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High-Grade Toxicity to Neoadjuvant Treatment for Upper Gastrointestinal Carcinomas: What is the Impact on Perioperative and Oncologic Outcomes?

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ABSTRACT

Background. Perioperative oncologic treatments provide a survival benefit for junctional and gastric adenocarcinoma (JGA) and esophageal cancer (EC). Whether neoadjuvant therapy toxicity (NTT) correlates with increased perioperative risk remains unclear. We aimed to evaluate the impact of grade III/IV NTT on postoperative and oncologic outcomes in resected upper gastrointestinal malignancies.

Methods. A multicenter retrospective analysis was performed on consecutive patients who benefited from neoadjuvant chemo(radio)therapy followed by surgery between 1997 and 2010 for JGA (first cohort, $n = 653$) and for EC (second cohort, $n = 640$). Data between patients who experienced NTT were compared to those who did not.

Results. NTT was associated with higher postoperative mortality after resection of JGA ($P = 0.001$) and after esophagectomy ($P < 0.001$), more non-R0 resections (JGA $P = 0.019$, EC $P = 0.024$), a decreased administration of adjuvant treatment among the JGA cohort ($P = 0.012$), and higher surgical morbidity (JGA $P = 0.005$, EC $P = 0.020$). Median survival was reduced in patients who experienced NTT in both cohorts (JGA $P = 0.018$, EC $P = 0.037$). After adjustment on confounding variables, NTT was independently associated with postoperative mortality in both cohorts ($P \leq 0.007$).

Conclusions. NTT is a predictor of postoperative mortality, correlates with higher postoperative morbidity, and negatively affects oncologic outcomes for upper gastrointestinal carcinomas.

Even when completely resected, junctional and gastric adenocarcinoma (JGA) and esophageal cancer (EC) remain a group of tumors with a poor prognosis.[1–3] If treated with surgery alone, approximately only 70 % benefit from a R0 resection (no residual microscopic or macroscopic disease) with 5-year survival of less than 25 %.[4,5] Consequently, many investigators have looked at combinations of neoadjuvant and/or adjuvant treatments, with perioperative chemotherapy, adjuvant chemotherapy, or chemoradiation all having shown survival benefit.[2]

No matter what the perioperative strategy, most patients with upper gastrointestinal tract malignancies receive neoadjuvant chemotherapy, as trial evidence has demonstrated improved survival with good treatment tolerance.[4–6] Despite this robust evidence, concern exists that patients who poorly tolerate neoadjuvant chemo(radio)therapy have higher perioperative risk, including the risk of perioperative death.[7] The suggestion that high-grade neoadjuvant toxicity has detrimental effects is opposed by reports that high-grade toxicity to normal host tissues correlates with good tumor response to therapy, and paradoxically is a significant prognostic marker.[8,9]

This multicenter retrospective study evaluated the impact of high-grade neoadjuvant toxicity on outcomes in patients

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undergoing surgery for JGA. A second independent group of EC patients was used to corroborate our observations.

PATIENT AND METHODS

Patient Cohorts

A multicenter database of 2,670 consecutive patients undergoing resection for JGA in 19 French centers from January 1997 to March 2010 was established, with an independent monitoring team auditing data capture to minimize missing data. The current retrospective study included all patients who received neoadjuvant treatment before surgery with curative intent ($n = 653$). The same analysis was performed for a second independent cohort of 640 consecutive EC patients undergoing neoadjuvant treatment followed by surgical resection in the same time period but in our single tertiary referral institution.

Diagnosis and staging investigations were performed in accordance with French national guidelines (http://www.tncd.org). Investigations routinely included physical examination, routine laboratory tests, an esophagogastroduodenoscopy, thoracoabdominal computed tomographic scan, and selective endoscopic ultrasound evaluation and staging laparoscopy. Preoperative patient malnutrition was defined by weight loss $\geq$10 % of baseline body mass over a 6-month period, and postoperative mortality was defined as death within 30 days of surgery.

Neoadjuvant Treatment

Perioperative chemotherapy was considered for stage IB and higher JGA, mainly based on a regimen of epirubicin, cisplatin, and 5-flourouracil or a regimen of cisplatin and 5-fluorouracil.[4,5] Concomitant neoadjuvant radiotherapy was also considered for patients with locally advanced tumors predominantly invading the esophagus. All patients in the EC cohort received neoadjuvant chemotherapy, and the majority were also treated with radiotherapy. For patients in both cohorts, radiotherapy comprised 45 Gy administered in 25 fractions. Preoperative treatment was initiated 4–6 weeks after the first oncologic consultation. Poor tolerance to neoadjuvant therapy was defined by grades III or IV neoadjuvant therapy toxicity (NTT), according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0.

Surgical Approach

Details of the surgical approach to JGA resection have been previously described.[10] Briefly, for antropyloric tumors, a subtotal gastrectomy was performed, whereas for more proximal gastric tumors, a total gastrectomy was standard. Extended resections were performed for suspected or confirmed neoplastic invasion of adjacent structures. For Siewert type II tumors, either a total gastrectomy or esophagectomy was performed, depending on surgeon preference. When gastric resection was extended to the esophagus, it utilized either a transthoracic or transhiatal approach with a dedicated mediastinal lymphadenectomy.[2] An esophagectomy was performed for proximal junctional tumors. Patients without metastatic disease at diagnosis but found to have metastases at the time of surgery were included in the analysis.

In the EC population, all patients had an esophagectomy, which was classified according to whether patients underwent a two-field operation (abdomen and chest, or abdomen and neck) or three-field operation (abdomen, chest, and neck).

Histopathologic Analysis

Histologic staging of all tumors was based on the 6th edition of the International Union Against Cancer tumor, node, metastasis (TNM) classification system.[11] A radical resection with tumor-free margins was considered an R0 resection; an R1 resection indicated a microscopically positive resection margin; and an R2 resection indicated a macroscopically positive resection margin. Patients who were found to have metastatic disease at the time of surgery but who underwent resection were graded as having an R2 resection, and tumors showing a complete pathologic response were graded as ypT0N0.

Patient Follow-up

In both cohorts, patients surviving the surgery were followed until death or time of database closure. French national guidelines (http://www.tncd.org) for esophagogastric cancers stipulate that patients undergo abdominal ultrasonography/computed tomography and chest radiography every 6 months for 5 years and yearly thereafter.

Study End Points

The primary end point was to evaluate the impact of NTT on 30-day postoperative mortality. The secondary end point was to evaluate the impact of NTT on oncologic outcomes.

Statistical Analysis

Data are shown as prevalence and percentages, or median (range). Discrete variables were compared by the Chi

square test, and continuous variables were analyzed by the Mann–Whitney *U* test. A stepwise binary logistic regression model was built to identify factors predictive of postoperative mortality. A *P* value of ≤0.2 on univariable analysis, pre- or perioperative data, and nonredundancy between variables were required for entry into multivariable analysis. All statistical tests were two-sided; the threshold for significance was set at $P < 0.05$. Overall survival was estimated by the Kaplan–Meier method and included postoperative death; equality of censoring distribution between groups was assumed. The study was accepted by the regional institutional review board, and the multicenter database had previously been registered on the ClinicalTrials.gov Web site (identifier NCT01249859). Data analysis was performed by SPSS software, version 19.0 (IBM, Armonk, NY).

RESULTS

Demographics

The primary study cohort comprised 653 patients with JGA, 516 men and 137 women. The median age at diagnosis was 60.3 (range 20.3–84.4) years. The EC cohort comprised 640 patients, 568 men and 72 women, with a median age at diagnosis of 64.1 (range 33.0–81.0) years.

Neoadjuvant and Perioperative Treatment

All patients received neoadjuvant chemotherapy. Of the JGA population, 215 patients (32.9 %) also received radiotherapy, with neither treatment having an effect on postoperative mortality ($P = 0.27$) (Table 1). The majority of chemotherapy regimens were based on fluorouracil–platinum therapy, with doublet therapy in 289 patients (44.3 %) or triplet therapy with epirubicin in 138 patients (21.1 %). Other combinations included epirubicin, oxaliplatin, and capecitabine ($n = 60$, 9.2 %), fluorouracil and irinotecan ($n = 52$, 8.0 %), fluorouracil and oxaliplatin ($n = 41$, 6.3 %), and combinations in doublet or triplet forms with docetaxel ($n = 73$, 11.1 %). Data regarding NTT were available for 632 patients (96.8 %) (Table 2). It occurred in 94 patients (14.4 %). Sixty-one had hematologic toxicities (predominantly leucopenia and thrombocytopenia), and 33 had high-grade digestive tract toxicity (predominantly vomiting and diarrhea).

In the EC cohort, 84 patients (13.1 %) received neoadjuvant chemotherapy only and 556 (86.9 %) neoadjuvant chemoradiotherapy. Chemotherapy comprised doublet therapy for 600 patients, of whom 587 (97.8 %) received 5-flourouracil- and platinum-based treatment. Data regarding treatment toxicity were available for all patients. NTT occurred in 68 (10.6 %) of 640 patients (Table 2), with 28 patients exhibiting grade III or IV hematologic toxicities (predominantly leucopenia and thrombopenia) and 40 patients high-grade digestive tract toxicity (predominantly mucositis).

Impact of NTT on Postoperative Mortality

For all JGA patients, the 30-day postoperative mortality rate was 3.5 % ($n = 23$), and in-hospital mortality was 5.8 % ($n = 38$). Patients with NTT had a rate of postoperative mortality of 9.6 % compared to 2.6 % for patients with good treatment tolerance ($P = 0.001$) and had higher in-hospital mortality ($P = 0.002$) (Table 2). In the overall JGA population, variables associated with postoperative mortality were cTNM stage ($P = 0.002$), NTT ($P = 0.001$) and ypTNM stage ($P = 0.046$) (Table 1).

For EC patients, the 30-day postoperative mortality rate was 4.5 % ($n = 29$), and in-hospital mortality was 5.8 % ($n = 37$). Like the JGA population, in the EC population, those patients who experienced NTT had a rate of postoperative mortality of 13.2 % compared to 3.5 % for patients with good neoadjuvant treatment tolerance ($P < 0.001$) (Table 1). Variables associated with postoperative mortality were gender ($P = 0.025$), American Society of Anesthesiologists score ($P = 0.001$), NTT ($P < 0.001$), three-field resection ($P < 0.001$), and a non-R0 resection ($P = 0.030$).

After adjustment for confounding variables, NTT was independently associated with postoperative mortality in both populations (JGA: odds ratio 4.3, 95 % confidence interval [CI] 1.5–12.6, $P = 0.007$; EC: odds ratio 2.2, 95 % CI 1.3–3.5, $P = 0.002$).

Impact of NTT on Oncologic Outcomes

After NTT, patients undergoing resection of JGA were less likely to receive adjuvant therapy ($P = 0.012$) (Table 2). In both the JGA and EC population, NTT was associated with a higher non-R0 resection rate ($P = 0.019$ and $P = 0.024$, respectively) and more early surgical morbidity ($P = 0.005$ and $P = 0.020$, respectively).

Because an association between NTT and tumor regression grade (TRG) after neoadjuvant chemoradiation has been reported in rectal cancer, we examined the association between NTT and tumor regression in patients receiving neoadjuvant chemoradiation.[9] In both cohorts, patients were divided into those with good tumor response (TRG1–2) and poor/no tumor response (TRG3–5) to treatment. No correlation was found between treatment toxicity and tumor response after neoadjuvant chemoradiation for patients with JGA ($P = 0.99$) or EC ($P = 0.90$) (Table 3).

TABLE 1 Characteristics associated with 30-day POM in patients receiving neoadjuvant therapy for JGA ($n = 653$) and EC ($n = 640$)

Characteristic	Variable	JGA, *n* (%)			EC, *n* (%)		
		No POM ($n = 630$)	POM ($n = 23$)	*P*	No POM ($n = 611$)	POM ($n = 29$)	*P*
Preoperative patient and tumor characteristics							
Gender	Male	496 (78.7)	20 (87.0)	0.34	546 (89.4)	22 (75.9)	0.025
	Female	134 (21.3)	3 (13.0)		65 (10.6)	7 (24.1)	
Age	≤60 years	299 (47.5)	11 (47.8)	0.97	357 (58.4)	13 (44.8)	0.15
	>60 years	331 (52.5)	12 (52.2)		254 (41.6)	16 (55.2)	
Weight loss (% baseline)	<10 %	447 (71.0)	17 (73.9)	0.34	455 (74.5)	26 (89.7)	0.064
	≥10 %	143 (22.7)	3 (13.1)		156 (25.5)	3 (10.3)	
	Unknown	40 (6.3)	3 (13.1)		0 (0)	0 (0)	
cTNM stage	I	32 (5.1)	0 (0.0)	0.002	25 (4.1)	2 (6.9)	0.68
	II	128 (20.3)	0 (0.0)		254 (41.6)	13 (44.8)	
	III	422 (67.0)	17 (73.9)		332 (54.3)	14 (48.3)	
	IV	48 (7.6)	6 (26.1)		0 (0)	0 (0)	
ASA score	I	204 (32.4)	8 (34.8)	0.36	136 (22.3)	0 (0)	0.001
	II	336 (53.3)	9 (39.1)		362 (59.2)	17 (58.6)	
	III	88 (14.0)	6 (26.1)		113 (18.5)	12 (41.4)	
	IV	2 (0.3)	0 (0.0)		0 (0)	0 (0)	
Neoadjuvant therapy	Chemotherapy	425 (67.5)	13 (56.5)	0.27	83 (13.6)	1 (3.4)	0.11
	Radiochemotherapy	205 (32.5)	10 (43.5)		528 (86.4)	28 (96.6)	
Neoadjuvant treatment grades III/IV toxicity	No	524 (83.2)	14 (60.9)	0.001	552 (90.3)	20 (69.0)	<0.001
	Yes	85 (13.5)	9 (39.1)		59 (9.7)	9 (31.0)	
	Unknown	21 (3.3)	0 (0.0)		0 (0)	0 (0)	
Surgery							
Gastrectomy	Total	319 (50.6)	13 (56.5)	0.62	–	–	–
	Partial	80 (12.7)	3 (13.0)				
Esophagectomy	Two fields	195 (31.0)	5 (21.7)	0.65	513 (84.0)	17 (58.6)	<0.001
	Three fields	36 (5.7)	2 (8.7)		98 (16.0)	12 (41.4)	
Pathologic analysis							
ypTNM stage	1	203 (32.2)	7 (30.4)	0.046	114 (18.7)	8 (27.6)	0.15
	2	117 (18.6)	4 (17.4)		91 (14.9)	3 (10.3)	
	3	237 (37.6)	5 (21.8)		137 (22.4)	2 (6.9)	
	4	73 (11.6)	7 (30.4)		269 (44.0)	16 (55.2)	
Resection radicality	R0	526 (83.5)	17 (74.0)	0.060	513 (84.0)	19 (65.5)	0.030
	R1	82 (13.0)	3 (13.0)		55 (9.0)	5 (17.2)	
	R2	22 (3.5)	3 (13.0)		43 (7.0)	5 (17.2)	

JGA junctional and gastric adenocarcinoma, *EC* esophageal cancer, *POM* postoperative mortality, *TNM* tumor, node, metastasis classification system, *ASA* American Society of Anesthesiologists

In the JGA population, the median overall survival was 23.6 months (95 % CI 21.0–26.3)—significantly lower for patients with rather than without NTT (respectively, 17.1 months [95 % CI 11.9–22.3] vs. 24.8 months [95 % CI 21.2–28.5], $P = 0.018$). The median cancer-specific survival was comparable between NTT and no NTT (respectively, 21.9 months [95 % CI 14.0–29.7] vs. 24.6 months [95 % CI 14.2–34.4], $P = 0.18$). After esophagectomy, the median overall survival was 30.3 months (95 % CI 28.9–33.3)—again significantly lower for patients who experienced NTT than those who did not (respectively, 27.0 months [95 % CI 24.4–32.3] vs. 35.8 months [95 % CI 29.1–38.2], $P = 0.037$). Median cancer-specific survival was again comparable between NTT and no NTT (respectively, 29.1 months [95 % CI 22.0–35.7] vs. 31.2 months [95 % CI 24.1–38.8], $P = 0.44$).

TABLE 2 Thirty-day postoperative mortality associated with grade III and IV NTT for patients with JGA ($n = 632$) and EC ($n = 640$)

Characteristic	Variable	JGA, *n* (%)			EC, *n* (%)		
		No NTT ($n = 538$)	NTT ($n = 94$)	*P*	No NTT ($n = 572$)	NTT ($n = 68$)	*P*
Preoperative patient and tumor characteristics							
Gender	Male	432 (80.1)	66 (70.2)	0.027	513 (89.7)	55 (80.9)	0.030
	Female	106 (19.9)	28 (29.8)		59 (10.3)	13 (19.1)	
Age	≤60 years	261 (48.5)	37 (39.4)	0.10	341 (59.6)	29 (42.6)	0.007
	>60 years	277 (51.5)	57 (60.6)		231 (40.4)	39 (57.4)	
Weight loss (% baseline)	<10 %	389 (72.3)	63 (67.0)	0.09	427 (74.7)	54 (79.4)	0.39
	≥10 %	113 (21.0)	28 (29.8)		145 (25.3)	14 (20.6)	
	Unknown	36 (6.7)	3 (3.2)		–	–	
cTNM stage	I	29 (5.4)	3 (3.2)	0.52	23 (4.0)	4 (5.9)	0.46
	II	109 (20.2)	17 (18.1)		243 (42.5)	24 (35.3)	
	III	357 (66.4)	63 (67.0)		306 (53.5)	40 (58.8)	
	IV	43 (8.0)	11 (11.7)		–	–	
ASA score	I	178 (33.1)	32 (34.0)	0.87	126 (22.0)	10 (14.7)	0.37
	II	285 (53.0)	47 (50.0)		336 (58.8)	43 (63.2)	
	III	73 (13.6)	15 (16.0)		110 (19.2)	15 (22.1)	
	IV	2 (0.3)	0 (0.0)		–	–	
Postoperative outcomes							
Death within 30 days of surgery	No	524 (97.4)	85 (90.4)	0.001	552 (96.5)	59 (86.8)	<0.001
	Yes	14 (2.6)	9 (9.6)		20 (3.5)	9 (13.2)	
All postoperative deaths	No	513 (95.4)	82 (87.2)	0.002	546 (95.5)	57 (83.8)	<0.001
	Yes	25 (4.6)	12 (12.8)		26 (4.5)	11 (16.2)	
Overall postoperative morbidity	No	261 (48.5)	31 (33.0)	0.042	293 (51.2)	26 (38.2)	0.039
	Yes	277 (51.5)	63 (67.0)		279 (48.8)	42 (61.8)	
Surgical postoperative morbidity	No	397 (73.8)	56 (59.6)	0.005	493 (86.2)	50 (73.5)	0.020
	Yes	141 (26.2)	38 (40.4)		79 (13.)	18 (26.5)	
Medical postoperative morbidity	No	402 (74.7)	69 (73.4)	0.79	372 (65.0)	40 (58.8)	0.23
	Yes	136 (25.3)	25 (26.6)		200 (35.0)	28 (41.2)	
Adjuvant treatment received	No	274 (50.9)	61 (64.9)	0.012	500 (87.4)	63 (92.6)	0.45
	Yes	264 (49.1)	33 (35.1)		72 (12.6)	5 (7.4)	
ypTNM stage and resection radicality							
ypTNM	1	178 (33.1)	28 (29.8)	0.52	110 (19.3)	12 (17.6)	0.82
	2	98 (18.2)	20 (21.2)		86 (15.0)	8 (11.8)	
	3	199 (37.0)	31 (33.0)		122 (21.3)	17 (25.0)	
	4	63 (11.7)	15 (16.0)		254 (44.4)	31 (45.6)	
Resection radicality	R0	456 (84.8)	69 (73.5)	0.019	476 (83.2)	56 (82.4)	0.024
	R1	64(11.9)	18 (19.1)		49 (8.6)	11 (16.2)	
	R2	18 (3.3)	7 (7.4)		47 (8.2)	1 (1.4)	

NTT neoadjuvant treatment toxicity, *JGA* junctional and gastric adenocarcinoma, *EC* esophageal cancer, *TNM* tumor, node, metastasis classification system, *ASA* American Society of Anesthesiologists, *TRG* tumor regression grade

DISCUSSION

The evidence is clear: for patients with JGA and EC, perioperative oncologic treatment downsizes tumors, increases rates of R0 resection, and improves survival. At the outset of neoadjuvant therapy, it remains unpredictable which patients will tolerate treatment well, have a smooth perioperative course, and have an improved prognosis. In this study of 653 patients undergoing resection for JGA and 640 patients for EC, all patients received neoadjuvant treatment, and the overall 30-day postoperative mortality rate was 3.5 and 4.5 %, respectively, which compares well

TABLE 3 JGA and EC treated with CRT according to tumor regression grade and NTT

Tumor regression grade	JGA, *n* (%) (*n* = 215)			EC, *n* (%) (*n* = 556)		
	No NTT	NTT	*P*	No NTT	NTT	*P*
1–2	74 (41.3)	10 (38.5)	0.99	200 (40.2)	21 (36.2)	0.90
3–5	105 (58.7)	16 (61.5)		298 (59.8)	37 (63.8)	

JGA junctional and gastric adenocarcinoma, *EC* esophageal cancer, *CRT* chemoradiotherapy, *NTT* neoadjuvant treatment toxicity

with many other reports [12–14] After JGA resection, patients who experienced NTT fared badly, with an increased risk of postoperative mortality, early surgical morbidity, non-R0 resection, noncompletion of adjuvant treatment, and worse long-term survival. These principal findings were replicated in a second independent population of patients being treated with curative surgical intent for EC.

In the pivotal European trials establishing neoadjuvant treatment in JGA and EC, postoperative morbidity and mortality have consistently been reported as being similar between experimental and control groups, but without subgroup analysis examining how patients tolerating treatment badly fared after surgery.[4–6] Studies examining the effect of high-grade toxicity on perioperative outcomes are few; the only study we have found that analyzed the NTT effect on perioperative outcomes is a retrospective study of 238 patients operated on after neoadjuvant treatment for EC.[7] Similar to our own findings, patients with grade III or IV toxicity had higher postoperative mortality compared to patients with grade I or II toxicity (6.9 vs. 1.1 %, $P = 0.026$). Evidence is emerging of similar consequences after neoadjuvant chemotherapy toxicity in patients with hepatic metastases from colorectal cancer. Here chemotherapy is administered to render metastases resectable, improve R0 resection rates, and prolong progression-free survival.[15] Despite these therapeutic benefits, chemotherapy-induced sinusoidal injury may correlate with shorter recurrence-free survival, overall survival, and more intrahepatic recurrences.[16] However, in contrast, reports in the setting of rectal cancers have suggested that high-grade toxicity during preoperative chemoradiation may predict good tumor response.[9] Such a correlation does not appear to exist in upper gastrointestinal carcinomas; our analysis did not find that NTT correlated with enhanced TRG in either population.

In the population of JGA, NTT correlated with early surgical morbidity, and strategies to limit toxicity in this neoadjuvant phase should be developed. Perioperative correction of malnutrition and the use of immunonutrition have been shown to correlate with reduced surgical morbidity.[17,18] Enteral nutritional support during neoadjuvant chemotherapy for EC has also been shown to reduce hematologic toxicities and moderate host immune responses.[19,20] Whether immunonutrition may improve treatment tolerance, reduce perioperative morbidity, and improve rates of uptake of adjuvant therapy is the subject of an ongoing multicenter European trial.[21] Recent suggestions that the carboplatin–paclitaxel regime utilized in the CROSS trial offer low toxicity with at least equivalent efficacy needs further validation by direct comparison with other regimes in comparable patient populations.[22,23] We do not suggest the avoidance of surgery in patients who have tolerated preoperative treatment poorly. Instead, our findings mean that we must maximize strategies that limit toxicity, enhance the host's reserves, and consider the appropriate timing of definitive surgery.

In both patient groups, NTT was associated with higher rates of non-R0 resection, increased postoperative mortality, and poorer long-term survival, whereas in the JGA cohort it was also associated with noncompletion of adjuvant treatment. Poorer long-term survival is likely to be related in part to the higher postoperative mortality after NTT and in part to the higher non-R0 resection rate and lower rate of administration of adjuvant therapy when this is planned for JGA. To examine the hypothesis that NTT is more deleterious to the host than the tumor, we assessed cancer-specific survival and found no difference in disease-specific survival between NTT and no NTT in either population. Deaths unrelated to cancer appear to be more frequent after high-grade neoadjuvant toxicity, supporting the idea that host impairment is the major factor explaining poor outcome.

This study is limited by its retrospective nature, which may lead to missing data and may introduce bias. The overall sample size, however, gives sufficient statistical robustness, and the multicenter data collection allows for more universal results. Even if we found no definitive demonstration of causation, our findings strongly suggest that patients who struggle through the neoadjuvant phase of treatment also fare poorly perioperatively. The findings in both populations are similar, highlighting both the originality and importance of this message. Future prospective trials should include in their end points the impact of NTT on perioperative and oncologic outcomes.

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