Prognostic and predictive implication of hormonal receptors expression and tumor infiltrating lymphocyte in epithelial ovarian cancer

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Objective

The effect of systemic treatment for solid tumors is generally depends on the subtypes. However, unlike breast or prostate cancer, the subtypes classified by hormone receptor status is still unclear in epithelial ovary cancer (EOC). In addition, tumor infiltrating lymphocytes (TILs) are considered to be an independent factor for tumor shrinkage and disease prognosis. Therefore, here we assessed the subtypes of EOC by hormone receptor status and the relevance of TILs in patients of EOC by hormone receptors.

Materials & Methods

Immunohistochemical analysis of estrogen receptor α (ER α), estrogen receptor β (ER β), progesterone receptor (PR), androgen receptor (AR) and glucocorticoid receptor (GR) were performed by using tissue microarray analysis of 358 ovarian tumors and the data were compared with clinicopathological variables, including the survival. Cluster analysis was performed to identify subgroup based on hormone receptor expression profile. Receptor expression was correlated to progression free survival (PFS) and overall survival (OS) in uni-, and multivariate analysis. We also assessed the amount of CD4+ and CD8+ of ovarian tumors tissues. We assessed CD4+ and CD8+ score (low, intermediate, and high) and compared the clinical outcome.

Result

Expressions of AR, GR and PR were significantly lower in ovarian cancer tissues than in normal epithelium ($p < 0.001$, $p = 0.014$, $p = 0.007$ respectively). Expression of ER α and ER β were significantly higher in ovarian cancer tissues than in normal epithelium ($p < 0.001$, $p = 0.036$ respectively). Using cox proportional hazards model, high expression of ER α, ER β and low expression of AR, GR and PR, a combined AR/ ER α expression [HR = 3.25 (95% CI: 1.56–6.98), $p = 0.003$] and a combined GR/ER α expression [HR = 1.93 (95% CI: 1.01–3.68), $p = 0.046$] were revealed to be a poor prognostic subtypes. The cox proportional hazard model showed that increasing CD4+ and CD8+ were significantly associated with longer overall survival [HR = 0.77 (95% CI: 0.68-0.87) $p=0.036$, HR = 4.43 (95% CI: 0.88-22.3) $p=0.049$, respectively]. Survival analysis carried out for the EOC suggested that the high CD4+ and CD8+ were associated with good prognosis. Finally, in the association between CD4/CD8 and AR-/ER α+ and GR-/ ER α+ were analyzed by cox proportional hazards model. The increased of CD4/CD8 was associated with longer overall survival (OS) in AR -/ER α+ and GR-/ER α+ subtypes [HR = 1.95 (95% CI: 1.02-3.73), $p=0.041$].

Conclusions

- In conclusion, this study investigated expression 5 different hormone receptors, ER α, ER β, PR, AR, and GR by immunohistochemistry in large number of EOC patients by means of image analysis for IHC scoring. Each hormone receptors were significantly related to OS and DFS. Clustering subgroup analysis showed AR+/GR+/ER α+/ER β- showed the significant worst outcome. We also investigated the relationship between hormone receptor and CD4,CD8, CD4/CD8 ratio. The CD4/CD8 ratio was significantly related with the worst outcome subgroup. The assessment of these TILs in EOC is essential for investigating the patient group for immunotherapy.
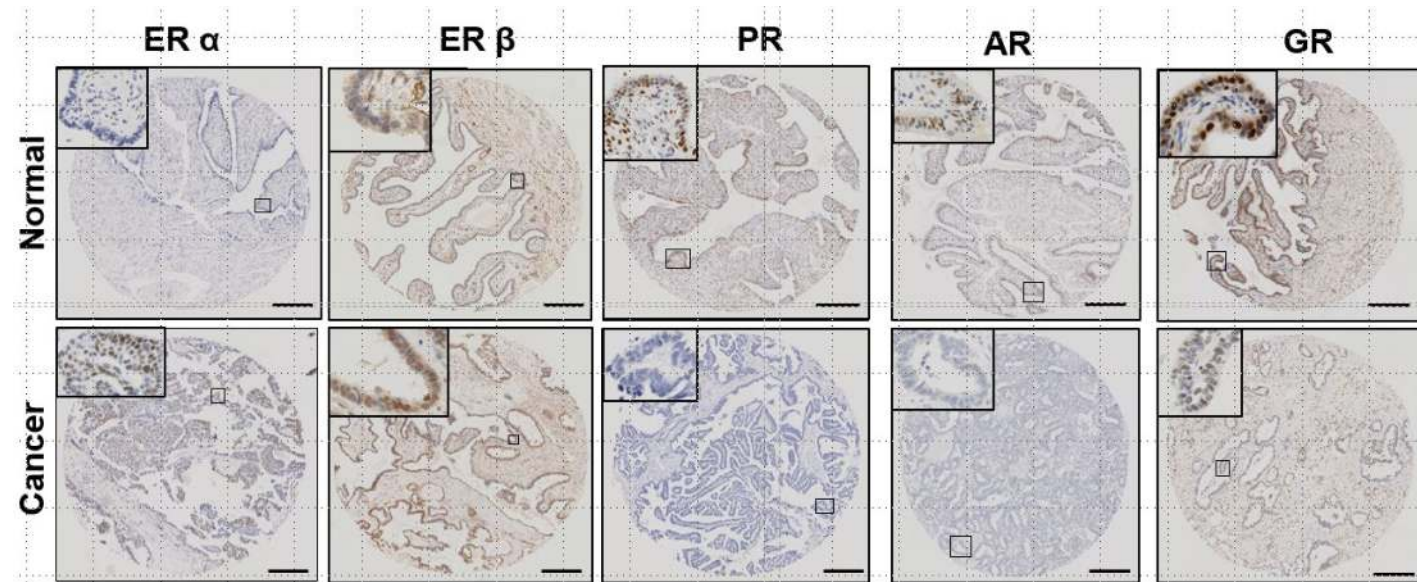

Figure 1.

Representative IHC staining of each hormone receptor ER α, ER β, PR, AR and GR. Scale bar: 50μm
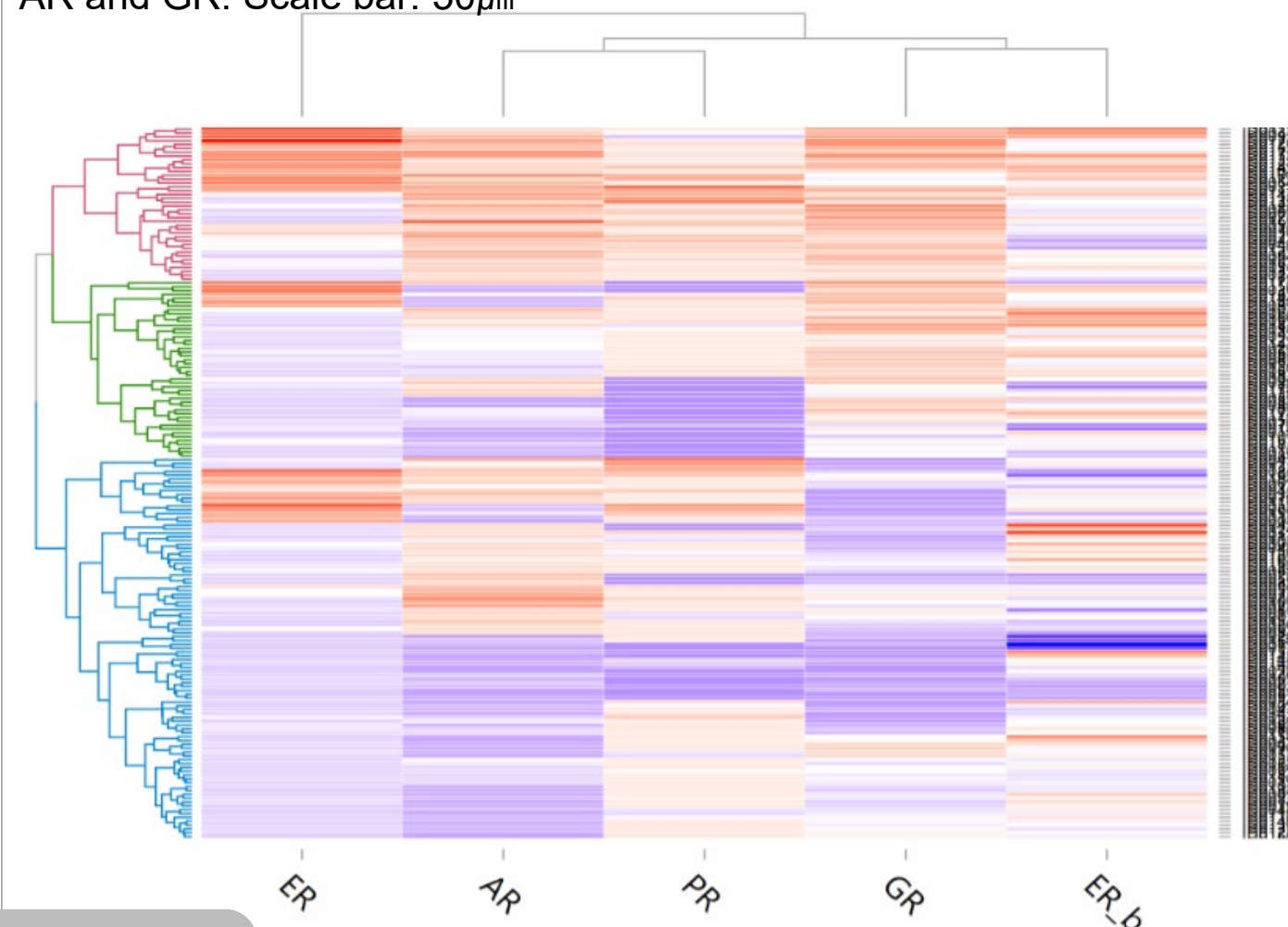

Figure 1.

Clustering analysis of all patients in whom staining for all five receptor isoforms was available. Clustering was based on commonalities in receptor expression in individual patients (aligned vertically in right side). Horizontally. The expression for the difference receptors is depicted with purple indicating negative expression, and orange for positive expression. Color scaling was based on the semi-quantitative immunoscores.

Table 1.

Relationship between CD4,CD8 and CD4/CD8 and hormone receptors

Variable	CD4		CD8		CD4/CD8	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value
AR+ (≥10.85)	8.21±15.66	0.30	7.82±15.68	0.40	1.04±1.00	0.38
ER α+ (≥49.12)	8.12±16.60	0.64	9.23±17.76	0.82	0.87±0.93	0.62
ER β- (≤ 105.97)	8.71±16.42	0.61	8.29±14.69	0.79	1.05±1.12	0.53
GR+ (≥l 8.65)	9.74±17.23	0.67	9.05±15.87	0.23	1.07±1.09	0.30
PR – (≤ 21.18)	8.53±16.69	0.72	6.52±14.64	0.34	1.30±1.14	0.53
AR+/GR+/ER α+/ERβ-	25.10±34.32	0.35	18.91±35.03	0.53	1.32±0.98	0.002
AR+/GR+/ER α+/PR-	10.25±18.52	0.89	7.97±19.98	0.82	1.28±0.93	0.82
AR+/GR+/ER β-/PR-	4.34±9.87	0.02	4.91±8.84	0.05	0.88±1.12	0.07
AR+/ER α+/ER β-/PR-	9.79±19.51	0.96	2.61±2.50	0.001	3.75±7.80	0.23
GR+/ ER α+/ER β-/PR-	7.65±15.12	0.81	6.29±8.68	0.68	1.21±1.74	0.54