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Prognostic value of HER2/neu expression in patients with prostate cancer: a systematic review

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ABSTRACT

Introduction: The prognostic value of Her2-positive expression has been investigated for malignancies such as breast cancer. We aimed to study the association between Her2 gene overexpression and clinical progression of hormone-independent prostate cancer.
Methods: PubMed was searched to obtain the relevant articles without language or date limit. Reference list of the relevant articles was also searched to prevent missing any relevant article. Data were extracted regarding the patients' survival and disease-free survival.
Results: Overall, 15 articles were obtained, which studied the prognostic value of Her2 overexpression in patients with prostate cancer. Based on obtained hazard ratio and calculated log-rank test, overexpression of Her2 was significantly associated with disease recurrence, overall survival and cause-specific survival.
Discussion: Her2 expression can be considered as a mortality rate indicator in patients with metastatic prostate cancer and higher risk of disease recurrence (increase in PSA level) has been suggested in these patients with over expression of Her2.
Conclusion: Despite various differences in included articles regarding methodology, results, sample size and individual differences, Her2 overexpression showed a positive relation with poor prognosis of prostate cancer regarding survival and disease recurrence.

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Introduction

Her2/neu or Her2 is an oncogene, 185-kD transmembrane tyrosine kinase receptor, which has a considerable homology with epidermal growth factor receptor. Moreover, it is 1 out of 4 ErbB family proteins, which can be named c-erbB-2.

The responsible gene for Her2 locates on chromosomal 17q21. Her2 signaling pathway stimulates cell proliferation and prevents cell death through RAS–MAPK pathway. Results obtained from experimental studies show the involvement of Her2 signaling pathway in the prostate carcinogenesis. Her2 expression is also proposed as one of the molecular biomarkers in prostate cancer pathogenesis (1).

Almost 30% of breast cancer patients have shown Her2/neu overexpression. Therefore, Her2/neu expression is related to the prognostic value and has become a therapeutic target for breast and ovarian malignancies, which are associated with poor prognosis (2). Prostate cancer has the highest incidence rate in men and it is the second most common cause of death.

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The prevalence of this malignancy has shown an increasing trend during the last 10-15 years (3). It has been reported that metastatic condition will be occurred in almost one third of patients with radical prostatectomy, which indicates the necessity of more accurate prognostic markers. Androgen receptor signaling axis plays a principal role in development, function and hemostasis of prostate and it involves in the initiation and progression of prostate cancer as well. Androgen-deprivation therapy is known as the main treatment in prostate cancer patients; however, disease recurrence, high serum prostate-specific antigen (PSA), increased tumor size and tumor metastasis have been reported after a median of 18-24 months (4). There are several studies that propose Her2 overexpression as a putative stimulus of function of androgen receptor signaling axis leading to the development of androgen-dependent disease.

PSA is a protein secreted by epithelial cells of prostate gland, which is a routine screening test for the presence or recurrence of prostate cancer in men. Almost 40% of patients under treatment of the prostate cancer have revealed an increased in PSA level during the follow-up duration.

Detection of the prognostic factors can be helpful in the diagnosis of patients with cancer and the selection of the best therapeutic approach. There are controversial findings regarding the role of Her2 expression in human prostate cancer. In this regard, we aim to systematically review of the literatures evaluating the prognostic value of Her2 in patients with prostate cancer and its correlation with prostate carcinoma progression.

Methods

Literature search

PubMed was searched to obtain the relevant articles with the following search terms: prostate cancer and (c-erbB-2 or c-erbB2 or Neu or HER2 or HER-2 or erbB2). Irrelevant articles were excluded firstly based on the title and abstract and eventually by studying the full texts of articles. Reference list of relevant articles was searched to obtain the possible missed articles.

Study selection

We did not have any date and language limitations in our search strategy. Inclusion criteria were all the articles studied the prognostic value of Her2 overexpression, overall survival and disease-free survival in patients with prostate cancer. Exclusion criteria were articles, which did not report the overall survival and disease-free survival of patients following Her2 overexpression.

Data extraction

Following data were extracted from each articles: first author, publication year, total number of patients, number of Her2-positive and Her2-negative patients, number of Her2-positive and -negative patients with disease recurrence, patients` survival and Hazard ratio (HR).

The time of the increased PSA level during follow-up period was considered as a disease-free survival time. Data regarding the number of disease relapse, which was the first increased PAS during the follow-up and death event were retrieved from a previous systematic review and meta-analysis by Neto et al in 2010 (5).

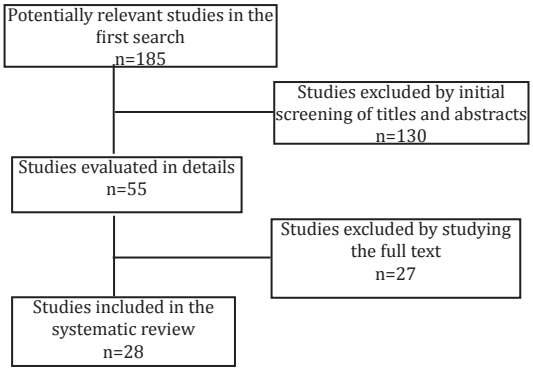
Outcome variable

We compared the data extracted from studies regarding the prognostic capability of Her2 over-expression in patients with prostate cancer including disease-free survival and overall survival. Relapse-free survival was proposed as the date of relapse or date of the last follow-up if no recurrence was detected.

Results

Extraction of the main articles is detailed in Figure 1 and the quality assessment of these included articles is provided in Table 1.

Figure 1. PRISMA flow chart of the study



Kaplan-Meier analysis was used almost in all the extracted articles to provide relapse-free survival and to obtain rate and time of disease recurrence based on the date of earliest increase of serum PSA during the follow-up period. Quality of the extracted articles is summarized in Table 2.

Search results

Overall, 185 articles were obtained following the first search of PubMed. After studying the titles and abstracts of the articles, irrelevant articles were excluded and only 15 articles were extracted as the most relevant articles in concordance with the purpose of this study.

Table 1. Quality assessment of the included study

Author Reference	Type of cancer	Follow-up duration	Method of outcome evaluation (death or recurrence)	Adjustment for important confounding variables
Zhang (6)	Prostate cancer	Range 3–107 months	Progression was defined as a rise in PSA after antiandrogen treatment. PCa-specific death was defined as death in patients with metastasis showing any progression following hormonal therapy	Yes
Tobiume (7)	Patients with M1b prostate cancer	43 months (median)	PSA relapse was diagnosed by three consecutive increases in the PSA level, and the day of the first increase was defined as the day of PSA relapse	Yes
Veltri (8)	Prostate cancer with radical prostatectomy	228 months (median)	Rise in postoperative PSA level of >0.2 ng/ml	Yes
Ricciardelli (9)	Prostate tumors from patients undergoing retropubic radical prostatectomy	78 months (median)	The time of PSA relapse was determined as the earliest date that the postoperative serum PSA level was detectable above the (>0.3 ng/ml)	No
Dai (10)	Patients with metastatic prostate cancer	34.5 months (median)	Mortality	Yes
Mori (11)	Prostate cancer with radical prostatectomy	-	Rise of PSA above the undetectable level of <0.3 ng/mL	No
Isharwal (12)	Prostate cancer with radical prostatectomy	204 months (median)	Rise in postoperative PSA of >0.2 ng/ml	Yes
Yamada (13)	Metastatic prostate cancer	48.7 months (median)	Three consecutive increases in PSA level, with the first counted as the date of recurrence	No
Di Lorenzo (14)	Localized and metastatic disease	36 months (median)	Three consecutive increases of PSA were required to confirm disease relapse, but the time to relapse was taken as the time of the first detectable PSA value increase	Yes
Edward (15)	Metastatic prostate cancer	52.5 months (median)	Two consecutive increases of PSA greater than 10%	Yes
Hernes (16)	Metastatic prostate cancer	-	Death	No
Shi (17)	Prostate cancer with prostatectomy	144 months (median)	Serum PSA level of 0.4 ng/ml. or greater on 2 consecutive tests	No
Morote (18)	Radical prostatectomy	3-98 months	Death	No
Ross (19)	Patients with prostate adenocarcinoma who underwent radical retropubic prostatectomy	42 months (mean)	Disease recurrence was defined as a postoperative serum PSA level ≥ 0.4 ng/mL	Yes
Fox (20)	Prostatic adenocarcinomas	3 to 216 months	Death	No

Table 2. Extracted data from the included studies

Author Year Reference	Number of patients	PSA relapse/ Total Her2+	PSA relapse/ Total Her2-	Death/ Total Her2+	Death/ Total Her2-	Outcome
Tobiume 2011 (7)	102 prostate cancer	26/30	50/72	40.9%	67.3%	[1]DFS:[2]HR(95% CI): 2.044 (1.094–3.816) [3]MCox: HR(95% CI): 2.697 (0.850–3.387) Specific survival: HR(95% CI): 2.058 (1.124–3.766) MCox: HR(95% CI): 2.155 (1.097–4.232)
Zhang 2011 (6)	135 prostate biopsies of prostate cancer patients	*	*	*	*	DFS: HR (95% CI): 3.18 (1.53–6.63) Specific survival: HR (95% CI): 1.95 (0.59–6.5) MCox: HR (95% CI): 1.45 (0.66–3.16)
Ricciardell 2008 (9)	53 prostate cancer with proetatectomy	18/37	3/16			DFS: Log-rank statistics:4.1 P=0.043 Overall survival: Log-rank statistics:4.59 p=0.032
Veltri 2008 (8)	105	45/84	5/21			DFS: [4]UCox: HR: 3.26 (1.40–7.59). MCox:HR: 2.41 (1.00–5.80)
Dai 2008 (10)	104 metastatic prostate cancer	-	-	8/10	57/94	Specific survival: UCox: HR: 1.628 (1.093–2.588) MCox: HR: 1.592 (1.025–2.474)
Mori 2008 (11)	148 prostatectomy patients	70/98	16/50	48/98	17/50	Overall survival :UCox: HR: 1.5 for patients with 0.01<Her2/neu≤0.04, and 1.37 for patients with >0.04 Her2 expression DFS: UCox: HR 2.44 for patients with 0.01<Her2/neu≤0.04, and 1.35 for patients with >0.04 Her2 expression
Isharwal 2008 (12)	252 patients with prostatectomy	106/167	31/85	31/167	5/85	Specific survival: Diffuse Her2+: UCox:HR: 3.28 (1.20-8.96) Focal Her2+: UCox:HR: 3.30 (1.20-9.09) MCox:HR: 3.39 (1.30-8.83) DSF: Diffuse Her2+: UCox:HR: 2.21 (1.42-3.45) Focal Her2+: UCox:HR: 2.17 (1.93-3.39) MCox:HR: 2.06 (1.36-3.10)
Yamada 2007 (13)	49 patients with metastatic prostate cancer	-		16/21	10/28	Specific survival rate: Log-rank statistics:0.0084 DFS:Log-rank statistics: p=0.0485
Edwards 2006 (15)	74 metastatic patients			31/50	11/24	DFS: MCox:HR : 0.18(0.04-0.76) Overall survival: MCoz:HR: 0.58(0.12-2.7)
Hernes 2004 (16)	106 metastatic patients			27/35	43/71	Overall survival logrank statistics: p=0029
Di Lorenzo 2002 (14)	74	19/30	13/44			DFS: Log-rank test: 0.07 MCox:HR: 1.98 (0.82–4.76)
Shi 2001 (17)	81 prostatectomy patients	5/41	8/40	6/41	6/40	Overall survival:log-rank statistics:0.04 DFS:log-rank statistics:0.2213
Morote 1999 (18)	70 metastatic patients			35/45	13/25	Specific survival:log-rank: p= 5 0.0312
Ross 1997 (19)	113 prostate cancer with prostatectomy	12/33	16/80			DFS:logrank: p= 0.029
Fox 1994 (20)	45 prostatic adenocarcinomas			10/16	5/29	Overall survival: Logrank test: p= 0.0 3 16

[1]DFS: disease-free survival;[2]HR: Hazard ratio;[3]MCox: Multivariate Cox Regression; [4]UCox: Univariate Cox Regression

Description of the included studies

Included studies were published between 1994 and 2011. Sample size of included studies varied from 45 to 252 patients.

Immonuhistochemical staining was used to detect Her2 expression in tumor tissues by applying the different types of antibodies. Coding method was applied to explain the expression level of Her2 that was defined as follows: 2+ (moderate) and 3+ (high or overexpression) as positive and 0 (no expression) and 1+ (weak or no expression) as negative. Kaplan-meier diagram and log-rank statistic were present in all the included studies. Only 8/15 included articles stated hazard ratio (HR) as a prognostics effect size.

Discussion

Identifying the responsible molecular cascades for proliferation, angiogenesis, neuroendocrine differentiation, apoptosis and alterations of cancerous cells during the progression of prostate malignancy is vital. The prognostic importance of Her2 overexpression as an important molecular cascade that might involve in the development of androgen-dependent disease has been evaluated in some clinical studies on prostate cancer patients following prostatectomy, luteinizing hormone-releasing hormone analogues and antiandrogens therapy or on those with hormone-refractory metastatic disease. Estimating the expression rate of Her2 might be important in the diagnosis of the patients with higher risk of recurrence or mortality.

Survival rate

Specific survival rate has been estimated in patients with metastatic prostate cancer. Some studies proposed the HR effect size that showed the higher cause-specific mortality rate due to cancer in patients with Her2 overexpression compared to expression rate in Her2-negavie patients (6,7,10,12,13,18). In this regard, Her2 expression can be considered as a mortality rate indicator in patients with metastatic prostate cancer. Despite reported results, future clinical trials would be able to increase the accuracy of obtained conclusions.

Overall survival of prostate cancer patients treated with prostatectomy has been also evaluated in some studies (9,11,15-17,20). According to the obtained HR, patients with prostatectomy and overexpression of Her2 are associated with shorter survival time compared to patients with Her2-negative expression. Despite various different findings among studies, direct relation is apparent between Her2-overexpression and the risk of death in all the publications studied Her2-overexpression as a prognostic factor. In this regard, Her2 overexpression is associated with poor prognosis in prostate cancer patients.

Disease-free recurrence

During the follow-up period after prostatectomy, the earliest time of PSA relapse was proposed as the disease-free recurrence in prostate cancer patients with positive Her2 expression. Her2/neu oncogene overexpression has been proposed as a predictive factor in patients with prostate cancer. Higher risk of disease recurrence (increase in PSA level) has been suggested in a group of prostate cancer patients with overexpression of Her2.

Based on reported results, recurrence rate of prostate cancer will be higher in patients with positive Her2 expression compared with negative-Her-2/neu oncogene expression. Recurrence of the disease shows an increasing pattern of Her2 overexpression. However, included studies used different monoclonal or polyclonal antibodies, tissue preparing methods, immunohistochemistry procedures, Her2 expression definition and sample size, which might influence on the illustration of the effect of Her2 overexpression on cancer development. Moreover, expression of Her2 could be considered in the initial processes of prostate cancer progression. In this regard, Her2 signaling cascade can be proposed as a therapeutic target in postoperationive treatment procedures to inhibit the tumor growth and development. The quality of the included studies was different based on presented information and data regarding the survival and recurrence rates. Although some studies did not reveal the hazard ratio of recurrence and survival rates and only presented their results based on log-rank test, positive relation between Her2 expression and shorter survival rate and higher incidence of disease relapse was significant.

Conclusion

According to obtained results, patients with positive Her2 expression have higher risk of disease recurrence and shorter survival; however, more clinical trials with larger sample size and more accurate methods could evaluate the accuracy of these findings. Her2 expression could be regarded as an indicator of poor prognosis and unfavorable outcomes in prostate cancer patients and should be used as a therapeutic target in these patients.

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Conflict of Interest

The authors declare no conflict of interest.

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