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TREATMENT RESULTS AND LONG-TERM SURVIVAL AFTER INDUCTION CHEMOTHERAPY PLUS SURGERY VERSUS SURGERY ALONE IN THORACIC ESCC: A SINGLE-CENTER EXPERIENCE

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ABSTRACT

Objective: This research was intended to demonstrate the long-term results of the surgical treatment of patients with operable esophageal scuamouse cell cancer by comparing the group treated with neoadjuvant chemotherapy with the group treated with surgery alone. **Patients and Method:** 37 patients, who were documented in archives of the Republic scientific center of oncology and radiology of Uzbekistan from 2021 to 2024 years, treated with neoadjuvant chamotherapy following curative intend esophagectomy (nCS) were included to our study. For control group, patients with comparable gender and age parameters, the degree of concomitant diseases and the volume of surgery who underwent only surgical procedure (S) during the specified period were randomized. **Results:** Median OS was 31 months in nCS group versus 24 months in S group. 3-year survival rates were 41.65% and 29.9% respectively. Common chemotherapy complications were hematotoxicity (leukopenia) 81.1% and nausea/vomiting 67.5%. Postoperative complications were recorded in 15/37 (40.54%) patients in the nCS group and in 11/35 (31.42%) patients in the S group. One patient (8.1%) in the nCS group died within 30 days of surgery. Frequency of non-fatal therapeutic postoperative complications was almost the same in both groups. **Conclusion:** Thus, it can be concluded that preoperative chemotherapy does not affect a significant increase in the incidence of surgical and therapeutic complications in patients with resectable cancer of the thoracic esophagus, while it has been proven to prolong the overall survival. However, individualization of the combined treatment regimen in this group of patients is necessary.

KEYWORDS: esophageal cancer, neoadjuvant chemotherapy, curative surgery, complications.

BACKGROUND

Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype of esophageal cancer worldwide, accounting for up to 90% of cases in the Eastern Hemisphere. Despite radical treatment, prognosis remains poor, with 5-year survival rates of approximately 20–30%. This is largely due to the high proportion of patients presenting with locally advanced disease and occult metastases at diagnosis. Given the high risk of locoregional recurrence and disease progression, combined treatment strategies incorporating surgery and systemic chemotherapy have gained increasing attention.[1-7]

Preoperative (neoadjuvant) chemotherapy may improve the likelihood of achieving an R0 resection through tumor downstaging and can contribute to symptom relief.[1,8,9] In addition, systemic therapy is considered effective in eradicating micrometastatic disease and circulating tumor cells. Recent advances in the understanding of cancer metastasis have highlighted the importance of early systemic dissemination, which may occur even in the initial stages of disease, rather than being limited to advanced cancer. These findings support the potential survival benefit of preoperative chemotherapy in esophageal cancer.[2,3,10,11] In this study, we report the long-term outcomes of surgical treatment in patients with resectable esophageal squamous cell carcinoma (ESCC), comparing those who received neoadjuvant chemotherapy (nCS) with those who underwent surgery alone (S).

PATIENTS AND METHODS

The number of patients included in the study was 37 patients in the nCS group and 35 patients in the S group . All eligible patients had histologically confirmed esophageal squamous cell carcinoma and surgery was performed at the RSSPMCO&R from 2021 to 2024. Patients were considered resectable if the tumor was clinically limited to the local region (tumor stage 1, 2, 3, or 4a; any nodal stage and no distant metastases). Patients with distal esophageal carcinoma and suspected celiac lymph node involvement (M1a) were also considered eligible for surgery. Exclusion criteria: unresectable cases identified during surgery. Patients scheduled for preoperative chemotherapy were treated with two cycles followed by assessment of clinical response. Response was assessed two to three weeks after the last cycle of chemotherapy. The clinical response after chemotherapy was assessed using esophagogastroscopy and MSCT of the chest and abdomen with *per os* contrast. Tumor responses were assessed according to World Health Organization (WHO) criteria. The complete absence of any signs of malignant disease, including negative results of a biopsy from the area of the former tumor, was regarded as a complete regression (CR). Partial regression (PR) was defined as > 50% reduction in tumor volume without the appearance of new lesions. Stable process (SP) was defined as tumor progression up to 25% or the appearance of a new lymph node. Patients with a complete or partial response received two additional courses of chemotherapy, while patients who did not respond to treatment (stable disease or progressive disease) were referred for immediate surgery. Patients with progressive disease (T4b or M1b disease) were treated palliatively and were followed up. Patients, who were randomized to surgery alone, were operated as soon as possible. Patients receiving chemotherapy went to surgery on 4-6 weeks after the last cycle of treatment.

Neoadjuvant chemotherapy

For neoadjuvant chemotherapy, were used chemotherapy regimens with Cisplatin + 5-fluorouracil (5FU) (PF), Cisplatin (carboplatin) + Pacletaxel (TP/TC) and Docetaxel + Cisplatin + 5FU (DCF). Cisplatin at a dose of 80 mg/m^2 was administered intravenously over 4 hours on the first day of each cycle before and after adequate hydration. 5-FU at a dose of 750 mg/m^2/day on days 1-4 was administered intravenously as a 96 hour infusion. In the second regimen, Cisplatin at a dose of 80 mg/m^2 was also administered intravenously for 4 hours on the first day of each cycle before and after adequate hydration (with concomitant diseases of the cardiovascular system of moderate severity, with subcompensated impaired liver and kidney function, Carboplatin was used [AUC 5]). Pacletaxel at a dose of 175 mg/m^2 was administered intravenously over 2 hours on the first day of each cycle, preceded by promedication, dexomethasone at a dose of 8 mg was administered intravenously, up to 12, 6 and 1 hours before the chemotherapy infusion. These cycles were repeated at week 4 (every 21 days). In the case of a clinical response, two subsequent courses of chemotherapy were performed at the 7th and 10th weeks. All patients received prophylactic anti-nausea treatment with 5-HT3 receptor antagonists during chemotherapy. Treatment-related toxicity was measured according to WHO guidelines. Retreatment with the next cycle was allowed only with an absolute neutrophil count of at least 3000/mm^3 and a platelet count of at least 80,000/mm^3. Treatment can be delayed up to 2 weeks.

Surgery and Histological examination

For tumors of the upper third of the intrathoracic esophagus, a three-zone esophagectomy (MacKeown operation – 2 cases), for tumors of the middle and lower third of the intrathoracic esophagus, the Ivor -Lewis type surgery (35 in nCS and 35 in S groups) was performed. The tumor and adjacent lymph nodes are excised as a single block. The continuity of the digestive tract was restored by the formation of the gastric tube. Tumor stage after resection was classified according to the TNM classification of the International Cancer Committee. Resections were classified as radical when all margins were free of tumor cells on microscopic examination (R0). Resections were considered non-radical if microscopic examination revealed tumor cells on the resection line (R1) or the presence of non-removed macroscopically tumor tissues (R2).

Overall survival (OS) was calculated from the date of random assignment to date of death from any cause and surviving patients were censored at the date they were last known to be alive. Statistical analyses were performed using the Graph Pad Prism statistical package.

RESULTS

From 2021 to 2024, 37 patients, documented in the archives of the RSSPMCO&R were treated with neoadjuvant chemotherapy followed by surgery (nCS group, n=37). For the surgery group, patients with comparable gender and age parameters, the degree of concomitant diseases and the volume of surgery who underwent only surgical intervention during the specified period were randomized (S group, n=35). Exclusion criteria was any simultaneous and combined surgery.

Table 1 shows that two groups were similar in age, gender, location of the tumor process, and comorbidities that can affect the postoperative results of surgery.

Table 1: **Clinical and age-gender characteristics.**

Characteristics	nCS		S		Total		*p-value*
Age	**n**	**%**	**n**	**%**	**n**	**%**	***0.039***
≤49	**8**	**(21,62%)**	**6**	**(17,14%)**	**14**	**(19,44%)**	
50-69	**25**	**(67,56%)**	**24**	**(68,57%)**	**49**	**(68,05%)**	
≥70	**4**	**(10,81%)**	**5**	**(14,28%)**	**9**	**(12,5%)**	
Sex	**n**	**%**	**n**	**%**	**n**	**%**	***0.041***
Male	**12**	**(32,43%)**	**13**	**(37,14%)**	**25**	**(34,72%)**	
Female	**25**	**(67,56%)**	**22**	**(62,85%)**	**47**	**(65,27%)**	
Tumor location	**n**	**%**	**n**	**%**	**n**	**%**	***0.064***
Middle	**16**	**(43,24%)**	**15**	**(42,85%)**	**31**	**(43,05%)**	
Lower	**13**	**(35,13%)**	**12**	**(34,28%)**	**25**	**(34,72%)**	
Middle-lower	**8**	**(21,62%)**	**8**	**(22,85%)**	**16**	**(22,22%)**	
Concomitant disease	**n**	**%**	**n**	**%**	**n**	**%**	***0.05***
Ischemic heart disease	**19 (51,35%)**		**18 (51,42%)**		**37 (51,38%)**		***0.038***
FC1	**3 (8,1%)**		**3 (8,57%)**		**6 (7,47%)**		
FC2	**16 (43,24%)**		**15 (42,85%)**		**31 (49,53%)**		
Ischemic heart disease (arrhythmia)	**4 (10,81%)**		**4 (11,42%)**		**8 (11,1%)**		***0.76***
Paroxysm	**1 (2,7%)**		**2 (5,71%)**		**3 (4,67%)**		
Extrasystole	**3 (8,1%)**		**2 (5,71%)**		**5 (6,54%)**		
Hypertonic disease	**25 (67,56%)**		**23 (65,71%)**		**48 (66,66%)**		***0.041***
1 degree	**3 (8,1%)**		**2 (5,71%)**		**5 (6,54%)**		
2 degree	**18 (48,64%)**		**17 (48,57%)**		**35 (48,61%)**		
3 degree	**4 (10,81%)**		**4 (11,42%)**		**8 (11,1%)**		
Diabetes mellitus	**3 (8,1%)**		**4 (11,42%)**		**7 (9,72%)**		***0.061***
Compensated	**2 (5,4%)**		**3 (8,57%)**		**5 (6,54%)**		
Subcompensated	**1 (2,7%)**		**1 (2,85%)**		**2 (2,77%)**		
COPD	**4 (10,81%)**		**5 (14,28%)**		**9 (12,5%)**		***0.91***
Hepatitis	**9 (24,32%)**		**8 (22,85%)**		**17 (23,61%)**		***0.057***
Remission	**6 (16,21%)**		**6 (17,14%)**		**12 (16,66%)**		
Small activity	**2 (5,4%)**		**1 (2,85%)**		**3 (4,67%)**		
Moderate activity	**1 (2,7%)**		**1 (2,85%)**		**2 (2,77%)**		

FC – functional class, COPD – Chronic obstructive pulmonary disease

Chemotherapy

Among the 37 patients who underwent preoperative chemotherapy, 12 (32.43%) received two cycles followed by esophagectomy. Clinical response assessment after 2 cycles demonstrated disease stabilization in 9 (24.32%) patients and progression in 3 (8.1%) patients, manifested by the appearance of newly involved lymph nodes. These findings were considered direct indications for proceeding with curative-intent esophagectomy.

The remaining 25 (67.56%) patients received additional cycles of neoadjuvant chemotherapy (nCT) due to evidence of a favorable tumor response. Specifically, 18 (48.64%) patients completed 4 cycles, while 5 (13.51%) patients received 6 cycles. In addition, isolated cases of extended treatment up to 7 and 9 cycles were documented in regional centers; however, the rationale for such deviations from standard treatment protocols was not reported.

Post-neoadjuvant treatment evaluation revealed a complete clinical response in 6 (16.21%) patients, who were treated with the TC regimen, while in 4 (10,81%) patients recorded I stage of clinical pathomorphosis (table 2).

Table 2: **The structure of pathomorphological responses according to G.A. Lavnikov.**

Pathomorphosis stage	TC	PF	DCF
I		2 (5,4%)	2 (5,4%)
II	13 (35,1%)	8 (21,6%)	2 (5,4%)
III	1 (2,7%)	3 (8,1%)	
IV	6 (16,2%)		

Chemotherapy-related toxicity was predominantly gastrointestinal, with nausea and vomiting observed in 25 (67.5%) patients. Hematologic toxicity was also common, with grade I–II leukopenia reported in 30 (81.1%) patients and neutropenia in 7 (18.9%) patients. These adverse events were transient, clinically manageable, and responded well to symptomatic treatment. All patients received routine antiemetic prophylaxis, including 5-HT3 receptor antagonists and dexamethasone, throughout the course of chemotherapy.

Surgery

The mean time from hospitalization to surgery was 6 days in both groups. Two patients, per one in every group died within 30 days of surgery. Postoperative complications were recorded in 15/37 (40.38%) patients in the nCS group and in 11/35 (31.42%) patients in the S group. Frequency of non-fatal therapeutic postoperative complications was almost the same in both groups. However, respiratory complications doubled in nCS group (Table 3).

Table 3: **Therapeutic postoperative complications.**

Complications	nCS (n=37)	S (n=35)	*P-value*
Respiratory complications	**6 (16,2%)**	**3 (8,57%)**	***P=0.062***
Pneumonia	**2 (5,4%)**	**2 (5,7%)**	
RDS	**1 (2,7%)**	**0 (0%)**	
Plevritis	**3 (8,1%)**	**1 (2,85%)**	
Cardiovascular complications	**4 (10,8%)**	**3 (8,57%)**	***P=0.58***
Arrhythmia	**2 (5,4%)**	**1 (2,85%)**	
Cardiac failure	**1 (2,7%)**	**1 (2,85%)**	
TELA	**0 (0%)**	**1 (2,85%)**	
Mortality	**0 (0%)**	**1 (2,85%)**	***P=0.87***

RDS – respiratory distress syndrome, TELA – thromboembolism of lung arteries

Of the 37 patients in the nCS group who underwent surgical resection, 34 (91,9%) had a R0 resection, and 3 (8,1%) had a R2 resection. Of the 35 patients in the S group who underwent surgical resection, 26 (74,3%) patients had a R0 resection, 6 (17,1%) patients had a R1 resection, and 3 (8,6%) had a R2 resection. Although more patients in the nCS group had more R0 resections compared with the S group, no significant differences were observed in R2 resection (p=0.99). (Table 4).

Table 4: **Marginal research results.**

Resection margin	nCS	S	Total	*P-value*
R0	**34 (91,9%)**	**26 (74,3%)**	**60 (83,3%)**	***0.049***
R1	**0 (0%)**	**6 (17,1%)**	**6 (8,3%)**	***0.53***
R2	**3 (8,1%)**	**3 (8,6%)**	**12 (16,6%)**	***0.99***

As surgical complications after esophagectomy in our study groups, we took those complications that required active management. According to the incident of surgical complications, per 5 complications were observed in both groups, 13,5% and 14,3% respectively (P=0.43). Table 5 shows the structure of registered complications in study groups, which required surgical interventions to manage.

Table 5: **Surgical postoperative complications.**

Complications	nCTS (n=5)	S (n=5)	*p-value 0.43*
Anastomotic leakage	**1 (2,7%)**	**1 (2,85%)**	***0.87***
Transplant necrosis	**1 (2,7%)**	**2 (5,7%)**	***0.91***
Chylothorax	**2 (5,4%)**	**1 (2,85%)**	***0.73***
Reoperation	**1 (2,7%)**	**1 (2,85%)**	***1.0***
Mortality	**1 (2,7%)**	**0 (0%)**	***0.62***

Disease-free and overall survival

At the time of analysis, the median follow-up was 28 months in the nCS group and 24 months in the S group. In an intention-to-treat survival analysis, four patients from nCS group and 5 patients from S group that were directly lost to follow-up were censored. OS is shown in Figure 1. The median overall survival in the nCS group was 31 months, and in the S group 24 months. OS was better in the nCS group than in the S group (P = 0.003, HR 0.71; Figure 1A). Survival at one year was 89,2% for those allocated to chemotherapy, 91,2% for those allocated to surgery alone; at two years 57,5% and 50,4%; 3- years, survival was 41,6% and 29,9%, respectively.

DFS is demonstrated in Figure 1B. Kaplan–Meier analysis demonstrated significantly improved disease-free survival in the nCS group compared to the S group. The median DFS was 28 months in the nCS group versus 17 months in the S group. The log-rank test revealed a statistically significant difference between the survival curves (HR 0.72, p = 0.0008).

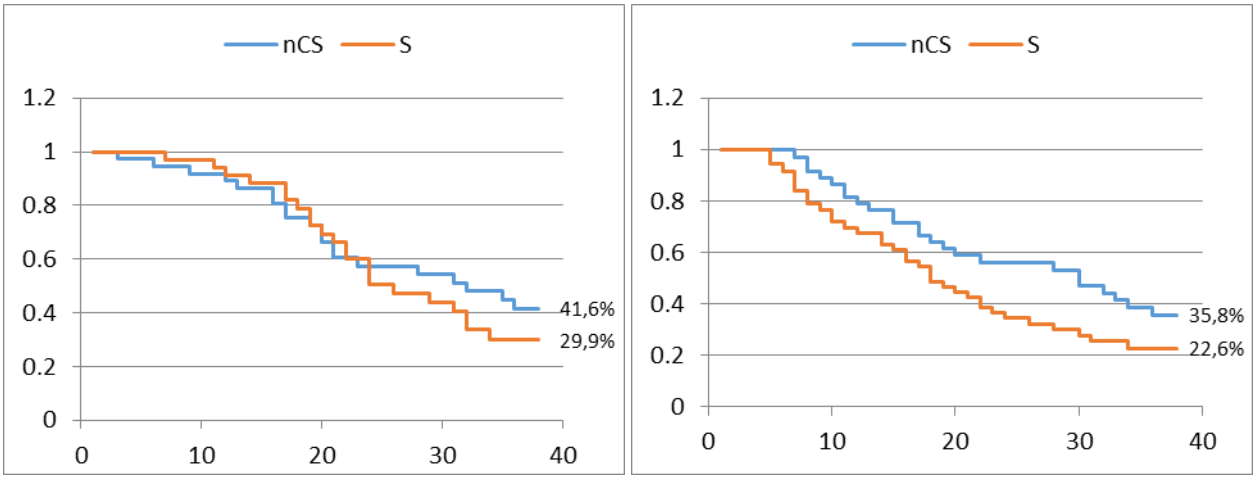

Figure 1: Overall and disease-free survival. A) Overall survival of all allocated patients. p = 0.003, HR 0.71. B) Disease-free survival of all patients p = 0.0008, HR 0.72.

DISCUSSION

The beneficial effect of neoadjuvant chemotherapy on survival outcomes in patients with esophageal squamous cell carcinoma (ESCC) is now well established. Nevertheless, recent literature increasingly reports conflicting evidence regarding the influence of this relatively toxic treatment modality on the incidence of postoperative complications.[12,13] Notably, contemporary studies specifically addressing the impact of neoadjuvant chemotherapy on short-term outcomes following extensive surgical procedures in ESCC patients remain limited. In many instances, neoadjuvant chemotherapy is administered in combination with radiotherapy, which may substantially alter patients' overall physiological condition.[1,10] Therefore, the present study was designed to isolate and evaluate the effect of chemotherapy alone on 30-day postoperative outcomes.

Shogenov M.S. et al. reported the results of combined modality treatment in ESCC patients in comparison with surgery alone. The study population was divided into two cohorts: the main group (n=26), which received multimodal treatment, and the control group (n=30), which underwent surgery only. The neoadjuvant regimen consisted of two cycles of chemotherapy. Surgical management involved subtotal esophagectomy with intrapleural anastomosis and gastric conduit reconstruction. R0 resection rates were achieved in 24 (92.3%) patients in the main group and 26 (86.7%) patients in the control group. Analysis of postoperative outcomes demonstrated that non-surgical (therapeutic) complications occurred in 17 (65%) patients in the combined treatment group compared with 18 (60%) in the surgery-only group. Surgical complications were slightly more frequent in the multimodal treatment group, with an incidence of 26.9% versus 20% in the control group. Postoperative mortality was observed in one patient (3.84%) in the combined treatment group.[7]

In a study conducted by J. Boonstra et al., the impact of preoperative chemotherapy on short-term outcomes in patients with esophageal squamous cell carcinoma (ESCC) was evaluated. A total of 169 patients were allocated into two groups: a combined treatment group (CTS, n=85) and a surgery-only group (S, n=84). Within the CTS group, 66 patients (77.6%) proceeded to esophagectomy following neoadjuvant chemotherapy, whereas in the control group, 70 of 84 patients (83.3%) underwent surgical resection. All patients received transthoracic esophagectomy with reconstruction, including cervical anastomosis when indicated. Although the rate of R0 resections was higher in the CTS group compared to the surgery-only group, no statistically significant differences were observed in overall resection radicality. The incidence of anastomotic leakage was identical in both cohorts, occurring in 8 patients (11%) in the CTS group and 9 patients (11%) in the surgery-only group. Thirty-day postoperative mortality was reported at 5% in the CTS group and 8.3% in the control group.[10]

Evidence regarding the influence of neoadjuvant chemotherapy on surgical outcomes in ESCC remains relatively limited in the global literature. A meta-analysis by Kidane V. et al., which included 13 randomized controlled trials encompassing a total of 2,362 patients with resectable esophageal cancer, sought to clarify this issue. Patients were categorized into two groups: those receiving neoadjuvant chemotherapy followed by surgery (group I) and those undergoing surgery alone (group II). According to the pooled analysis, R0 resection rates were 58% in the neoadjuvant group and 52% in the surgery-only group. The incidence of postoperative complications was 33% in the combined treatment group compared with 36% in the control group. Anastomotic leakage occurred in 5.8% and 6.3% of patients in the respective groups. Postoperative mortality rates were comparable, at 6.3% in the neoadjuvant group and 6.8% in the surgery-only group. Overall, the findings of this meta-analysis suggest no statistically significant differences in postoperative complication rates between the two treatment strategies.[9]

In a retrospective cohort study conducted by Hurmuzlu M. with co-authors to study the effect of high-dose chemoradiotherapy followed by surgery or only surgical treatment for esophageal cancer, 107 patients were selected (the first group included patients who were treated with only surgical intervention (n=45); in the second group, treatment started with preoperative CRT followed by surgery (n=62)). It was shown that postoperative complications occurred within 30 days after surgery in 73.3% patients of first group and in 80.6% patients of second group. The frequency of respiratory complications was 44.4% and 45.2% respectively. At the same time, anastomotic leakage occurred in 11.1% patients of the first group and in 6.4% patients of the second group. It should be noted that the authors also found no significant differences in the incidence of complications in the two compared groups.[14]

From a critical perspective, several important considerations must be acknowledged. First, the majority of available studies are retrospective or heterogeneous in design, with variability in chemotherapy regimens, radiation protocols, surgical techniques, and perioperative care. This heterogeneity limits the direct comparability of results and may obscure clinically meaningful differences. Second, selection bias remains a significant concern, as patients selected for neoadjuvant therapy are often fitter and more likely to tolerate aggressive treatment strategies. Third, the definition and reporting of postoperative complications are not standardized across studies, further complicating interpretation. Additionally, short-term outcomes such as 30-day morbidity and mortality may not fully capture the broader impact of neoadjuvant therapy, including delayed complications and quality-of-life outcomes.

Another critical aspect is the balance between treatment-related toxicity and oncological benefit. While neoadjuvant chemotherapy appears not to significantly increase postoperative risk, its systemic toxicity may still affect functional recovery, nutritional status, and immune competence, particularly in frail patients. Therefore, individualized treatment planning based on patient comorbidities, performance status, and tumor characteristics remains essential.

Future research should focus on well-designed prospective randomized trials that isolate the effect of chemotherapy from combined modality approaches. The integration of modern perioperative care protocols, including enhanced recovery after surgery (ERAS) pathways, should be evaluated in the context of neoadjuvant treatment. The role of biomarkers and molecular profiling in predicting response to chemotherapy and risk of complications also represents a promising area for investigation, potentially enabling more personalized therapeutic strategies. Interpretation of PET/CT results, demonstrating metabolic activity of tumor process and affected lymph nodes (SUV) might be prospective in the assessing of neoadjuvant treatment efficacy. The issue is also an objective for further researches. Finally, future studies should incorporate patient-reported outcomes and long-term functional results to provide a more comprehensive assessment of treatment impact.

CONCLUSION

In this manner, it can be concluded that preoperative CT does not affect a significant increase in the incidence of early surgical and therapeutic complications in patients with resectable cancer of the thoracic esophagus. At the mean time, it has been proven to suggestively prolong the disease-free survival and overall survival. However, individualization of the combined treatment regimen in this group of patients is essential. Given the limitations of existing data, further high-quality research is required to optimize patient selection and refine multimodal treatment strategies.

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