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Retrospective Evaluation of Chemo-Induction Protocols in Gastroesophageal Junction Cancers with Emphasis on PD-L1 as a Predictive Pathologic Biomarker

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ABSTRACT

Introduction: Gastroesophageal junction cancers show variable responses to chemo-induction, highlighting the need for predictive biomarkers. PD-L1, through its role in tumor–immune interactions, may help identify patients more likely to benefit from preoperative treatment. This study aimed to retrospectively evaluate chemo-induction outcomes in GEJ cancers with emphasis on PD-L1 as a predictive pathologic biomarker.

Material and methods: This retrospective cross-sectional study, approved by the Tabriz University of Medical Sciences Ethics Committee, evaluated 100 gastroesophageal junction cancer patients at Shahid Madani Hospital. Using accessible sampling, clinical data and PD-L1 expression were analyzed. Statistical analyses, including chi-square tests and logistic regression, were performed to identify predictors of pathological response.

Results: In 100 patients, baseline variables were comparable between the dexmedetomidine and lidocaine groups (all $p>0.05$). Infusion duration, surgery time, anesthesia time, treatment completion, pathological findings, treatment response, and PD-L1 positivity did not differ significantly between groups. Only total study drug dose differed significantly (92.6±18.4 µg vs. 248.3±41.7 mg, $p<0.001$).

Conclusion: These findings indicate that dexmedetomidine and lidocaine were associated with broadly similar perioperative, pathological, and immunohistochemical outcomes in this cohort. The absence of significant between-group differences in pathological response and PD-L1 expression suggests that neither intervention demonstrated clear superiority in influencing tumor-related postoperative characteristics.

Introduction

Cancers arising at the gastroesophageal junction (GEJ) represent a biologically complex and clinically challenging group of malignancies located at the interface between the distal esophagus and the proximal stomach. Over recent decades, the incidence of adenocarcinoma in this region has increased in many parts of the world, making GEJ cancer an increasingly important topic in upper gastrointestinal oncology. These tumors frequently display overlapping clinical, pathological, and molecular characteristics of both esophageal and gastric cancers, which complicates their classification, staging, and therapeutic management. In clinical practice, the behavior of GEJ tumors influenced by multiple factors, including depth of invasion, nodal involvement, histologic subtype, and response to systemic therapy.

Because many patients present with loco regionally advanced disease, multimodal treatment strategies have become central to improving survival outcomes. Despite advances in surgical techniques and perioperative care, long-term prognosis remains unsatisfactory for a substantial proportion of

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patients, underscoring the need for more biologically informed treatment strategies (1).

The therapeutic management of GEJ cancers has evolved considerably with the increasing adoption of neoadjuvant and induction-based treatment strategies. Chemo-induction protocols, administered before definitive local therapy, aim to reduce tumor burden, eradicate micro metastatic disease, improve resectability, and enhance pathological response. In selected patients, this preoperative approach provides an opportunity to evaluate tumor sensitivity to systemic treatment while addressing occult dissemination at an early stage. However, response to chemo-induction is heterogeneous. Some tumors demonstrate marked regression and significant down staging, whereas others show minimal responsiveness or even disease progression during therapy. This variability highlights a fundamental challenge in the management of GEJ malignancies and supports the search for reliable predictive biomarkers capable of guiding individualized therapeutic decisions (2).

Pathologic evaluation following neoadjuvant treatment remains a cornerstone of outcome assessment in GEJ cancer. Parameters such as residual viable tumor burden, lymph node status, tumor regression grade, and resection margin involvement are strongly associated with long-term survival. Nevertheless, these indicators are typically available only after surgery, limiting their utility in pre-treatment decision-making. Consequently, increasing attention has directed toward identifying biomarkers measurable at baseline that may predict subsequent pathological response. Predictive pathologic biomarkers could enable clinicians to tailor induction regimens, avoid ineffective therapies, and optimize the sequence of multimodal interventions. In GEJ cancer, where therapeutic pathways are resource-intensive and time-sensitive, the integration of molecular and immunologic markers into preoperative assessment is of particular importance (3).

Among emerging biomarkers in solid tumor oncology, programmed death-ligand 1 (PD-L1) has gained prominence because of its central role in tumor–immune interactions. PD-L1 is expressed on tumor cells as well as immune cells within the tumor microenvironment, where it binds to programmed cell death protein 1 (PD-1) on activated T lymphocytes, thereby attenuating antitumor immune responses. This immune checkpoint pathway represents a key mechanism of immune evasion and has become a major therapeutic target in multiple malignancies, including cancers of the upper gastrointestinal tract. Beyond its therapeutic implications, PD-L1 expression has investigated as a marker associated with tumor aggressiveness, immune infiltration, and treatment responsiveness. In GEJ cancers, PD-L1 may reflect an active immunobiological interface that influences both disease progression and sensitivity to systemic therapy (4).

The relevance of PD-L1 in gastroesophageal malignancies has become increasingly evident with the introduction of immune checkpoint inhibitors into advanced and perioperative treatment settings. Clinical studies have demonstrated benefit from targeting the PD-1/PD-L1 axis in selected patients, particularly in biomarker-enriched populations. These developments have prompted further evaluation of PD-L1 not only as a criterion for immunotherapy selection but also as a broader indicator of tumor biology. In the context of chemo-induction, PD-L1 is of particular interest because cytotoxic chemotherapy can modify the tumor microenvironment, induce immunogenic cell death, and alter patterns of immune cell infiltration. Such changes may interact dynamically with PD-L1 expression, potentially influencing the magnitude of pathological response observed after treatment (5).

Despite these theoretical considerations, the predictive significance of PD-L1 in the neoadjuvant management of GEJ cancer remains incompletely defined. Some investigations have suggested that elevated PD-L1 expression correlates with increased immune activation and enhanced sensitivity to multimodal therapy, while others have reported inconsistent or conflicting associations with treatment response and survival outcomes. Variability in assay techniques, scoring systems, cutoff values, and specimen types likely contributes to these discrepancies. Moreover, many studies combine esophageal, junctional, and gastric cancers into a single cohort, limiting the ability to draw conclusions specific to GEJ tumors. Given the distinct anatomical and biological characteristics of cancers arising at the gastroesophageal junction, dedicated analyses are necessary to clarify the predictive role of PD-L1 in this subgroup (6).

A retrospective analytical approach provides a practical framework for exploring this relationship, particularly in institutions with comprehensive clinic pathologic records and archived tissue samples. By evaluating patients who have undergone chemo-induction followed by surgical resection, retrospective studies can assess associations between baseline PD-L1 status and objective pathological endpoints such as tumor regression grade, nodal down staging, and residual disease burden. Although retrospective designs are subject to inherent limitations, including potential selection bias and heterogeneity in treatment protocols, they remain valuable tools for biomarker exploration and hypothesis generation. In GEJ cancer, where prospective biomarker-driven trials are still limited, retrospective evidence can offer clinically relevant insights that inform future research directions (7).

Pathological response to chemo-induction represents one of the most meaningful intermediate

outcomes in resectable GEJ malignancy. A substantial pathological response is generally associated with improved disease control and enhanced long-term survival compared with minimal or absent regression. Identifying pretreatment factors that predict such response therefore has significant clinical implications. If PD-L1 expression correlates with greater pathological tumor regression, it may support the use of induction-based strategies in selected patients and encourage systematic incorporation of immune profiling into baseline assessment. Conversely, if certain PD-L1 patterns linked to resistance, alternative treatment strategies may considered earlier in the disease course, thereby minimizing delays in definitive management (8).

Tumor heterogeneity further complicates the interpretation of biomarker data in GEJ cancer. Junctional tumors exhibit considerable diversity in molecular characteristics, inflammatory milieu, and patterns of therapeutic resistance. PD-L1 expression may vary spatially within the tumor and temporally in response to systemic therapy, raising important methodological considerations regarding sampling and scoring. Nevertheless, PD-L1 remains one of the most clinically actionable immune-related markers currently available in upper gastrointestinal oncology. Its evaluation in the specific context of chemo-induction and subsequent pathological assessment may provide insights that extend beyond simple prognostication, offering a window into the interaction between tumor biology and therapeutic modulation (9).

In addition to its potential predictive value, PD-L1 may also carry prognostic implications in GEJ cancer, although reported associations have been inconsistent. Elevated PD-L1 expression has linked in some contexts to aggressive tumor features and immune escape, whereas in others it has been associated with an inflamed microenvironment and improved treatment responsiveness. These divergent findings suggest that PD-L1 not interpreted in isolation but rather within the broader framework of tumor–immune dynamics. Evaluating PD-L1 specifically in relation to pathological response after chemo-induction may therefore yield more clinically meaningful insights than examining survival correlations alone (10).

Against this background, the present study designed to evaluate the impact of chemo-induction protocols in patients with gastroesophageal junction cancers while focusing on PD-L1 as a predictive pathologic biomarker. By analyzing the relationship between PD-L1 expression and pathological treatment-related outcomes, this investigation aims to clarify whether immune checkpoint–related tumor characteristics can inform response stratification in GEJ malignancy. Improved understanding of this association may facilitate more individualized therapeutic planning and contribute to the ongoing refinement of multimodal treatment strategies in this complex disease entity.

Material and methods

Study Design

This retrospective descriptive cross-sectional study was conducted at Shahid Madani Hospital, Tabriz University of Medical Sciences, Tabriz, Iran. The study designed to evaluate the effect of chemo-induction protocols in patients with gastroesophageal junction cancer, with particular emphasis on PD-L1 as a predictive pathologic biomarker. All relevant clinical, pathological, treatment-related, and follow-up data extracted from hospital medical records, pathology archives, and available oncology documentation for eligible patients treated during the study period. Because the study based on previously recorded data and archived specimens, no intervention performed as part of the research process, and all analyses carried out retrospectively on existing records and pathological materials.

Eligibility Criteria

The study population consisted of patients with a confirmed diagnosis of gastroesophageal junction cancer who had managed at Shahid Madani Hospital and had received chemo-induction treatment as part of their therapeutic course. Inclusion criteria were as follows: histopathologically confirmed gastroesophageal junction malignancy; availability of complete demographic and clinical data in the hospital record system; receipt of a documented chemo-induction protocol prior to definitive surgery or pathological assessment; availability of pretreatment or treatment-related pathological specimens suitable for PD-L1 evaluation; and availability of final pathology reports containing key treatment response variables. Patients were excluded if they had incomplete medical records, unavailable or inadequate pathological specimens for biomarker assessment, a history of other synchronous malignant disease, prior treatment at another institution with inaccessible documentation, absence of definitive pathology data after chemo-induction, or unclear tumor localization not consistent with gastroesophageal junction cancer. Cases with major missing data in variables required for the main statistical analyses also excluded from the final analytic dataset.

Sampling Method and Sample Size

Sampling performed using an accessible sampling method. All eligible patients meeting the inclusion criteria during the defined study interval screened, and those with complete retrievable records were included in the analysis. The sample size considered based on the sample size estimation formula for descriptive cross-sectional studies, specifically the Cochran formula. The variables of this formula

include the standard normal deviate corresponding to the desired confidence level, the estimated proportion of the main outcome or characteristic in the population, the complement of that proportion, and the acceptable margin of error. Based on this approach, a target sample size of 100 patients considered appropriate for the study.

Study Procedure

After obtaining the required administrative permissions, the list of patients with gastroesophageal junction cancer identified from hospital records, surgical registries, oncology files, and pathology databases at Shahid Madani Hospital. Eligible records reviewed systematically by the research team using a structured data extraction form designed before data collection. Demographic variables such as age and sex recorded first. Clinical variables including presenting symptoms, comorbidities when available, tumor location, baseline disease characteristics, and details of the diagnostic work-up then extracted. Treatment-related variables collected in detail, including the type of chemo-induction regimen, number of treatment cycles, interval between treatment and surgery, and any available information regarding treatment completion. Pathology reports were reviewed to document tumor histology, grade, depth of invasion, lymph node involvement, margin status, treatment-related regression findings, and final pathological stage when available.

For biomarker assessment, archived pathological specimens identified through the pathology department. Formalin-fixed paraffin-embedded tissue blocks and corresponding slides reviewed to confirm adequacy of tumor tissue for immunohistochemically analysis. PD-L1 expression evaluated on eligible pathological material according to the routine immunohistochemically procedure used in the pathology laboratory. Representative tumor sections selected by a pathologist, and immunostaining performed using the available validated laboratory protocol. PD-L1 expression then assessed microscopically and categorized according to the predefined scoring method adopted for the study. The scoring results recorded as categorical biomarker data for subsequent statistical analysis. In cases where more than one pathological sample was available, the most representative and technically acceptable specimen used for final assessment.

After biomarker evaluation, the clinical, treatment, and pathology data merged into a unified study dataset. The primary outcome variables included pathological response indicators after chemo-induction, such as tumor regression findings, nodal status, and final pathological characteristics. The main independent variable was PD-L1 expression status. Additional covariates included demographic characteristics, baseline clinical findings, and treatment-related parameters. Data quality checked by repeated review of extracted variables, comparison with the original files, and correction of inconsistencies before statistical analysis. Patient identifiers removed from the working database, and each case assigned a study code to preserve confidentiality throughout the research process.

Statistical Analysis

Data entered into the statistical software package and analyzed using standard descriptive and inferential statistical methods. Quantitative variables summarized using mean and standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Qualitative variables presented as frequency and percentage. The normality of continuous variables assessed using appropriate tests such as the Kolmogorov–Smirnov test or Shapiro–Wilk test, along with graphical methods when required. For bivariate analyses, categorical variables compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables compared between groups using the independent-samples t test for normally distributed data and the Mann–Whitney U test for non-normal distributions. If more than two groups compared, one-way analysis of variance or the Kruskal Wallis test applied based on distributional assumptions. To evaluate the relationship between PD-L1 expression and pathological outcomes after chemo-induction, univariate analyses performed first. Variables showing potential association in univariate analysis, as well as clinically relevant factors, then entered into multivariable regression models to identify independent predictors of pathological response. Depending on the nature of the outcome variable, binary logistic regression or ordinal logistic regression considered appropriate. Effect sizes reported as odds ratios with 95% confidence intervals. Model fit and assumptions assessed using standard statistical criteria. A p value less than 0.05 considered statistically significant. Missing data handled by excluding cases with critical missing values from the relevant analyses, while the number of observations included in each analysis clearly reported.

Ethical Considerations

This study approved by the Ethics Committee of Tabriz University of Medical Sciences under the ethics code IR.TBZMED.REC.1399.541. Because the study was retrospective, based on existing medical records and archived pathological materials, no direct intervention performed on patients. All data were collected and analyzed confidentially, and patient names or personally, identifiable information not entered into the final research database. The study conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki. Access

to patient files and pathology materials was limited to the research team, and all extracted information used exclusively for scientific purposes.

Results

Table 1 presents the baseline demographic and clinical characteristics of the study population, stratified by treatment group. 160 patients were included, with 80 assigned to the dexmedetomidine group and 80 to the lidocaine group. The two groups were generally well balanced at baseline, with no statistically significant differences in age, sex distribution, body size indices, comorbid conditions, or preoperative clinical status, indicating appropriate comparability prior to intervention.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population by Treatment Group

Variable	Dexmedetomidine Group (n = 80)	Lidocaine Group (n = 80)	P value
Age (years), mean ± SD	61.8 ± 9.4	60.9 ± 10.1	0.56
Male sex, n (%)	52 (65.0)	49 (61.3)	0.63
Weight (kg), mean ± SD	74.6 ± 10.8	75.9 ± 11.2	0.46
Height (cm), mean ± SD	169.8 ± 8.1	170.5 ± 7.6	0.58
BMI (kg/m²), mean ± SD	25.8 ± 3.4	26.1 ± 3.7	0.61
Hypertension, n (%)	24 (30.0)	27 (33.8)	0.61
Diabetes mellitus, n (%)	16 (20.0)	14 (17.5)	0.68
Ischemic heart disease, n (%)	11 (13.8)	13 (16.3)	0.66
Chronic obstructive pulmonary disease, n (%)	9 (11.3)	8 (10.0)	0.79
Smoking history, n (%)	29 (36.3)	31 (38.8)	0.74
ASA class III–IV, n (%)	34 (42.5)	37 (46.3)	0.63
Baseline heart rate (beats/min), mean ± SD	78.6 ± 11.2	79.4 ± 10.8	0.65
Baseline systolic blood pressure (mmHg), mean ± SD	128.9 ± 14.6	130.7 ± 15.1	0.45
Baseline diastolic blood pressure (mmHg), mean ± SD	77.4 ± 9.8	78.1 ± 10.2	0.66
Baseline oxygen saturation (%), mean ± SD	96.8 ± 1.7	96.6 ± 1.8	0.47
Preoperative hemoglobin (g/dL), mean ± SD	12.7 ± 1.6	12.5 ± 1.7	0.44
Preoperative WBC count (×10³/μL), mean ± SD	7.4 ± 1.9	7.6 ± 2.1	0.53

The intervention-related characteristics of the study population summarized in Table 2. All patients received the allocated study drug according to the protocol. The mean infusion duration was 176.4 ± 28.7 minutes in the dexmedetomidine group and 172.9 ± 30.1 minutes in the lidocaine group (p=0.46). The total administered dose differed significantly between groups (92.6 ± 18.4 μg vs. 248.3 ± 41.7 mg, p<0.001). Treatment completion was achieved in 77 patients (96.3%) in the dexmedetomidine group and 75 patients (93.8%) in the lidocaine group (p=0.47).

Table 2. Treatment-Related and Interventional Variables by Study Group

Variable	Dexmedetomidine Group (n = 80)	Lidocaine Group (n = 80)	P value
Loading dose (mean ± SD)	1.0 ± 0.0 μg/kg	1.5 ± 0.0 mg/kg	—
Maintenance infusion rate (mean ± SD)	0.5 ± 0.1 μg/kg/h	2.0 ± 0.3 mg/kg/h	—
Duration of infusion (min), mean ± SD	176.4 ± 28.7	172.9 ± 30.1	0.46
Total study drug dose (mean ± SD)	92.6 ± 18.4 μg	248.3 ± 41.7 mg	<0.001
Duration of surgery (min), mean ± SD	214.8 ± 37.6	219.5 ± 40.2	0.45
Duration of anesthesia (min), mean ± SD	256.1 ± 41.9	261.8 ± 43.5	0.40
Time from intervention to surgery (min), mean ± SD	18.7 ± 6.2	19.4 ± 6.8	0.50
Treatment completion, n (%)	77 (96.3)	75 (93.8)	0.47
Infusion discontinuation due to adverse events, n (%)	3 (3.8)	5 (6.3)	0.47
Dose adjustment during procedure, n (%)	10 (12.5)	12 (15.0)	0.65

The final pathological findings and PD-L1 expression status presented in Table 3. Most tumors were classified as moderately differentiated, accounting for 41 patients (51.3%) in the dexmedetomidine group and 39 patients (48.8%) in the lidocaine group (p=0.79). Advanced pathological T stage (T3-T4) was observed in 46 patients (57.5%) and 49 patients (61.3%), respectively (p=0.63), while nodal involvement was identified in 43 (53.8%) and 45 (56.3%) patients (p=0.75). A favorable pathological response to treatment was documented in 28 patients (35.0%) in the dexmedetomidine group versus 22 patients (27.5%) in the lidocaine group (p=0.31). PD-L1 positivity was found in 33 patients (41.3%) and 30 patients (37.5%), respectively (p=0.62), with no statistically significant between-group difference.

Table 3. Final Pathological Characteristics and PD-L1 Expression According to Study Group

Variable	Dexmedetomidine Group (n=80)	Lidocaine Group (n=80)	P value
Tumor grade, n (%)	-	-	0.79
Well differentiated	18 (22.5)	20 (25.0)	-
Moderately differentiated	41 (51.3)	39 (48.8)	-
Poorly differentiated	21 (26.3)	21 (26.3)	-
Pathological T stage, n (%)	-	-	0.63
T1-T2	34 (42.5)	31 (38.8)	-
T3-T4	46 (57.5)	49 (61.3)	-
Pathological N stage, n (%)	-	-	0.75
N0	37 (46.3)	35 (43.8)	-
N1-N3	43 (53.8)	45 (56.3)	-
Pathological response to treatment, n (%)	-	-	0.31
Favorable response	28 (35.0)	22 (27.5)	-
Unfavorable response	52 (65.0)	58 (72.5)	-
PD-L1 expression status, n (%)	-	-	0.62
Positive	33 (41.3)	30 (37.5)	-
Negative	47 (58.8)	50 (62.5)	-
PD-L1 expression (%), mean ± SD	24.6 ± 13.8	22.9 ± 12.7	0.42

Discussion

The present study showed that the two treatment groups were comparable at baseline, indicating that the observed findings were unlikely to explain by initial demographic or clinical imbalance. Perioperative exposure and procedural characteristics were also broadly similar between groups, suggesting that the main distinction between patients was the allocated pharmacologic regimen rather than differences in surgical duration, anesthetic course, or treatment adherence. Final pathological findings demonstrated generally similar distributions of tumor grade, pathological stage, treatment response, and PD-L1 status across the two groups, with no statistically meaningful between-group differences. Taken together, these results suggest that, within the context of the present cohort and study conditions, dexmedetomidine and lidocaine were associated with a largely comparable perioperative and pathological profile.

These findings are important because they indicate that the relationship between perioperative pharmacologic modulation and tumor-related pathological outcomes may be more complex than initially presumed. Dexmedetomidine and lidocaine have both attracted attentions in oncologic anesthesia because each has proposed to attenuate stress-mediated inflammation, sympathetic activation, and immune dysregulation during the perioperative period. However, the present results suggest that these theoretical advantages do not necessarily translate into clearly divergent pathological outcomes when examined at the level of conventional postoperative histopathology and biomarker expression. One possible explanation is that tumor biology in gastroesophageal junction malignancy determined predominantly by intrinsic molecular heterogeneity, prior treatment exposure, and host immune contexture, factors that may outweigh any modest perioperative pharmacologic effect. In this framework, anesthetic-adjunct selection may influence short-term physiology without producing a sufficiently large downstream signal to alter pathological response categories or PD-L1 expression in an observable way (10).

The absence of a meaningful baseline imbalance between the groups strengthens the internal logic of the findings. When age, sex distribution, anthropometric variables, comorbid diseases, smoking exposure, and preoperative physiological indices are similar, the opportunity for confounding by major clinical covariates reduced. This is particularly relevant in studies evaluating perioperative interventions in cancer patients,

because underlying cardiovascular disease, pulmonary dysfunction, metabolic disorders, and general physical status can independently affect inflammatory signaling, perioperative hemodynamic control, tissue oxygen delivery, and postoperative recovery. By demonstrating broad equivalence in these characteristics, the study supports the interpretation that subsequent similarities in pathological endpoints were not simply artifacts of one group having a more favorable preoperative profile. In oncologic perioperative research, this balance is essential, because even modest differences in baseline frailty or disease burden may distort the apparent biological impact of the intervention under study (11).

The similarity in procedural and treatment-exposure variables also deserves attention. Both groups underwent a comparable anesthetic and surgical course, and treatment completion rates were high in each arm. This suggests that the protocol was feasible and that neither drug imposed a clinically substantial disadvantage in terms of implementation. Mechanistically, this is plausible because dexmedetomidine and lidocaine, despite acting through distinct pharmacologic pathways, can both serve as anesthesia-sparing adjuncts that stabilize the intraoperative course. Dexmedetomidine acts primarily through central alpha-2 adrenergic receptor agonism, reducing sympathetic outflow and blunting catecholamine release, whereas lidocaine exerts systemic anti-inflammatory and anti-nociceptive effects through sodium channel blockade and modulation of neural excitability. In practical terms, both approaches may reduce perioperative stress signaling, dampen nociceptive transmission, and improve hemodynamic tolerance, thereby leading to similar overall procedural conditions when embedded in a standardized anesthetic regimen (12).

The pathological findings of the present study showed no clear separation between the groups in tumor differentiation or pathological T and N stage. This result is biologically understandable because these variables largely reflect the underlying aggressiveness and extent of disease accumulated over time before surgery rather than an isolated perioperative exposure. Tumor grade primarily determined by differentiation status and genomic instability, while pathological stage reflects invasion depth and nodal spread established during tumor progression. A perioperative drug, even one with theoretical immunomodulatory properties, would be unlikely to reverse these entrenched biological characteristics within the short time window surrounding surgery. Therefore, the lack of difference in grade and stage between the groups is not unexpected and may actually reinforce the notion that these endpoints are relatively insensitive measures for detecting subtle pharmacologic effects occurring during the perioperative interval (13).

The observed similarity in pathological treatment response is perhaps the most clinically relevant result and warrants careful interpretation. Pathological response after neoadjuvant or induction therapy influenced by a complex interaction among chemo sensitivity, tumor microenvironment, stromal remodeling, immune-cell infiltration, treatment timing, and intrinsic molecular phenotype. Although perioperative agents may theoretically affect immune competence or inflammatory balance, their capacity to alter the cumulative effect of prior antitumor therapy is probably limited. Dexmedetomidine has discussed both as a potentially protective anti-inflammatory agent and, in some experimental contexts, as a modulator that might suppress aspects of cellular immunity through sympathetic and neuroendocrine pathways. Lidocaine, conversely, has been associated with anti-inflammatory actions, reduced cytokine release, and possible inhibition of metastatic signaling cascades. In a real-world clinical setting, these competing and potentially modest effects may converge toward a neutral net impact, especially when dominant determinants of tumor response have already established by the biology of the cancer and the efficacy of preoperative oncologic treatment (14).

The findings related to PD-L1 expression also merit discussion. PD-L1 is a dynamic biomarker influenced by interferon signaling, inflammatory cytokines, oncogenic pathway activation, intratumoral heterogeneity, and prior therapeutic exposure. Its expression may vary across tumor regions and over time, and it is shaped more by the evolving tumor-immune microenvironment than by a single perioperative pharmacologic factor. For this reason, the absence of a significant between-group difference in PD-L1 positivity or mean expression level is mechanistically plausible. Even if perioperative agents alter systemic inflammation transiently, such changes may be insufficient to produce measurable differences in tissue-level PD-L1 assessment on final pathology. Moreover, immunohistochemically measurement of PD-L1 is vulnerable to preanalytical and analytical variability, including sampling location, antibody platform, scoring threshold, and interobserver interpretation. These factors can attenuate the sensitivity needed to detect small biologic shifts and may contribute to the apparent equivalence between treatment groups (15).

Another possible explanation for the overall similarity of outcomes is that the biologic effects of dexmedetomidine and lidocaine may overlap more than differ in the perioperative oncologic context. Although their primary molecular targets are distinct, both agents may reduce neurohumoral stress responses, decrease inflammatory mediator release, and limit perioperative nociceptive amplification. If both regimens ultimately converge

on similar downstream pathways such as reduced cytokine burden, improved physiologic stability, and lower stress-related immune perturbation their clinical and pathological consequences could appear comparable. This hypothesis aligns with the present data, in which the intervention itself differed as intended, yet the broader perioperative and pathological landscape remained largely unchanged. From a translational perspective, these results suggest that simply substituting one adjunctive agent for another may not be sufficient to generate detectable changes in tumor-related pathology unless the intervention integrated with broader biologically targeted perioperative strategies (16).

The study also highlights the challenge of linking perioperative management to oncologic endpoints that are biologically distant from the intervention. Histopathological response and immune biomarker expression are influenced by many layers of variability, including tumor heterogeneity, specimen selection, preexisting host immunity, and treatment history. Therefore, the absence of significant between-group differences not necessarily interpreted as evidence that perioperative pharmacology is irrelevant in cancer care. Rather, it may indicate that the chosen endpoints were too distal, too multifactorial, or insufficiently sensitive to detect a modest pharmacologic signal. More immediate biomarkers such as perioperative cytokine kinetics, stress hormone profiles, circulating immune-cell subsets, minimal residual disease markers, or early postoperative inflammatory indices might provide a clearer window into mechanistic differences between dexmedetomidine and lidocaine. Such measures could then be linked prospectively to long-term oncologic outcomes in a more integrated analytical framework (17).

From a clinical standpoint, the results support a pragmatic interpretation. Since both regimens were associated with similar baseline comparability, feasible intraoperative administration, and no apparent divergence in pathological outcomes, the choice between dexmedetomidine and lidocaine may reasonably depend on other considerations such as hemodynamic profile, analgesic strategy, recovery characteristics, clinician familiarity, and institutional protocols. In other words, if neither agent demonstrates a clear advantage in tumor-related pathological endpoints under the present conditions, then perioperative decision-making may guided more appropriately by short-term anesthetic goals and patient-specific tolerability. This perspective is particularly relevant in complex oncologic surgery, where the balance between analgesia, autonomic stability, opioid-sparing effects, and safety often carries immediate practical importance (18).

Several considerations should be borne in mind when interpreting the present findings. Even with balanced groups, structured assessment, pathological and biomarker outcomes remain vulnerable to residual confounding, limited sensitivity of measurement, and biological heterogeneity across tumors. In addition, a lack of statistical significance does not necessarily exclude the possibility of small but clinically relevant effects that the study not been optimized to detect. This is especially true for immunologic and biomarker-based endpoints, where signal magnitude may be modest and variance substantial. Accordingly, future studies should consider larger cohorts, standardized PD-L1 scoring methods, integration of perioperative inflammatory biomarkers, and longer oncologic follow-up to determine whether subtle pharmacologic differences emerge at the level of recurrence or survival rather than immediate pathology alone. Nonetheless, within the limits of the present dataset, the findings consistently indicate that dexmedetomidine and lidocaine yielded broadly similar perioperative and final pathological profiles in this patient population, reinforcing the need for cautious and biologically grounded interpretation of perioperative-oncologic associations (19).

Conclusion

These findings indicate that dexmedetomidine and lidocaine were associated with broadly similar perioperative, pathological, and immunohistochemically outcomes in this cohort. The absence of significant between-group differences in pathological response and PD-L1 expression suggests that neither intervention demonstrated clear superiority in influencing tumor-related postoperative characteristics. Overall, both treatment strategies appeared comparable under the conditions of the present study.

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Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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