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Steroid Receptors and Prognosis in Operable (Stage I and II) Breast Cancer

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Abstract—*Four hundred and forty-seven women with operable (TNM stage I or II) breast cancer in whom oestrogen receptors (ER), progesterone receptors (PgR) or both receptors had been assayed were studied. Receptor status was independent of axillary nodal status, but infiltrating duct carcinomas that were ER–, PgR– or ER–PgR– were more likely to be anaplastic* ($P < 0.001$). *Four hundred patients with follow-up and uniform treatment were analysed for post-operative disease-free interval (DFI) and survival. No significant difference in DFI existed between patients with ER+ and ER– tumours or PgR+ and PgR– tumours, although there was a trend for longer DFI for ER+ and PgR+. DFI was longer in patients with better-differentiated (grade 1 and 2) tumours than with anaplastic (grade 3) tumours. In patients with ER+ tumours, those with grade 1 and 2 tumours had a longer DFI than those with grade 3 tumours* ($P < 0.005$). *Survival was significantly longer in patients with ER+ tumours compared to those with ER– tumours* ($P < 0.001$), *but there was no such association between tumour PgR and survival. Survival of patients with ER+PgR+ tumours was significantly longer than those with ER–PgR– tumours* ($P < 0.025$) *and, in patients with no evidence of axillary nodal involvement, significantly longer than those with ER+PgR– tumours. Survival in patients with nodal involvement was influenced by histological grade, being longer in those with grade 1 or 2 tumours compared to those with grade 3 tumours. For ER+ tumours, survival was longer in patients with grade 1 or 2 than with grade 3 tumours. These results suggest that steroid receptors significantly affect survival but not DFI. This effect is most closely related to ER content, with relatively little additional information accruing from analysis of PgR. Histological grade influences both DFI and survival, and analysis of both grade and ER content may give a more accurate indication of prognosis in operable breast cancer.*

INTRODUCTION

RECENT reports have suggested that oestrogen receptors (ER) [1, 2, 3] and progesterone receptors (PgR) [4, 5] give prognostic information in early breast cancer, but a general consensus on this has not yet emerged [6, 7]. We report here our results relating tumour content of ER and PgR to disease-free interval and survival in patients with operable (TNM stage I and II) breast cancer. Tumour grade is known to correlate with prognosis in operable breast cancer [8] and has been reported to be related to steroid receptor content [9]. Hence analyses have been undertaken to relate both tumour grade and receptor content to disease-free interval (DFI) and survival in this group of patients to determine whether grade and ER status provide independent information about prognosis.

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MATERIALS AND METHODS

All patients with operable breast cancer who presented to the Breast Unit, Guy's Hospital from February 1975 to March 1980 were studied prospectively. Patients eligible for this study had: (a) a histological diagnosis of infiltrating breast carcinoma; (b) stage I or II (T1,2,N0,1,M0)

tumours [10]; and (c) assays for ER (throughout the period of this study) or PgR (from March 1976 to March 1980) or both performed on primary tumour tissue. Age and menstrual status (pre-menopausal, last period <6 months; post-menopausal, last period ≥6 months) on presentation were noted. Information on axillary nodal metastases in the operative specimen was recorded.

Standard surgical treatment during the period of study was a modified radical mastectomy. Patients with uninvolved axillary nodes had no additional treatment, but those with pathologically involved axillary nodes were randomised to receive either melphalan 6 mg/m^2 (maximum 10 mg) orally for 5 days every 6 weeks for a total of 16 cycles or no additional treatment; no significant differences between these groups for DFI or survival have been observed. Forty-four patients who had other forms of adjuvant therapy (either radiotherapy or other adjuvant cytotoxic or hormone therapy) and 3 patients who were lost to follow-up were included in analysis of clinical features at presentation but excluded from analysis of DFI and survival.

Patients were followed-up regularly, usually 3-monthly but 6-weekly when on oral melphalan, with regular bone scintiscans, chest radiographs and biochemical screens (including liver function tests). Relapse was confirmed by biopsy, if possible, or unequivocal radiological evidence. Radiotherapy was given for localised recurrence, while generalised metastatic disease was managed by endocrine treatment (ovarian ablation +/- prednisolone if pre-menopausal, tamoxifen +/- prednisolone if post-menopausal), chemotherapy being reserved for progressive disease after failure on endocrine therapy.

DFI was from the date of operation to the date of confirmed first relapse, whilst survival was dated from the time of surgery to death. Survival from first recurrence was from the date of confirmed recurrence to death.

Analysis for ER and PgR was carried out by the method of King *et al.* [11]. A receptor value of less than 5 fmol receptor/mg cytosol protein was regarded as negative (respectively ER- and PgR-) and any value greater than this was considered positive (respectively ER+, PgR+).

Measurement of histological grade in 324 patients with infiltrating duct carcinomas (72% of total) was by the method of Bloom and Richardson [8].

Statistical significance between groups was determined by the χ^2 test. Differences between group mean values were examined by Student's *t* test. Analysis of DFI and survival was by the log rank method [12].

RESULTS

In 447 eligible patients assays for both ER and PgR were available in 314 tumours, for ER only in 123 and for PgR only in 10.

Patients with ER+ tumours (mean age 55.7 yr) were significantly older ($P<0.025$) than those with ER- tumours (mean age 53.2 yr) and similarly those with PgR- tumours (mean age 56.8 yr) were significantly older than those with PgR+ tumours (mean age 54.0 yr). In addition, patients with ER+PgR- tumours (mean age 58.5 yr) were significantly ($P<0.005$) older than those with ER+PgR+ (mean age 54.6 yr), ER-PgR+ (mean age 50.6 yr) and ER-PgR- tumours (mean age 53.5 yr). Menstrual status also influenced tumour receptor phenotypes, patients with PgR- and ER+PgR- tumours being predominantly post-menopausal (respectively 72 and 79%, $P<0.01$ and $P<0.005$). When age at presentation was examined in the menstrual subgroups, no differences between the various receptor phenotypes emerged.

Receptor phenotypes were independent of axillary nodal status, but there was a relationship between tumour receptor content and histological grade in infiltrating duct carcinomas (Table 1); ER-, PgR- and ER-PgR- tumours were more commonly anaplastic (grade 3).

Four hundred patients were eligible for analysis of DFI and survival. There was a trend for patients with ER+ tumours to have a longer DFI than those with ER- tumours, but this was not significant (Fig. 1a). When patients were divided into groups based on the presence or absence of axillary nodal involvement and menstrual status this trend persisted, but in no subgroup was it significant. When DFI and tumour PgR content were analysed, again there was a trend for a longer DFI with PgR+ tumours, but this was less marked than that for ER (Fig. 1b). This trend persisted when patients were analysed according to axillary nodal status. Because of the small number (11) of pre-menopausal patients with PgR- tumours, analysis in the menstrual subgroups was not performed. In patients with tumours analysed for both ER and PgR there was a trend for patients with ER-PgR- tumours to have a shorter DFI than those of any other receptor phenotypes (ER+PgR+, ER+PgR-, ER-PgR+) (Fig. 1c); this too was not statistically significant.

DFI was significantly ($P<0.005$) longer in patients with grade 1 or grade 2 tumours than with grade 3 tumours, but this difference occurred only in patients with involved axillary nodes and not those with uninvolved nodes. Attention to both tumour ER content and histological grade gave additional prognostic information to when each was used separately. In patients with ER+

Table 1. Association between histological grade and steroid receptor status in patients with infiltrating duct carcinomas

Receptor status	No. of patients Grade 1	Grade 2	Grade 3	
ER+ ($n=232$)	38	136	58	$P<0.001$
ER- ($n=84$)	5	22	57	
PgR+ ($n=143$)	28	78	37	$P<0.001$
PgR- ($n=89$)	3	42	44	
ER+PgR+ ($n=117$)	27	67	23	
ER+PgR- ($n=55$)	3	34	18	$P<0.001$
ER-PgR+ ($n=19$)	0	6	13	
ER-PgR- ($n=33$)	0	8	25	

Note: grading available on 224 tumours with both receptors analysed, 92 with ER only and 8 with PgR only.

tumours, those with grade 1 and 2 tumours had a longer DFI than those with grade 3 tumours (Table 2). In patients with uninvolved nodes and grade 2 tumours, 80% with ER+ tumours ($n=53$) were projected to be disease-free at 5 yr, compared to only 60% of those with ER- tumours ($n=13$) ($P<0.025$).

Survival was longer in patients with ER+ tumours than those with ER- tumours ($P<0.001$) (Fig. 2a). This difference occurred when axillary nodes were involved ($P<0.05$) or uninvolved ($P<0.001$). When patients were subdivided according to menstrual status, this survival difference between patients with ER+ and ER-

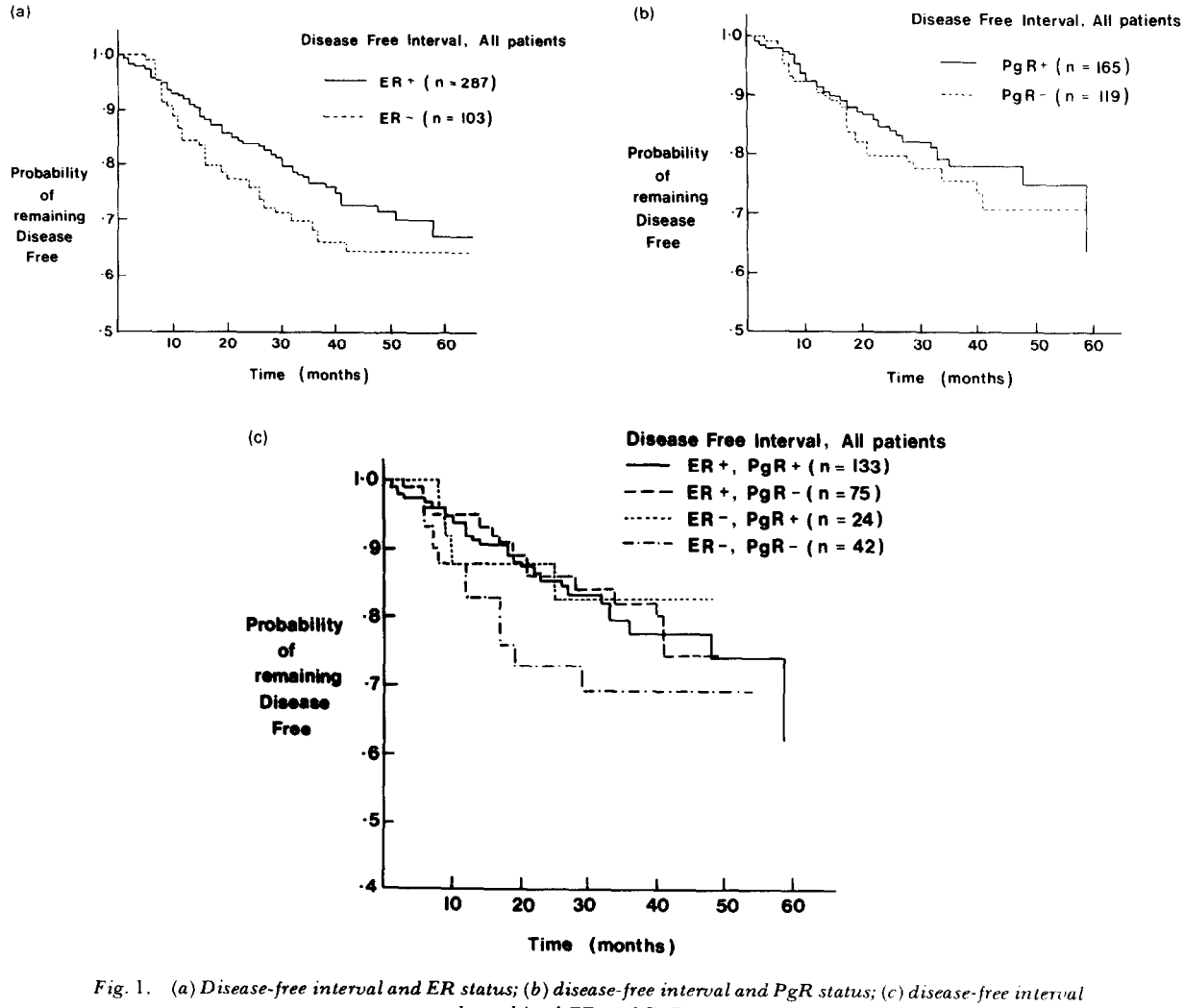

Fig. 1. (a) Disease-free interval and ER status; (b) disease-free interval and PgR status; (c) disease-free interval and combined ER and PgR status.

Table 2. Association of histological grade and disease-free interval for ER+ tumours

	% disease-free at 3 yr (No. at risk)	
	Uninvolved axillary nodes (N–)	Involved axillary nodes (N+)
Grade 1	100 (21)	93 (14)
Grade 2	90 (53)	80 (68)
Grade 3	80 (30)	40 (25)

Significances: N–: grade 1 vs 3, $P < 0.05$; N+: grade 1 vs 3, $P < 0.005$; N+: grade 2 vs 3, $P < 0.005$.

Table 3. Association between survival and tumour ER status, axillary node status and menstrual status

		% surviving at 5 yr (No. at risk)			
		Uninvolved axillary nodes		Involved axillary nodes	
All patients	ER+	89 (154)	$P < 0.05$	76 (133)	$P < 0.001$
	ER–	73 (68)		53 (35)	
Premenopausal	ER+	87 (55)	n.s.*	59 (51)	$P < 0.025$
	ER–	79 (22)		56 (20)	
Postmenopausal	ER+	89 (99)	n.s.	78 (82)	$P < 0.01$
	ER–	71 (46)		50 (15)	

n.s. = no significant difference.

Table 4. Association of tumour content of ER and PgR and patient survival

	% surviving at 30 months (No. at risk)	
	Uninvolved axillary nodes (N–)	Involved axillary nodes (N+)
ER+PgR+	100 (71)	86 (62)
ER+PgR–	90 (43)	94 (32)
ER–PgR+	94 (19)	*
ER–PgR–	94 (24)	66 (18)

*Only 5 patients with involved nodes had ER–PgR+ tumours.
Significances: N–: ER+PgR+ vs ER+PgR–, $P < 0.025$; N–: ER+PgR+ vs ER–PgR–, $P < 0.01$; N+: ER+PgR– vs ER–PgR–, $P < 0.05$.

Table 5. Effect of histological grade on survival in patients with ER+ infiltrating duct carcinomas

	% surviving at 5 yr (No. at risk)	
	Uninvolved axillary nodes (N–)	Involved axillary nodes (N+)
Grade 1	100 (21)	100 (14)
Grade 2	94 (53)	91 (68)
Grade 3	87 (30)	50 (25)

Significances: N–: grade 1 vs 3, $P < 0.025$; N–: grade 2 vs 3, $P < 0.005$; N+: grade 1 vs 3, $P < 0.05$; N+: grade 2 vs 3, $P < 0.001$.

tumours was not seen when nodes were uninvolved, but occurred in both pre-menopausal and post-menopausal patients with involved axillary nodes (Table 3). There was no difference in survival between patients with PgR+ or PgR– tumours (Fig. 2b). Patients with ER+PgR+ tumours had a longer survival than those with ER–PgR– tumours (Fig. 2c), this being attributable to a significant prolongation of survival after first relapse ($P < 0.005$). This difference occurred irrespective of axillary nodal status (Table 4). In patients with involved axillary nodes survival was longer with grade 1 or 2 tumours than with grade 3 tumours ($P < 0.005$). This significant difference was seen only in patients with involved axillary nodes; grade did not influence survival in those

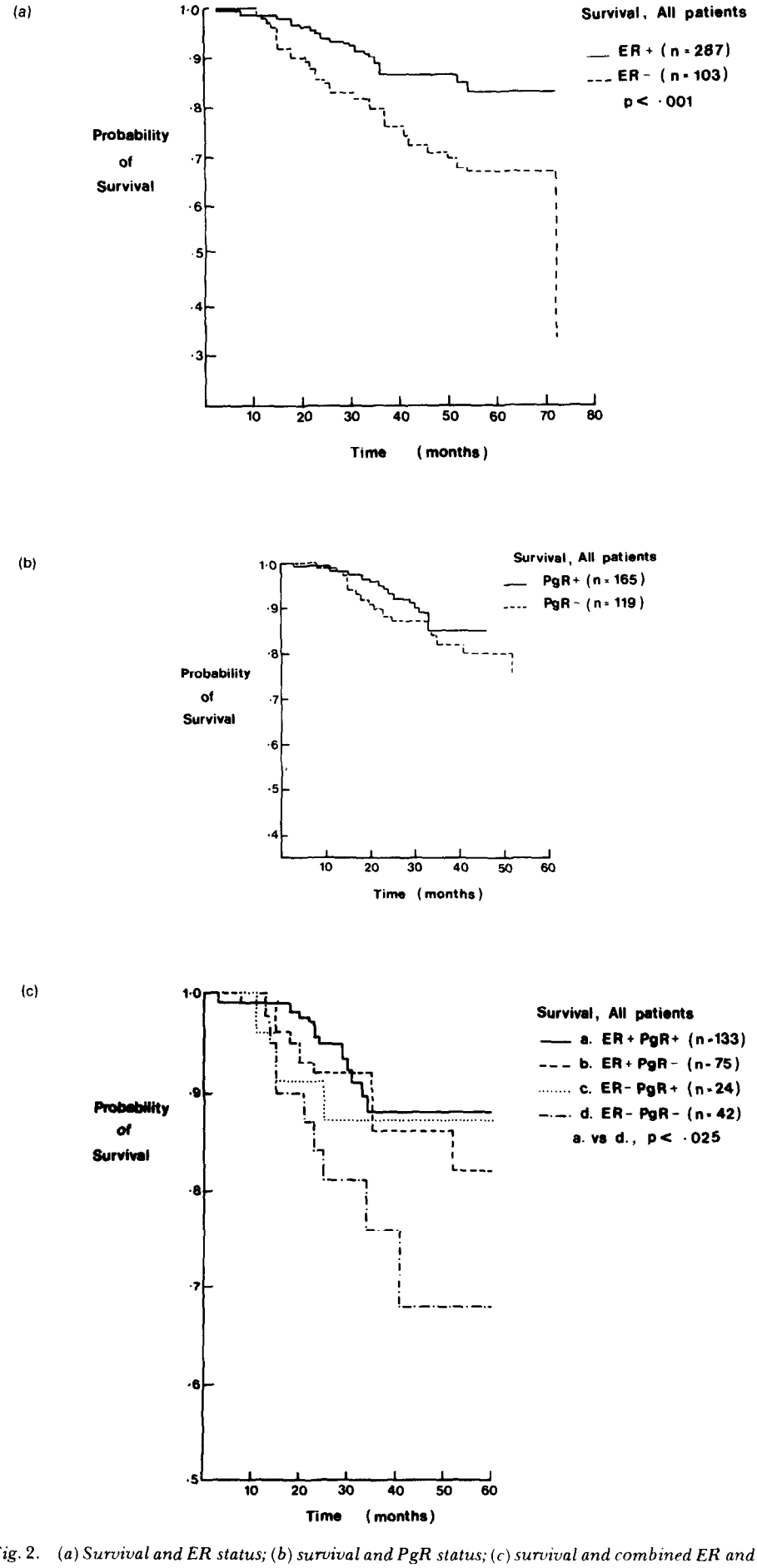

Fig. 2. (*a*) *Survival and ER status;* (*b*) *survival and PgR status;* (*c*) *survival and combined ER and PgR status.*

with uninvolved nodes. When survival was analysed according to both grade and ER status in patients with uninvolved nodes and grade 2 tumours, the 53 patients with ER+ tumours had a longer survival than the 15 patients with ER- tumours (94 vs 41% at 5 yr; $P < 0.001$). In patients with involved nodes and ER+ tumours, survival was longer in those whose tumours were grade 1 and 2 rather than grade 3 (Table 5).

DISCUSSION

There are differing views on the association between DFI and ER status. Knight *et al.* [13] reported that absence of ER was associated with early recurrence independent of node status and tumour size, although a significant difference was noted only in those patients with 4 or more involved axillary nodes. Other workers have also described an effect of ER status on DFI independent of node status [1, 3, 14–16]. The finding here that there was no significant effect of ER status on DFI is supported by other reports [6, 7].

There are little data published on the association between PgR status and DFI. PgR has been reported to be a better indicator of DFI than ER [5] and, in one study, presence of PgR was associated with a lower incidence of distant metastases but had no effect on local recurrence [4]. Others have shown no significant effect of PgR on DFI [1] and this study confirms this view on a larger series.

Our findings confirm an influence of tumour grade on DFI. When ER content and grade were analysed together, additional information on DFI was gained in some groups. In patients with ER+ tumours, higher grade led to lower DFI irrespective of axillary lymph node status.

There is more agreement on the influence of tumour steroid receptor content on overall survival in patients with operable breast cancer. Survival was significantly longer in patients with ER+ tumours than in those with ER- tumours, and this difference was irrespective of axillary nodal status and menstrual status. These findings support other published reports, suggesting that the influence of ER status on survival is independent of nodal or menopausal status [17]. Apart from one subgroup of patients (post-menopausal patients with uninvolved axillary nodes), there was no significant correlation between tumour PgR content and survival. When survival was analysed according to both tumour ER and PgR content, it was seen to be significantly longer in patients with ER+PgR+ tumours than in those with ER-PgR- tumours. This prolongation was independent of nodal status but, in part, dependent on menstrual status, being most marked in post-menopausal patients with uninvolved axillary nodes. The finding of prolonged survival in patients with no evidence of axillary nodal involvement and ER+PgR+ tumours compared to those of a similar nodal status and ER+PgR- tumours indicates that additional prognostic information may derive from analyses of both steroid receptors. The longer survival in receptor-positive groups is attributable to prolongation of survival after first relapse [18].

Histological grade also influenced survival, especially in patients with involved axillary nodes. When survival was analysed according to both tumour grade and ER content, additional independent prognostic information was obtained in certain subgroups. For example, in patients with uninvolved axillary nodes and grade 2 tumours, survival was significantly longer for ER+ than ER- tumours, and in patients with involved nodes and ER+ tumours, survival improved significantly with lowering of histological grade.

In conclusion, the ER status of the primary tumour was not of significant value in predicting DFI, and analysis of tumour content of PgR and combined ER and PgR provided no further information. DFI correlated with histological grade, and analysis of both tumour grade and ER content provided additional prognostic information in some subgroups of patients. Survival from mastectomy and from first recurrence were both significantly influenced by ER status, but again little additional information was obtained from PgR analysis. In some subgroups of patients additional information about survival was obtained from analysis of both tumour grade and ER content. A more accurate indication of prognosis in operable breast cancer may be obtained from analysis of both histological grade and ER content.

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