Supplementary Data

Supplementary Table 1 a and b:

Showing the number of observed cases and survival events for the different combinations of histopathological and genomic grade for Recurrence free survival (RFS)and Distant metastasis free survival (DMFS).

(a)

RFS

	Alldata		ER+ve		ER+veNode-ve		ER+ve Stage I		ER+veNode+ve	
	Observed	Event	Observed	Event	Observed	Event	Observed	Event	Observed	Event
GG1-HG1	129	14	123	14	90	12	66	6	30	2
HG1-GG3	17	8	14	7	10	4	6	2	4	3
HG2-GG1	243	70	229	64	160	40	91	15	64	24
HG2-GG3	130	62	111	52	65	29	40	17	43	23
HG3-GG1	54	18	51	17	47	15	29	10	4	2
HG3-GG3	271	108	158	66	118	53	52	22	37	13

(b)

DMFS

	Alldata		ER+ve		ER+veNode-ve		ER+ve Stage I		ER+veNode+ve	
	Observed	Event	Observed	Event	Observed	Event	Observed	Event	Observed	Event
HG1-GG1	72	7	70	7	46	6	31	3	22	1
HG1-GG3	12	5	10	4	7	2	5	1	3	2
HG2-GG1	162	35	153	31	110	20	59	6	39	11
HG2-GG3	91	39	78	32	48	19	30	11	29	13
HG3-GG1	50	16	47	15	46	14	28	9	1	1
HG3-GG3	225	86	130	50	107	44	50	22	22	6

Supplementary Table 2 :

Showing the *p* values for the difference between HG2-GG1 and HG2-GG2 tumors(i.e differences between high and low genomic grade tumors in histopathological grade 2) and for the difference between HG3-GG1 and HG3-GG3 tumors for Cox proportional hazards. The models are the same as those given in Tables 2 and 3 of the main article, with just a change in the reference variable. The hazard ratios of one group as compared to the other can easily be estimated from the original tables by dividing the hazard ratios of the two.

		Alldata	ER +ve	ER +ve Node -ve	ER +ve Stage I	ER +ve Node +ve
HG2-GG1 vs HG2-GG3		*p*	*p*	*p*	*p*	*p*
	RFS	<0.001	<0.001	<0.001	<0.001	<0.001
	DMFS	<0.001	<0.001	<0.001	<0.001	<0.001
HG3-GG1vs HG3-GG3		Alldata	ER +ve	ER +ve Node -ve	ER +ve Stage I	ER +ve Node +ve
	RFS	0.12	0.09	0.06	0.3	0.8
	DMFS	0.053	0.08	0.03	0.04	<0.001

Multivariate analysis

Supplementary Table 3 shows the estimates of the multivariate Cox model in ER positive tumors having the combined levels of histopathologic and genomic grade, nodal status and size as covariates. However, these estimates have to be treated with extreme caution as the hazard ratios of grade vary markedly in the present data between node positive and negative tumors, as well as between tumors having different sizes. Therefore, it may be totally inappropriate to assume that histopathological as well as genomic grade has a homogeneous hazard ratio cutting across nodal status and size. Using interaction terms between grade and nodal status and size may be a theoretical solution to the problem, but that led to many interaction covariates with very wide hazard ratios, representing an unstable model. Also the model with interaction terms has too many covariates which may lead to over-fitting and non generalizability of the estimates.

It may be noted that the aim of this study was to study whether traditional histopathological grading and modern genomic grading add prognostic information to each other. The results supplied in the

Tables 2 and 3 of the main article show that they do add to each other. By also showing significant hazard ratios in patients with ER positive tumors, node negative, stage I as well as node positive tumors, it is shown that histopathological and genomic grade give prognostic information over and above nodal status and size, even though the strength of the information may vary across the subgroups. Therefore, it may be argued that a conventional multivariate analysis adds very little to the conclusion (even though the results of the multivariate analysis agree generally with the conclusion of the article)

Supplementary table 3a and b:

Multivariate Cox Model in ER positive tumors containing the combined levels of histopathological and genomic grade, nodal status and Size. Table 3a contains the model without any interaction terms, Table 3b contains the model with interaction terms between combined levels of histopathological and genomic grade and nodal status as well as size.

(a)

Model without interaction terms

	Recurrence Free Survival		Distant Metastasis free Survival	
	Hazard Ratio	*95% CI* *p*	Hazard Ratio	*95% CI* *p*
HG1-GG3 vs HG1-GG1	5.0	2.2-11.2 <0.001	4.6	1.8-11.7 0.001
HG2-GG1 vs HG1-GG1	2.4	1.4-4.0 0.002	1.9	1.02-3.6 0.04
HG2-GG3 vs HG1-GG1	4.9	3.2-7.6 <0.001	5.1	3.1-8.2 <0.001
HG3-GG1 vs HG1-GG1	3.2	1.5-6.8 0.002	3.7	1.7-8.0 0.001
HG3-GG3 vs HG1-GG1	4.6	3.0-7.0 <0.001	4.8	2.7-8.5 <0.001
Size (>2 cm vs < 2cm)	1.6	1.1-2.4 0.01	1.4	0.9-2.1 0.2
Node (positive vs negative)	1.1	0.7-1.9 0.6	1.1	0.6-1.9 0.8

(b)

Model with interaction terms:

	Recurrence free Survival		Distant Metastasis free survival	
	HR	95%CI *p*	HR	95%CI *p*
MAIN EFFECTS				
HG1-GG3 vs HG1-GG1	4.3	1.2-15.2 (0.02)	2.4	0.5-12.5 (0.3)
HG2-GG1 vs HG1-GG1	2.2	1.6-3.1 (<0.001)	1.5	0.6-3.8 (0.4)
HG2-GG3 vs HG1-GG1	6.9	4.3-11.0 (<0.001)	5.7	2.5-12.8 (<0.001)
HG3-GG1 vs HG1-GG1	4.9	2.1-11.8 (<0.001)	4.6	1.5-14.4 (0.009)
HG3-GG3 vs HG1-GG1	6.5	2.9-14.6 (<0.001)	6.3	2.0-20.0 (0.002)
Size(>2cm vs < 2 cm)	3.6	1.7-7.6 (<0.001)	2.7	0.8-9.8 (0.1)
Node(+ve vs -ve)	0.5	0.1-2.3 (0.4)	0.3	0.04-3.0 (0.3)
INTERACTION EFFECTS				
HG1-GG3:Node	4.2	0.6-29.8 (0.2)	3.7	0.2-74.7 (0.4)
HG2-GG1:Node	3.3	0.7-15.1 (0.1)	5.1	0.5-56.8 (0.2)
HG2-GG3:Node	2.6	0.7-9.2 (0.1)	3.1	0.3-30.7 (0.3)
HG3-GG1:Node	3.5	0.6-20.2 (0.2)	9.3	0.97-88.8 (0.052)
HG3-GG3:Node	1.7	0.5-5.6 (0.4)	2.0	0.3-12.7 (0.5)
HG1-GG3:Size	0.6	0.1-2.9 (0.5)	1.4	0.1-24.1 (0.8)
HG2-GG1:Size	0.6	0.3-1.2 (0.2)	0.7	0.2-2.9 (0.6)
HG2-GG3:Size	0.3	0.1-0.9 (0.02)	0.5	0.1-2.0 (0.3)
HG3-GG1:Size	0.3	0.1-0.6 (0.001)	0.3	0.1-1.4 (0.1)
HG3-GG3:Size	0.4	0.1-1.1 (0.09)	0.4	0.1-1.5 (0.2)