary tumor	3.05 (0.8-11.9)
pN1	113
pN2a or pN3a	22
The invasion diameter of the primary lesion	
≤ 20 mm	67
< 50 mm	55
≥ 50 mm	11
NA	2
Maximal diameter of metastasis in the sentinel lymph nodes (mm)	3 (0.1-25)
The number of SLN metastasis	
1	112
2	19
3	4
ER	
Positive	118
Negative	14
Unknown	3
HER2	
Positive	8
Negative	125
Unknown	2
Nuclear grade of biopsy specimen	
1, 2	103
3	26
Unknown	6
FDG accumulation of axillary lymph nodes	
Yes	19
No	116

SUV: Standardized uptake value; NA: Not applicable; SLN: Sentinel lymph node; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; FDG: Fluorodeoxyglucose.

treatment with radiation therapy postoperatively. The presence or absence of postoperative radiation may also affect the choice of reconstructive technique. Radiation during the insertion of an expander is associated with a greater risk of complications, while radiation after implant placement or to autologous tissue is reported to have fewer complications[2,3]. Pre- and postoperative prediction of the number of ALNMs affects not only the optimal extent of axillary dissection, but also the choice of radiotherapy and, indirectly, reconstruction methods. In the present study, we searched for predictors of upstaging from clinical N0 to pN2a/pN3a using factors identified pre- or intraoperatively, including FDG-PET/CT. This imaging modality is generally considered useful in searching for ALNMs[12]. However, few reports have specified whether preoperative PET/CT was performed when examining factors predicting non-SLN metastasis. As a result of examining various factors for upstaging, we extracted SLNDmax, mild accumulation of FDG in the axilla, and the number of SLN metastasis. The SLNDmax and the number of SLN metastasis have been reported in the past as predictors of metastasis to non-SLNs[13-16]. This is the first study to show that these factors are also important in upstaging from N0 to pN2a/pN3a. Various cut-offs for the SLNDmax have been reported as a predictor of non-SLN

Table 2 Comparison between pN1 and pN2a/pN3a

Total (n = 135)	pN1	pN2a/pN3a	P value
	n = 113	n = 22	
Age	57.96 ± 12.14	59.64 ± 12.73	0.56
The invasion diameter of the primary lesion (mm)	22.77 ± 14.76	39.86 ± 21.73	< 0.001
Maximal diameter of metastasis in the SLNs	3.46 ± 2.80	9.19 ± 5.66	< 0.001
The number of SLN metastasis			0.014
1	98	14	
2 and more	15	8	
ER			0.47
Positive	100	18	
Negative	11	3	
Unknown	2	1	
HER2			1
Positive	7	1	
Negative	104	21	
Unknown	2	0	
Nuclear grade of biopsy specimen			0.77
1, 2	87	16	
3	21	5	
Unknown	4	1	
SUVmax of the primary tumor	3.80 ± 2.50	4.13 ± 2.77	0.61
FDG accumulation of axillary lymph nodes			< 0.001
No	104	11	
Yes	8	11	
Unknown	1	0	

ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; SLN: Sentinel lymph node; SUV: Standardized uptake value; FDG: Fluorodeoxyglucose.

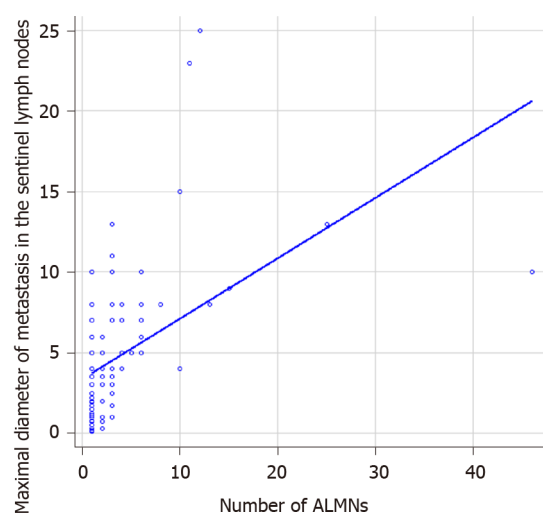
metastasis, and we used ROC curves in our search. As a result, the predictor for upstaging from N0 to pN2a/pN3a was set at 5 mm. If the number of SLN metastasis is large (that is, two or more) or the diameter of metastasis is large (more than 5 mm), or if FDG accumulation in the axilla is mild even if no metastases have been confirmed, irradiation to the chest wall and supraclavicular region may need to be considered even in cases where axillary dissection has been omitted. PET/CT is often performed preoperatively for different cancers. On the other hand, findings from this modality are reportedly less significant for low-stage BC, given the low likelihood of distant metastasis. Some reports have suggested that SUV at the primary site may offer a useful predictor of metastasis to non-SLNs[17]. Ueda *et al*[18] evaluated ALNMs using PET/CT and reported low sensitivity but high specificity. In the present study, we found PET/CT to be useful in predicting multiple ALNMs, but the positive predictive value was not particularly high (57.9%). Many questions remain unanswered, such as the optimal cut-off value for integrated SUV, the influence of the histological type of the primary tumor, and the suitable timing of biopsy.

Further accumulation and analysis of cases are needed. Institutions that aggressively omit axillary dissection should be aware of the dangers of remaining ignorant of the number of ALNMs when multiple risk factors are identified pre- or intraoperatively.

Table 3 Uni- and multivariate logistic regression analysis of risk factors associated with upstaging pN2a/pN3a

Factors	Univariate logistic regression analysis to predictive factors of pN2a/pN3a			Multivariate logistic regression analysis to predictive factors of pN2a/pN3a		
	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Age (yr) (< 50 <i>vs</i> ≥ 50)	0.863	0.333-2.24	0.76			
ER (positive <i>vs</i> negative)	0.66	0.167-2.60	0.55			
HER2 (positive <i>vs</i> negative)	0.833	0.954-7.28	0.87			
Invasive diameter of the primary site (≤ 20 mm <i>vs</i> > 20 mm)	4.3	1.48-12.50	0.007	3.53	0.963-13.0	0.057
Nuclear grade (1, 2 <i>vs</i> 3)	1.29	0.426-3.393	0.65			
Total positive SLNs (1 <i>vs</i> 2 and more)	3.73	1.34-10.40	0.012	3.92	1.01-15.3	0.048
Maximal diameter of metastasis in the SLNs (< 5 mm <i>vs</i> ≥ 5 mm)	21.2	4.68-96.3	< 0.001	15.6	3.08-79.2	< 0.001
SUVmax of primary tumor (< 3.1 <i>vs</i> ≥ 3.1)	0.96	0.351-2.62	0.94			
FDG accumulation of axillary lymph nodes (yes <i>vs</i> no)	13	4.32-39.2	< 0.001	4.84	1.29-18.2	0.02

ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; SLN: Sentinel lymph node; SUV: Standardized uptake value; FDG: Fluorodeoxyglucose.

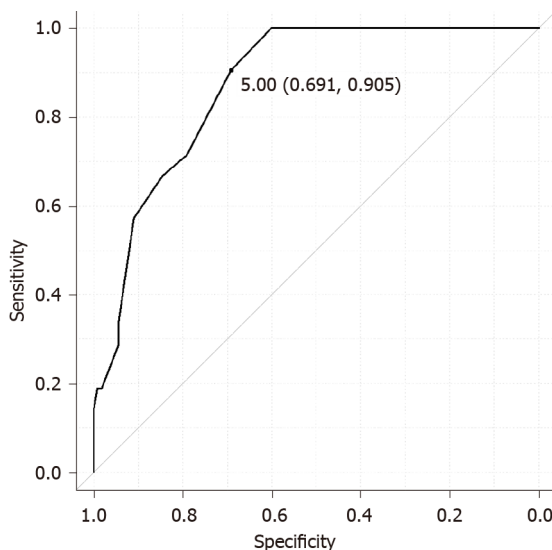


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Figure 2 Correlation between the maximal diameter of metastasis in the sentinel lymph nodes and number of axillary lymph node metastases. A strong correlation is evident between maximal diameter of metastasis in the sentinel lymph nodes and the number of axillary lymph node metastases ($P < 0.001$). ALMNs: Axillary lymph node metastases.

CONCLUSION

The present study investigated factors predictive of upstaging from clinical N0 to pN2a/pN3a. Factors such as the number of metastases and SLNDmax, which have previously been reported as predictors of metastasis to non-SLNs, were also useful in predicting upstaging to pN2a/pN3a and emphasized the utility of FDG-PET/CT. The only factor that predicts preoperatively, but not intraoperatively, is the result of FDG-PET/CT.



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Figure 3 Cut-off value for the maximal diameter of metastasis in the sentinel lymph node from the receiver operating characteristic curve and cut-off for upstaging from N0 to pN2a/pN3a set to 5 mm (area under the curve: 0.873, 95%CI: 0.808-0.931).

ARTICLE HIGHLIGHTS

Research background

With sentinel node metastasis in breast cancer (BC) patients, axillary lymph node (ALN) dissection is often omitted from cases with breast-conserving surgery. Omission of lymph node dissection reduces the invasiveness of surgery to the patient, but it also obscures the number of metastases to non-sentinel nodes.

Research motivation

The possibility of finding ≥ 4 lymph nodes (pN2a/pN3a) preoperatively is important given the ramifications for postoperative treatment.

Research objectives

The purpose of this study is to search for clinicopathological factors that predict upstaging from N0 to pN2a/pN3a.

Research methods

Patients who were SLN-positive and underwent ALN dissection between September 2007 and August 2018 were selected by retrospective chart review. All patients had BC diagnosed preoperatively as N0 with axillary evaluation by fluorodeoxyglucose (FDG) positron emission tomography/computed tomography and ultrasound (US) examination. When suspicious FDG accumulation was found in ALN, the presence of metastasis was reevaluated by second US. We examined predictors of upstaging from N0 to pN2a/pN3a.

Research results

Among 135 patients, we identified 1-3 ALNs (pN1) in 113 patients and ≥ 4 ALNs (pN2a/pN3a) in 22 patients. Multivariate analysis identified the total number of SLN metastasis, the maximal diameter of metastasis in the SLN (SLNDmax), and FDG accumulation of ALN as predictors of upstaging to pN2a/pN3a.

Research conclusions

We identified factors involved in upstaging from N0 to pN2a/pN3a. The SLNDmax and number of SLN metastasis are predictors of ≥ 4 ALNs (pN2a/pN3a) and predictors of metastasis to non-sentinel nodes, which have been reported in the past. Attention should be given to axillary accumulations of FDG, even when faint.

Research perspectives

It is somewhat possible to predict upstaging to pN2a/pN3a by searching for clinicopathological factors

FOOTNOTES

Author contributions: Oda G contributed to the conceptualization, methodology, software, validation, formal analysis, visualization and writing-original draft preparation; Hanazawa R, Hirakawa A contributed to the statistical checks; Oda G, Nakagawa T, Mori H, Onishi I, Fujioka T, Mori M, and Kubota K contributed to the investigation, resources; Oda G and Mori M contributed to the data curation; Nakagawa T contributed to the writing-review and editing; Okamoto K, Ishikawa T and Uetakeszsz H contributed to the supervision; All authors have read and agreed to the published version of the manuscript.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Tokyo Medical and Dental University, Tokyo, Japan (M2019-137, date of approval: 19 September 2019).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at odasrg2@tmd.ac.jp.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Neoadjuvant immunotherapy in non-small-cell lung cancer: Times are changing—and fast

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Abstract

Recent data from a phase 3 trial have shown that the addition of immunotherapy to neoadjuvant chemotherapy improves event-free survival in patients with non-small-cell lung cancer (NSCLC). This is the first positive phase 3 trial in this setting, although several phase 3 trials are currently investigating the efficacy of neoadjuvant and adjuvant immunotherapy in resectable NSCLC.

Key Words: Neoadjuvant; Immunotherapy; NSCLC; Perioperative; Checkmate-816; nivolumab; Chemo-immunotherapy

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Core Tip: Recent data from a phase 3 trial show that the addition of immunotherapy to neoadjuvant chemotherapy in patients with non-small-cell lung cancer (NSCLC) improves pathologic complete response and event-free survival. This is the first positive phase 3 trial in this setting, although several other phase 3 studies are currently investigating the efficacy of neoadjuvant and adjuvant immunotherapy in resectable NSCLC. We describe the results of the CheckMate-816 phase 3 trial, which found that neoadjuvant chemoimmunotherapy was superior to chemotherapy alone. We also briefly review the main phase 3 studies currently underway to evaluate the role of immunotherapy in the perioperative setting of NSCLC.

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TO THE EDITOR

The management of localized non-small-cell lung cancer (NSCLC) is set to undergo an important change in the first few months of this year (2022) due to the recent publication of the second primary endpoint—event-free survival (EFS)—from the Checkmate-816 trial. The data show that the combination of chemotherapy + nivolumab yielded a mean disease-free survival of 31.6 m in the experimental arm *vs* 20.8 m [hazard ratio (HR): 0.63] in the control arm (chemotherapy alone), with a 2 year-EFS rate of 64% *vs* 45%, respectively[1]. These results, in addition to previously reported results showing an improvement in pathological complete response (pCR) of 24% *vs* 2%, confirm the combination of three cycles of chemotherapy + neoadjuvant nivolumab as the new standard of care in resectable NSCLC[2].

This is the first time that pCR has been validated as a surrogate marker for survival in a randomized trial. In the experimental arm, the median EFS was 26.6 m in patients without pCR and not reached in those with pCR (HR: 0.13). Although the results in terms of overall survival are still immature, a trend towards better survival was observed in the experimental arm, in which 12% more patients were alive at 2 years (HR: 0.57).

This new change in clinical practice comes with several questions that need be resolved in the next few years, including the following: The role of adjuvant therapy; the selection of the most suitable candidates; comparison with adjuvant chemoimmunotherapy; the optimal approach in stage I-II disease; standardization of pathological response assessment; changes in resectability criteria; and changes in the preoperative algorithm.

The perioperative management of NSCLC will undoubtedly undergo a major transformation in the coming years due to the arrival of targeted therapy in this clinical setting, mainly the incorporation of pre- or post-operative immunotherapy[3]. The CheckMate 816 study was the first phase 3 trial to report positive results for the addition of immunotherapy to neoadjuvant chemotherapy[1]. However, other ongoing phase 3 trials evaluating other PD-1 axis inhibitors are expected to report results soon, such as the Impower-030 trial (atezolizumab)[4], KeyNote-671 trial (pembrolizumab)[5], and the Aegean trial (durvalumab)[6] (Table 1). Likewise, atezolizumab has already obtained FDA approval for use in the adjuvant setting in patients with resected PD-L1 positive stage II-IIIa NSCLC[7], and positive results have also been reported from an interim analysis of the KeyNote-091 trial, showing the benefits of pembrolizumab in resected stage IB-IIIa NSCLC[8]. Nivolumab and durvalumab are also being evaluated in the adjuvant setting in several other phase 3 trials (ANVIL, NADIM-Adjuvant, Mermaid-1) [9-11] (Table 2). As a result, the panorama for the treatment of early-stage NSCLC is becoming increasingly interesting, and the data suggest that it will be crucial to personalize treatment to offer the best treatment scheme for each individual patient.

These new options bring hope of a cure to a greater number of patients, but also new challenges for the multidisciplinary team and other professionals involved in the treatment of these patients. Once again, coordinated multidisciplinary work will be essential, especially among medical oncology, thoracic surgery, and radiation oncology.

Table 1 Main phase 3 trials evaluating neoadjuvant chemoimmunotherapy in non-small-cell lung cancer

Neoadjuvant NSCLC				
Study	IO agent	Strategy	Objective	Status
CheckMate-816[1]	Nivolumab (anti-PD1)	ChT + IO	EFS and pCR	FDA approved
Impower-030[4]	Atezolizumab (anti-PD-L1)	ChT + IO	PFS and OS	Completed. Results pending
KeyNote-671[5]	Pembrolizumab (anti-PD1)	ChT + IO	EFS and OS	Active, not recruiting
Aegean[6]	Durvalumab (anti-PD-L1)	ChT+ IO	pCR and EFS	Recruiting

IO: Immunotherapy; ChT: Chemotherapy; EFS: Event-free survival; pCR: Pathologic complete response; PFS: Progression-free survival; OS: Overall survival; FDA, Food and Drug Administration; NSCLC: Non-small-cell lung cancer.

Table 2 Main phase 3 trials evaluating adjuvant immunotherapy in non-small-cell lung cancer

Adjuvant NSCLC				
Study	IO agent	Strategy	Objective	Status
Impower-010[7]	Atezolizumab (anti-PD-L1)	IO mono	OS in selected PD-L1 population	FDA approved in II-IIIa NSCLC PD-L1+
KeyNote-091 (PEARLS)[8]	Pembrolizumab (anti-PD-L1)	IO mono	DFS	Interim analysis: positive in IB-IIIa NSCLC all corners
ANVIL[9]	Nivolumab (anti-PD1)	IO mono	OS and DFS	Active, not recruiting
NADIM-Adjuvant[10]	Nivolumab (anti-PD-1)	ChT + IO	DFS	Recruiting
Mermaid-1[11]	Durvalumab (anti-PD-L1)	ChT + IO	DFS in MRD+	Recruiting

IO: immunotherapy; mono: monotherapy; OS: overall survival; NSCLC: non-small-cell lung cancer; DFS: disease-free survival; ChT: chemotherapy; MRD: minimal residual disease; FDA, Food and Drug Administration; NSCLC: Non-small-cell lung cancer.

FOOTNOTES

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