Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

The association between serum squamous cell carcinoma antigen and recurrence and survival of patients with cervical squamous cell carcinoma: A systematic review and meta-analysis

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HIGHLIGHTS

- Serum SCC-Ag was associated with cervical cancer recurrence and survival.
- Pretreatment SCC-Ag cutoff ranged from 1.1 to 40.0 ng/mL for recurrence and death.
- Posttreatment SCC-Ag cutoff level of 0.9–3.5 ng/mL was associated with recurrence.
- Posttreatment SCC-Ag cutoff from 1.5 to 2.0 ng/mL was also associated with death.
- This marker has potential in predicting newly diagnosed cervical cancer prognosis.

ARTICLE INFO

Article history:
Received 30 November 2017
Received in revised form 19 March 2018
Accepted 20 March 2018
Available online xxxx

Keywords:
Squamous cell carcinoma antigen
Recurrence
Cervical cancer
Mortality
Systematic review
Meta-analysis

ABSTRACT

Objective. The aim of this systematic review and meta-analysis was to pool association effects of serum squamous cell carcinoma antigen (SCC-Ag) on recurrence and mortality in mainly squamous cell cervical cancer patients.

Methods. MEDLINE and Scopus databases were searched up to June 29, 2016. Studies assessing effects of SCC-Ag on recurrence and death in cervical cancer patients were included. Data extraction was independently performed by two reviewers. A meta-analysis was applied for pooling the effects (i.e., risk ratio (RR), hazard ratio (HR), and unstandardized mean difference (USMD)) of SCC-Ag measured before and after treatment on recurrence and death.

Results. A total of 61 studies were included. For pretreatment SCC-Ag and recurrence, the pooled RR, HR, and USMD for high versus low serum SCC-Ag were 2.44(95% CI: 1.91, 3.13), 2.23(95% CI: 2.03, 2.45), −7.7(95% CI: -31.7, 16.4), respectively. The corresponding effects for the posttreatment period were 3.91(95% CI: 2.96, 5.16), 3.14(95% CI: 1.29, 7.65), and 3.2(95% CI: -10.6, 17.0), respectively. In addition, patients with high level of pretreatment serum SCC-Ag were also at a higher risk for death than patients with low serum SCC-Ag with a pooled RR of 3.66(95% CI: 2.24, 5.98), pooled HR of 2.50(95% CI: 1.85, 3.37), and pooled USMD of 7.10(95% CI: 4.26, 9.94). The posttreatment serum SCC-Ag effects also reflected a similar trend.

Conclusions. The serum SCC-Ag was consistently associated with recurrence and mortality of newly diagnosed cervical cancer. This marker may be useful in monitoring disease progression in cervical cancer patients. Prospero registration number is: CRD42016044024.

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https://doi.org/10.1016/j.ygyno.2018.03.056

Contents

1. Introduction

Cervical cancer was the fourth most common global cancer in women in 2012 [1]. The global incidence was about 527,600 and the annual death rate was 265,700 [2]. Squamous cell carcinoma was the most common cell type, whereas adenocarcinoma accounted for approximately 20%. The standard treatment approaches are composed of surgery, concurrent chemoradiation therapy, and systemic chemotherapy depending on the stage of disease. The International Federation of Gynecology and Obstetrics (FIGO) staging system has been developed and applied for standardization, comparison of treatment efficacy, and disease prognosis. The disease prognosis is dependent on the stage at diagnosis, i.e., 5-year survival for stages I, II, III and IV was about 81–96%, 65–87%, 35–50% and 15–20%, respectively [3]. The rate of recurrence also varied from 10% to 42% for stages IB to IVA [4], which was associated with tumor size and node involvement. Disease surveillance after treatment is therefore very important to detect recurrence as early as possible. It comprises clinical evaluation, a review of systems, physical examination, recto-vaginal and abdominal examination, and cervical/vaginal vault cytology. However, the effectiveness of these surveillance methods remains inconsistent [5]. As a result, >90% of patients with distant recurrence died from the disease within 5 years [6]. Thus recurrence of cervical cancer is still a major problem in cervical cancer patients' care, so the early identification, the longer survival benefit.

Serum biomarkers also play important roles in cancer management. Among them, a well-known biomarker is squamous cell carcinoma antigen (SCC-Ag), discovered in 1977 [7], which is produced through squamous formation of cervical squamous epithelium, and increases during the neoplastic transformation of the cervical squamous epithelium [8]. Elevated serum SCC-Ag level was detected in 28% to 88% of cervical squamous cell carcinomas [9]. The 99th percentile of circulating SCC-Ag in healthy women was 1.9 μg/L [10,11]. Consequently, most studies used cutoff points ranging from 2.0 to 2.5 μg/L, but there was no specific cutoff for cervical cancer. However, the serum SCC-Ag is not cervical cancer specific. Elevated SCC-Ag was also found in patients with other squamous cell carcinomas, e.g., vulva, vagina, head and neck, esophagus, and lung, as well as benign diseases of the skin (e.g., psoriasis, eczema), lung (e.g., sarcoidosis), liver, and kidney.

Although many studies have investigated the roles of SCC-Ag in squamous cell cervical cancer, applying its roles to clinical practice is still debatable. Some studies assessed the predictive effects of pretreatment SCC-Ag on disease progression (i.e., recurrence or death) after receiving treatments either as an additional predictor in the presence of other previously known predictors [12,13] or by itself [14–19], as well as in monitoring the response to treatment [20]. In addition, SCC-Ag was also found to be associated with disease progression in some studies [19,21–25]. Although association effects of SCC-Ag were consistent across these studies, their magnitudes were still varied. To our knowledge, there was only one systematic review which collected the prognostic values of SCC-Ag, along with other cell biological markers, in cervical cancer patients [26]. However, this review did not pool effects of SCC-Ag on disease progression by applying meta-analysis and did not make a distinction between pretreatment and posttreatment SCC-Ag. Therefore, this study was conducted to pool the magnitude of effects of pre- and posttreatment serum SCC-Ag on recurrence and death in squamous cell cervical cancer.

2. Methods

2.1. Selection of studies

We searched MEDLINE and Scopus databases from initiations to June 29, 2016 to identify potential relevant studies. Search strategies for both databases were described in Appendices A and B. When there were multiple publications with the same or overlapped studied subjects, which could be detected by authorship lists, setting, study period and subjects, the most complete and/or recent results were selected.

Studies were selected by one reviewer (C.C.). Original studies published in English were selected if they met the following criteria: patients were mainly squamous cell cervical cancer who received primary treatment, serum SCC-Ag data were provided for either pretreatment or posttreatment, and having any of recurrence and death outcomes of interest. Studies were excluded if there were insufficient data for pooling (i.e., if they did not report numbers of recurrence/death by SCC-Ag groups, reported hazard ratio (HR) without standard error or 95% confidence interval (CI)) or if they were non-human.

Please cite this article as: C. Charakorn, et al., The association between serum squamous cell carcinoma antigen and recurrence and survival of patients with cervical squamous cell ..., Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.03.056