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ORIGINAL ARTICLE – COLORECTAL CANCER

Impact of Perineural and Lymphovascular Invasion on Oncological Outcomes in Rectal Cancer Treated with Neoadjuvant Chemoradiotherapy and Surgery

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ABSTRACT

Background. The prognostic significance of perineural and/or lymphovascular invasion (PLVI) and its relationship with tumor regression grade (TRG) in patients with locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy (CRT) and surgery.

Methods. A total of 324 patients with LARC were treated with CRT and operated on between January 1992 and June 2007. Tumors were graded using a quantitative 5-grade TRG classification and the presence of PLVI was histologically studied.

Results. At a median follow-up of 79.0 months (range 3–250 months), a total of 80 patients (24.7 %) relapsed. The observed 5- and 10-year overall survival (OS) was 83.2 and 74.9 %, respectively. The 5- and 10-year disease-free survival (DFS) was 75.1 and 71.4 %, respectively. A significant correlation was found between the TRG and survival (log rank, $p < 0.001$). The 10-year OS was 32.7 % for grade 1, 63.8 % for grade 2, 75.0 % for grade 3, 90.4 % for grade 3+, and 96.0 %,for grade 4. The 10-year DFS was 31.8 % for grade 1, 58.6 % for grade 2, 70.4 % for grade 3, 88.4 % for grade 3+, and 97.1 % for grade 4. In patients with PLVI, the TRG had no impact on survival. When excluding patients with PLVI, the TRG was an independent prognostic factor for OS and DFS.

Conclusions. The presence of PLVI is a more powerful prognostic factor than TRG in LARC patients treated with neoadjuvant CRT followed by surgery. PLVI denotes an aggressive phenotype, suggesting that these patients may benefit from adjuvant systemic therapy.

The current standard of care for locally advanced rectal carcinoma (LARC) is neoadjuvant chemoradiotherapy (CRT) followed by proctectomy based on the principles of total mesorectum excision (TME).[1–7] Despite a 40 % reduction in local recurrence and a higher incidence of sphincter-saving procedures, no improvement in disease-free survival (DFS) has been reported in the last decade. Two well-defined subpopulations of patients have been described for the tumor response to CRT, a poor response phenotype and a near or complete pathological response (pCR), with a DFS of 58.5 and 90.5 %, respectively.[4,8–12]

Identifying the subpopulation of patients with worse prognosis is crucial to implementing or updating the systemic chemotherapy.[3,13] Currently, the only robust prognostic factor is the pathological response grade after proctectomy.[4,8,10] Imaging studies and biomarkers are limited in their ability to provide valuable information regarding prognosis.[14–17] However, despite controversies between some authors, TNM, the tumor regression grade (TRG) response to CRT, and the circumferential resection margin are still the main prognostic factors.[4,10,18–20]

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In addition, perineural invasion (PNI) and lymphovascular invasion (LVI) have a negative impact on the oncological outcome of rectal cancer. However, most studies were performed in the adjuvant era and limited by a small sample size and short follow-up.[21–27]

The present study investigated the prognostic significance of PNI and/or LVI and their relationship with TRG in a large cohort of patients with LARC who underwent TME after CRT.

MATERIALS AND METHODS

Patients

The analysis was conducted according to strengthening the reporting of observational studies in epidemiology (STROBE).[28] Between January 1992 and June 2007, 621 patients diagnosed with rectal cancer underwent surgery at the Clínica Universidad de Navarra. A cohort was selected of 324 consecutive patients diagnosed with locally advanced primary rectal adenocarcinoma (cT3–4 or cN1 classification and/or clinically bulky). Adenocarcinoma was confirmed by biopsy and located <15 cm from the anal verge. The exclusion criteria were: emergency surgery, coexistence of other malignancies, concurrent inflammatory bowel disease, prior surgery in the rectum, the presence of distant metastatic disease, or intraoperative radiation therapy.

Neoadjuvant treatment was applied by a multidisciplinary team of oncologists, radiotherapists, and surgeons with a special dedication to colorectal disease. The closing date of the study was 30 December 2007. All patients provided informed consent for treatment. This retrospective analysis was approved by the institutional review board.

Treatment Plan

Two different protocols were used for neoadjuvant chemotherapy: 5-fluorouracil (5-FU) alone (225 mg/m^2 on days 1–4 and 24–28) or capecitabine (825 mg/m^2 twice daily Monday through Friday) in combination with oxaliplatin (60 mg/m^2 on days 1, 8, and 15). Concomitant preoperative external beam irradiation was delivered using either a 3- or 4-field technique, or a 7-field intensity-modulated technique. The results of the 3- or 4-field technique have been reported elsewhere.[8,29,30] Fifty-three percent of the patients received adjuvant chemotherapy for 6 months.[1]

Surgical Resection

Surgery was scheduled 5–6 weeks after the completion of CRT and performed according to the principles of TME [5,31] for all tumors located in the middle and lower thirds of the rectum. For tumors in the upper third of the rectum, the mesorectum was sectioned with a macroscopic safety margin of at least 5 cm from the distal margin. The type of surgery (i.e., anterior resection, Hartmann or Miles procedures) was performed at the surgeon's discretion based on the condition of each patient.

Pathological Analysis

A pathological examination was performed by a specialized gastrointestinal pathologist (J.J.S.) specifically for this study to obtain the most accurate assessment of the TRG. Staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification of malignant tumors.[32] In addition, circumferential radial margins, distal resection margins, LVI, and PNI were documented.

A positive circumferential margin was defined as the presence of tumor cells within 1 mm of the margin of resection. Perineural invasion was defined as the presence of viable tumor cells within any layer of the nerve sheath or tumor foci outside of the nerve with involvement of >33 % of the nerve's circumference in the perineural space.[22–24] Lymph and/or blood vessel invasion was assessed according to Sato et al.[33] and current practice guidelines.[34]

The tumor response to CRT was determined using the 5-point scale[7] proposed by Ruo et al.[18] and Shia et al.[12] This classification takes into account the percentage of tumor cells that remain visible in the surgical specimen: grade 0 (no response to treatment), grade 1 (response <33 % of the tumor), grade 2 (response between 33 and <66 %), grade 3 (response between 66 and <95 %), grade 3+ (95–99 % response, foci of microscopic residual tumor), and grade 4 (pCR, no viable tumor identified in the primary tumor and/or nodes). The extent of residual tumor in the specimen as well was classified according to the TNM classification.[32]

Surveillance

Patients were followed-up every 3 months for 2 years, every 6 months for the next 3 years, and then annually thereafter, according to the National Comprehensive Cancer Network guidelines.[1,35] Local recurrence was defined as clinical or radiological tumor regrowth within the previous pelvic treatment field. Distant recurrence was defined as tumor growth in any other area. Relapse was diagnosed based on two consecutive CT scans within 4–6 weeks. Histopathological verification was performed when feasible.

Statistical Analysis

Results were expressed as medians (25th–75th percentiles) for continuous variables and proportions for

TABLE 1 Clinical and pathological features of the series

Variable	Patients ($n = 324$ (%))
Age (years)	59 (52–67)
Sex (males)	219 (67.6 %)
BMI (kg/m^2)	25.7 (23.1–28.1)
Location (rectal third)	
Lower	145 (44.8 %)
Middle	135 (41.7 %)
Upper	44 (13.6 %)
Distance from the anal verge (cm)	6 (4–10)
Procedure	
Anterior resection	228 (70.4 %)
Miles	84 (25.9 %)
Hartmann	12 (3.7 %)
Chemotherapy	
Preoperative	140 (43.2 %)
Preoperative and postoperative	174 (53.7 %)
No chemotherapy	10 (3.1 %)
Chemotherapy schedule	
5FU + leucovorin	25 (8.0 %)
5FU + carboplatin	177 (56.3 %)
5FU + oxaliplatin	112 (35.7 %)
RT^2	
Three fields	96 (29.6 %)
Four fields	139 (42.9 %)
Intensity-modulated	78 (24.1 %)
Time RT to surgery (days)	39 (33–42)
Length RT (days)	34 (29–38)
Dose RT (cGy)	4,680 (4,500–5,040)

TNM classification	Preoperative	Pathological
T		
T0		44 (13.6 %)
T1		18 (5.6 %)
T2	13 (4 %)	104 (32.1 %)
T3	280 (86.4 %)	145 (44.8 %)
T4	31 (9.6 %)	13 (4.0 %)
N		
N0	161 (49.7 %)	235 (72.5 %)
N+	163 (50.3 %)	89 (27.5 %)
Stage		
0		43 (13.3 %)
I	3 (0.9 %)	100 (30.9 %)
II	157 (48.5 %)	92 (28.4 %)
III	164 (50.6 %)	89 (27.5 %)

5FU 5-fluorouracil, *cGY* centigray, *BMI* body mass index (kg/m^2), *RT* radiotherapy

Quantitative variables are expressed as median (interquartile range) and frequencies are expressed as n (%)

TABLE 2 Pathological findings in rectal cancer after neoadjuvant chemoradiotherapy

TRG categories	n	%
1	11	3.4
2	92	28.4
3	122	37.7
3+	57	17.6
4 (pCR)	42	13
Perineural invasion	68	20.4
Lymphatic vessel invasion	23	7.1
Vascular invasion	54	16.7
PLVI	92	29

pCR complete pathological response, *PLVI* perineural and/or lymphovascular invasion, *TRG* tumor regression grade (according to Shia et al.[12] and Ruo et al.[18])

qualitative variables. The Mann–Whitney *U* test or the Kruskal–Wallis test was used to compare means in two or more groups and the $\chi 2$ test was used to compare proportions. Follow-up data were taken from the time of the last clinic appointment (before the end of the study on 30 December 2007) or event (recurrence or death). Deaths from unrelated causes were censored for the purpose of survival analysis. DFS and OS were expressed as percentages (standard errors) and analyzed using the Kaplan-Meier method. Survival curves were compared using the log-rank test. Independent prognostic factors for survival were determined by multivariate Cox regression analysis, in which the likelihood ratio method was used instead of Wald's. All statistical tests were two-sided at the 5 % level of significance and performed using SPSS/PC version 15 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Patients

The clinical and tumor characteristics of the patients are summarized in Table 1. Low anterior resection was the most frequent procedure, and half of the patients (49.2 %) with a tumor located in the lower third of the rectum could benefit from a sphincter-saving procedure.

Pathological Analysis

Involvement of the distal edge ($\leq$1 mm) was observed in one patient (0.3 %) and the circumferential margin ($\leq$1 mm) was affected in 19 patients (5.9 %). The median distance between the lower edge of the tumor and the

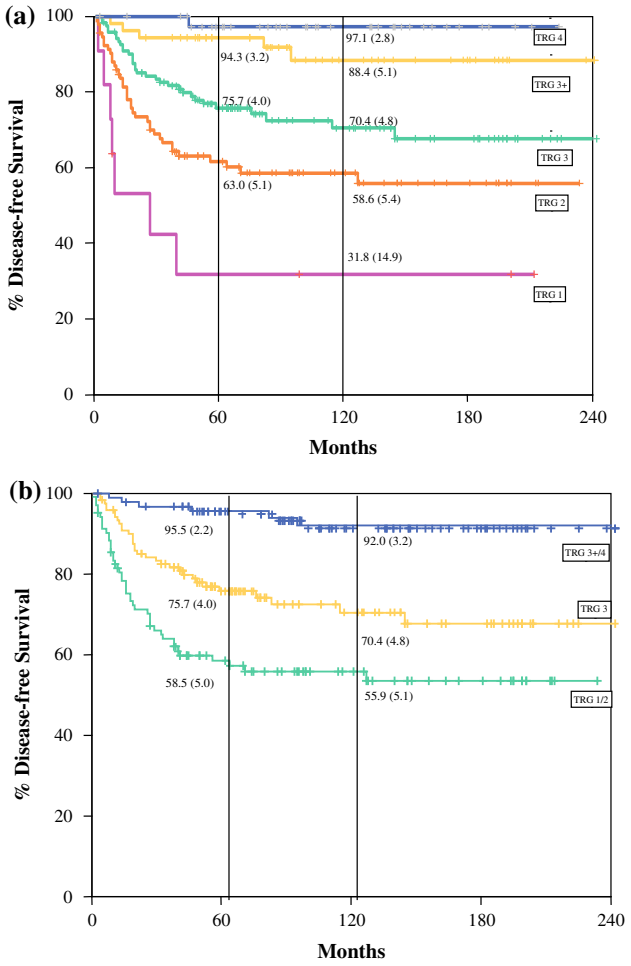

FIG. 1 Kaplan–Meier disease-free survival is stratified by 5 (**a**) and 3 grade (**b**) pathological response. Cumulative disease-free survival at 5 and 10 years is expressed as a percentage (standard error)

section limit was 3 cm. The pathologic response to CRT is summarized in Table 2. Some type of perineural and/or lymphovascular invasion (PLVI) was observed in almost one-third of the patients (Table 2).

Survival Analysis

At a median follow-up of 79.0 months (range 3–250 months), 100 patients (30.9 %) died, 70 due to disease progression (21.6 %) and 30 due to other causes (9.3 %). A total of 80 patients (24.7 %) developed either local or distant cancer relapse: 8 (2.5 %) local recurrence, 69 (21.3 %) distant metastases, and 3 (0.9 %) synchronous local and distant recurrence. OS for the entire group of patients was 83 and 75 % at 5 and 10 years, respectively, and DFS was 75 and 71 %, respectively.

TABLE 3 Cox multivariate analysis of variable associated with survival

Variable	OS			DFS		
	HR	95 % CI	*p* Value	HR	95 % CI	*p* Value
TRG			0.062			0.020
1–2 (vs. 3+/4)	2.78	0.97–7.93	0.067	3.32	1.26–8.74	0.009
3 (vs. 3+/4)	3.22	1.08–8.62	0.020	3.07	1.24–7.58	0.008
pN+	1.78	1.02–3.11	0.043	1.93	1.17–3.19	0.010
Presence of PLVI	3.70	1.99–6.86	<0.001	2.96	1.70–5.16	<0.001
Positive margins	4.73	2.47–9.09	<0.001	2.32	1.22–4.40	0.017
Rectal third			NS			0.010
Lower vs. upper				2.30	1.09–4.88	0.017
Middle vs. upper				0.97	0.43–2.16	0.935

CI confidence interval, *DFS* disease-free survival, *HR* hazard-ratio, *NS* not significant, *OS* overall survival, *PLVI* perineural and/or lymphovascular invasion, *pN+* (node positive) presence of lymph node invasion, *TRG* tumor regression grade, *vs.* versus

Correlation between Pathological Findings and Survival

A significant correlation was found between the five different grades of TRG and survival (log rank, $p < 0.001$). Ten-year OS was 32.7 % (15.0) for TRG 1; 63.85 % (5.7) for TRG 2; 75.0 % (4.7) for TRG 3; 90.4 % (5.5) for TRG 3+; and 96.0 % (3.9) for TRG 4. DFS is shown in Fig. 1a. As only 11 patients exhibited a grade 1 pathological response, and the survival curves for grades 3+ and 4 were similar, further analysis was restricted to three categories: TRG1/2, TRG3, and TRG3+/4. These categories also significantly correlated with survival. The 10-year OS was 92.8 % (3.6) for TRG 3+/4, 75.0 % (4.7) for TRG 3, and 60.1 % (5.5) for TRG 1/2. DFS is shown in Fig. 1b.

In univariate analysis, only rectal third, postoperative chemotherapy and the pathological variables (i.e., TNM classification, TRG, positive margins and PLVI) were significantly associated with OS and DFS. When these factors were analyzed by multivariate Cox regression model, the TRG remained as an independent prognostic factor for DFS while it showed a statistical trend to associate with OS (Table 3).

In patients with PLVI, only presence of lymph node invasion and positive margins were significantly associated with OS ($p = 0.086$ and 0.004, respectively) and DFS ($p = 0.042$ and 0.037, respectively) in the univariate analysis, and TRG was not one of them. These variables lost their significance in the multivariate analysis of patients with

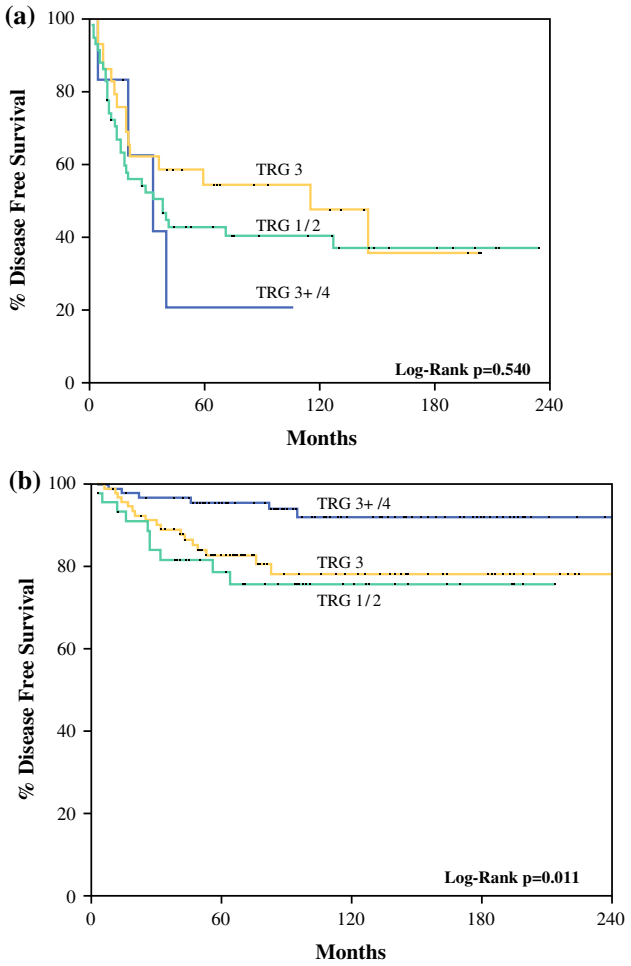

FIG. 2 Disease-free survival according to perineural and lymphovascular invasion (PLVI). **a** In the presence of PLVI, TRG lost its influence on outcome. **b** In the absence of PLVI, the categories of TRG were significantly associated with survival. *TRG* tumor regression grade

PLVI. As shown in Figure 2a, in the presence of PLVI, TRG also lost its influence on outcome as rectal location.

Because of this great impact of PLVI on survival, we decided to study the association of different variables with both OS and DFS in patients without PLVI. In this group of patients, the 3-grade tumor response was significantly associated with survival (Fig. 2b). When the pathological variables previously considered in univariate analysis were entered into a multivariate analysis, almost all of them remained significantly associated with both OS and DFS (Table 4). The observed hazard ratio (HR) for DFS indicated that, after adjusting for lymph node status, positive margins, and rectal third, patients with a high TRG (3+/4) were, at least, 2.38 times more likely to be disease-free than those with a low TRG or unfavorable prognosis.

TABLE 4 Multivariate analyses of pathological variables for OS and DFS in patients without PLVI

Variable	OS			DFS		
	HR	95 % CI	*p* Value	HR	95 % CI	*p* Value
TRG			0.142			0.020
1–2	3.20	0.97–11.73	0.079	4.18	1.48–11.8	0.009
3	2.34	0.77–7.71	0.145	2.38	0.89–6.33	0.008
pN+	3.54	1.36–9.24	0.014	3.31	1.51–7.23	0.010
Positive margins	14.39	4.60–44.9	0.001	4.87	1.88–12.65	0.017
Rectal third			0.047			0.010
Lower	6.90	1.01–55.55	0.020	5.00	1.15–21.73	0.017
Middle	3.43	0.38–30.86	0.214	1.45	0.30–7.10	0.935

CI confidence interval, *DFS* disease-free survival, *HR* hazard-ratio, *OS* overall survival, *pN+* (node positive) presence of lymph node invasion, *PLVI* perineural and/or lymphovascular invasion, *TRG* tumor regression grade

DISCUSSION

The current standard treatment for LARC is neoadjuvant CRT followed by surgery based on the TME principle.[1–7,36] Despite a significant reduction in local failure, DFS has remained stable over the last decade,[4,8,11,12] promoting an exhaustive search for new predictive factors other than the pathological findings after proctectomy.[14,16,17,37] Unfortunately, predictive factors are still not clinically reliable, leaving pathological assessment as the most relevant prognostic factor. In our series, we found a significant association between the five grades of tumor response to CRT and survival. These findings are similar to previous reports that identified three well-defined subpopulations in regard to oncological outcomes: favorable, intermediate, and unfavorable.[4,7,8,11,12,38] These populations were also found in the present series (Fig. 2b).

Several authors have stressed the importance of surgical technique in the final outcome of rectal cancer.[5,31,39] A local recurrence rate of 2.5 % and a 5-year OS rate of 83.2 % indicates the highest quality standards, especially considering that this is a series of patients with stage II and III rectal tumors. In addition, the study included a large number of patients (n = 324) and had a median follow-up of 94 months for surviving patients.

Notably, PLVI reveals an aggressive phenotype. The present results provide further evidence for the recent studies that identified PLVI as an independent prognostic factor.[22–24,26,40] The impact of PLVI is so determinant that TRG loses its influence on survival when PLVI is present.

Ceyhan et al.[24] described a PNI rate of 18.5 % in the neoadjuvant setting and Liebig et al.[23] reported an incidence of 30 % in untreated rectal tumors, which is in-line

with the current and previous studies.[40] In these previous studies, PNI was an independent negative prognostic factor of OS, DFS, and distant relapse. Strong evidence indicates that PNI is more like invasion than simple diffusion.[41,42]

Park et al.,[11] Shia et al.,[12] and Rodel et al.[19] reported an incidence of LVI of 14.3, 19.2, and 20 % respectively, in preoperative CRT patients, which is in-line with the present study. Others, such as Sato et al.[33] and Talbot et al.[43] described a higher incidence of LVI of 70.6 and 52 %, respectively, without preoperative therapy. Interestingly, all authors confirmed the significant association between LVI and decreased survival, which resulted in the recommendation of adjuvant therapy in these cases. The last AJCC Staging Manual, 7th edition, recommends that PNI and LVI should be included as prognostic parameters.[44]

These findings have immediate practical consequences, confirming that the presence of PNLV in the specimen after CRT denotes an aggressive phenotype and is a harbinger of decreased survival. A stronger value that the approval of tumor regression grade[45–48] suggests that these patients will be a subsidiary of adjuvant systemic therapy.

In the present study, PLVI and tumor location in the distal third of the rectum were identified as risk factors for distant relapse, raising the clinical rationale to be upfront, and intensifying the chemotherapy in patients who are likely to require chemotherapy as part of their treatment. A number of phase II trials have assessed the addition of neoadjuvant chemotherapy to the standard treatment of LARC with encouraging results, indicating a potential benefit of systemic therapy prior to local treatment and raising the possibility that radiotherapy could be omitted in a select group of patients.[13,49,50,51] Schrag et al.[49] recently reported an incidence of pCR of 27 % with no local relapse.

Unfortunately, conclusive data is not available on the predictive factors such as imaging, epidermal growth factor receptor (EGFR), thymidylate synthase, and p21 biomarkers, for identifying the unfavorable population in regard to the tumor response to CRT [14,16,52,53] and clinical decision-making.

Most of the support for using adjuvant chemotherapy is an extrapolation from the outcomes available from colon cancer.[54,55]. In this study, we found that the presence of PNI and/or LVI greatly lower survival in stages II/III rectal cancer. Despite the absence of evidence-based efficacy of adjuvant chemotherapy after neoadjuvant CRT,[36,56] most of the guidelines recommend postoperative chemotherapy for patients with stage II/III rectal cancer after preoperative CRT and surgery, regardless of surgical pathology.[1,36,57]

The present study has some limitations, such as its retrospective nature. Nevertheless, clinical, surgical, and outcome data were collected prospectively and the pathological study was newly preformed. The CRT regimen was not homogeneous, given the evolution of chemotherapy and radiotherapy in the last decade. Another limitation is the "artificial" grouping of TRG 1 and 2, and TRG 3+ and 4. On the other hand, robust data from other groups with similar CRT regimens and the same pathological criteria performed a similar restrictive analysis regarding TRG response, and similar findings were described.[4,10,12,19]

CONCLUSIONS

The present study reveals a significant association between TRG and survival and provides further evidence of the prognostic value of PLVI. When PLVI is present, TRG loses much of its influence on outcome. PLVI, together with TRG, should be included in the routine pathological analysis of LARC treated with CRT. This information will help determine the most appropriate adjuvant treatment for a particular patient. In the subset of patients with PLVI, new alternative therapeutic approaches warrant further investigation.

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