

Prognostic value of Foxp3⁺ regulatory T cells in endometrial cancer: a meta-analysis

B.-H. Zhang¹, L. Li¹, J. Ji¹, J. Guo¹, X.-L. Zhou¹, H. Xu¹, F. Cao¹, X.-H. Tong²

¹Department of Obstetrics and Gynecology, Punan Hospital of Pudong New District of Shanghai, Shanghai

²Department of Obstetrics and Gynecology, Shanghai Changning Maternity & Infant Health Hospital, Shanghai (China)

Summary

Endometrial cancer is the second most common gynecologic cancer globally, and the prognosis of advanced or recurrent endometrial cancer is very poor. Currently, the prognostic value of Forkhead box protein P3 (FoxP3)⁺ regulatory T cells (Tregs) in endometrial cancer is unclear. This meta-analysis aimed to evaluate prognostic significance of Foxp3⁺ Tregs in endometrial cancer. The authors searched the literature from databases including PubMed, Cocohrane, and Web of Science, and selected four eligible studies for further analysis. Meta-analysis of the survival data from 869 endometrial cancer patients showed that there were no significant differences in overall survival, disease-free survival, relapse-free survival or disease-specific survival between patients with high levels of Foxp3⁺ Tregs infiltration, and those with low levels of Foxp3⁺ Tregs. In summary, this meta-analysis provided systemic evidence that Foxp3⁺ Tregs infiltration is not significantly associated with the prognosis of patients with endometrial cancer.

Key words: Foxp3; Tregs; Endometrial cancer; Prognosis; Meta-analysis.

Introduction

Endometrial cancer is the second most common gynecologic cancer globally [1, 2]. Currently, chemotherapy is the main therapy method for advanced or recurrent endometrial cancer, but the prognosis of advanced or recurrent endometrial cancer is very poor [3, 4]. Recent evidence has shown that tumor microenvironment is crucially involved in the initiation and progression of many types of tumors [5-7]. Regulatory T cells (Tregs) emerge as important player in tumor microenvironment due to their ability to suppress T cell immunity. The immunosuppression function of Tregs is dependent on Forkhead box protein P3 (FoxP3), a transcription factor considered as the marker for Tregs [8].

Due to immunosuppression function of Tregs, Foxp3⁺ Tregs infiltration in tumor could predict poor prognosis of cancer patients. Nevertheless, recent studies indicated that Foxp3⁺Tregs increased rather than decreased the survival of patients with certain cancer types [9-11]. Currently, the prognostic value of Foxp3⁺ Tregs in endometrial cancer remains undecided. Therefore, the authors performed a meta-analysis on eligible studies to determine the prognostic value of Foxp3⁺ Tregs in endometrial cancer.

Materials and Methods

Database of PubMed, Cocohrane, and Web of Science (up to September 2018) were screened with the strategy as below: (Foxp3 OR regulatory T cells), (endometrial cancer), (Survival

OR prognosis OR outcome OR mortality). The inclusion criteria were (1) all patients were confirmed as endometrial cancer, (2) FOXP3 Tregs were detected by immunohistochemical analysis; (3) survival data were available and Hazard ratio (HR), and 95% confidence interval (CI) were calculated; (4) The literature was in English. The data were independently extracted by two investigators, including publication year, the first author, the source and sample size of the subjects, follow-up duration, and patient survival. All studies were scored according to Newcastle-Ottawa Scale (NOS) criteria: (1) subject selection: 0-4, (2) comparability of subject: 0-2, and (3) clinical outcome: 0-3. Study was considered as good quality if the score was ≥ 7 [12]. All data were analyzed with STATA 12.0 program. $P < 0.05$ was deemed to be significant.

Results

The literature search was performed as shown in the flow diagram (Figure 1). A total of 17 studies published in English were selected via initial literature search. After reviewing the titles and abstracts, only six studies were selected. After careful reading the full text, only four studies were included as eligible studies because of the availability of the data on the prognosis of the patients [13-16].

The characteristics of four eligible studies are shown in Table 1 [13-16]. The authors extracted data on overall survival (OS), relapse-free survival (RFS), and disease-specific survival (DSS) from one study, respectively, and extracted data on disease-free survival (DFS) from two studies. The studied subjects were all from Europe: two studies in Netherlands, one study in Germany, and one

Table 1. — *Main features and methodological assessment of the included studies.*

Study	Year	Patients source	No. of patients	NOS score	Methods	Outcome	Follow-up (month)
Kubler [14]	2014	Germany	163	9	IHC	RFS	216
Workel [13]	2016	Netherland	305	9	IHC	DFS/DSS	240
Giatromanolaki [16]	2008	Greece	91	9	IHC	OS	200
De Jong [15]	2009	Netherland	310	9	IHC	DFS	64

IHC: Immunohistochemistry; RFS: relapse-free survival; DFS: disease-free survival; DSS: disease-specific survival; OS: Overall survival.

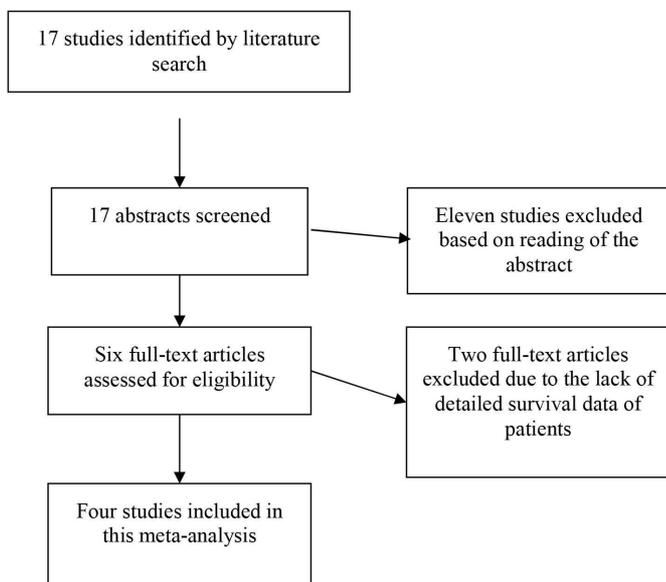


Figure 1. — Flow diagram of the procedure of literature search.

study from Greece. FOXP3+ Tregs were detected by immunohistochemical analysis in all four studies. All four studies had good quality with the NOS score of 9.

The authors analyzed OS data from 91 patients and revealed that OS showed no significant difference between patients with high Foxp3+ Tregs and those with low Foxp3+ Tregs (Figure 2). They analyzed RFS data from 163 patients and revealed that RFS showed no significant difference between patients with high Foxp3+ Tregs and those with low Foxp3+ Tregs (Figure 3). They pooled DFS data from two studies and revealed that DFS showed no significant difference between patients with high Foxp3+ Tregs and those with low Foxp3+ Tregs (Figure 4). They extracted DSS data from 305 patients and revealed that DSS showed no significant difference between patients with high Foxp3+ Tregs and those with low Foxp3+ Tregs (Figure 5).

Discussion

CD4+CD25+ Tregs represent 5-10% of peripheral CD4+ T cells and play an important role in modulating immune activity through suppressing the proliferation of effector T cells and the subsequent production of cytokines [17]. The immunosuppression role of Tregs leads to the evasion of tumor cells from anti-tumor immune response [18]. High levels of Tregs both in tumor microenvironment and in pe-

ripheral blood have been reported to be correlated with cancer progression and poor prognosis of cancer patients [19-21]. A previous study has shown that high FoxP3+ Tregs were associated with decreased OS in patients with type I and II endometrial cancer in Netherland [15]. However, a recent study reported that the presence of FoxP3+ Tregs demonstrated no correlation to the prognosis of African American and European American females with endometrial cancer [22]. These controversy results may be due to different study designs and different subjects. For example, the follow-up duration was only 64 months in the Netherland study [15].

Since the prognostic value of Foxp3+Tregs in endometrial cancer remains unclear and controversy, we performed this meta-analysis to pool all available survival data of patients with endometrial cancer and evaluate the prognostic significance of Foxp3+ Tregs. We pooled the survival data from 869 patients with endometrial cancer and revealed that high levels of Foxp3+ Tregs were not significantly associated with overall survival, disease-free survival, relapse-free survival or disease-specific survival of patients with endometrial cancer. The negative results may be explained by small sample size and short follow-up, because much less studies have investigated the prognostic value of Foxp3+ Tregs in patients with endometrial cancer, compared to other common cancer types such as gastric cancer and breast cancer.

Several limitations of this meta-analysis should be mentioned. Firstly, we searched the literatures published in English only. Second, we did not perform literature sensitivity or publication bias analysis because of the low number of eligible studies. However, we set strict criteria for eligible studies and all included studies were of high quality.

In summary, our meta-analysis provides systemic evidence that Foxp3+ Tregs infiltration is not significantly associated with the prognosis of patients with endometrial cancer.

Acknowledgements

This study was supported by Shanghai Pudong new area health and family planning commission leading personnel training project (Serial number: PWRI 2018-10).

Conflict of interest

The authors have no conflicts of interest relevant to this article.

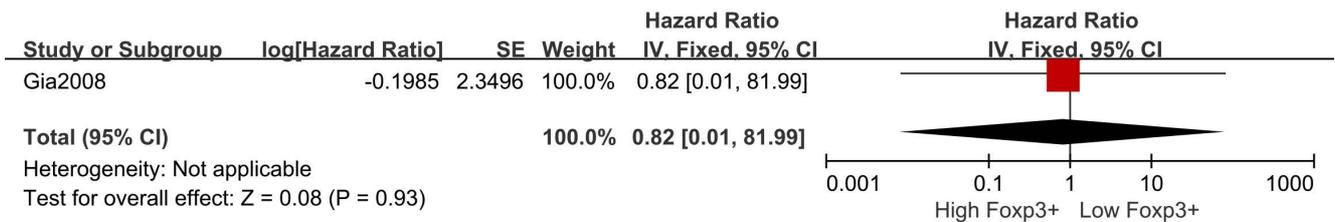


Figure 2. — No significant association of Foxp3+ Tregs with OS of patients with endometrial cancer.

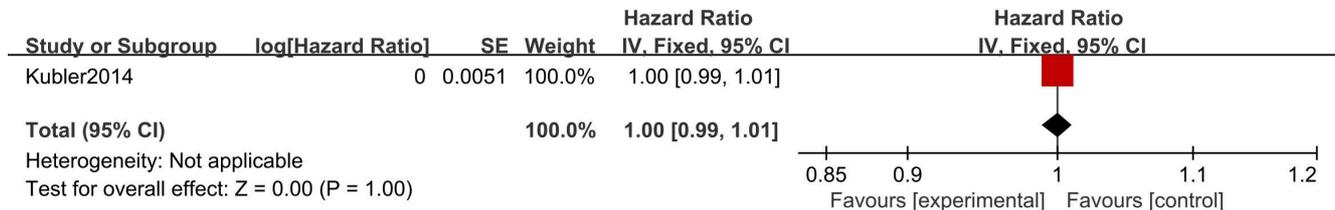


Figure 3. — No significant association of Foxp3+ Tregs with RFS of patients with endometrial cancer.

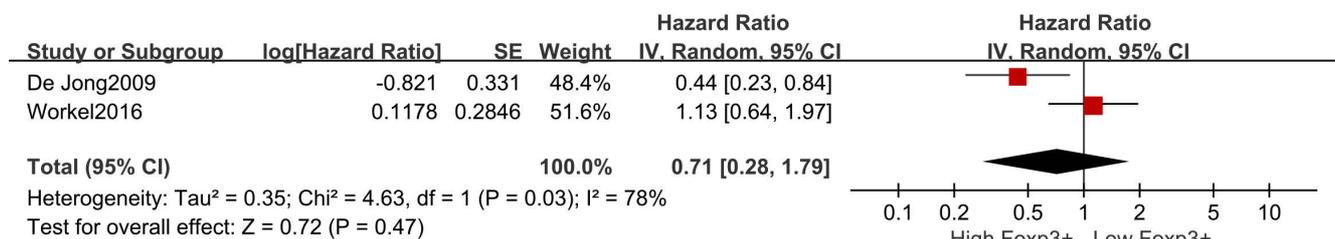


Figure 4. — No significant association of Foxp3+ Tregs with DFS of patients with endometrial cancer.

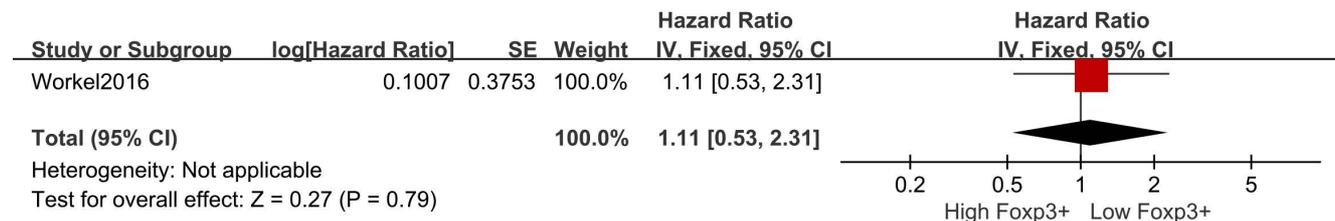


Figure 5. — No significant association of Foxp3+ Tregs with DSS of patients with endometrial cancer.

Submitted: January 22, 2019

Accepted: February 25, 2019

Published: June 15, 2019

References

- [1] Siegel R.L., Miller K.D., Jemal A.: "Cancer statistics, 2015". *CA Cancer J. Clin.*, 2015, 65, 5.
- [2] Erdemoglu E., Yalcin Y., Bozkurt K.K., Erdemoglu E.: "Surgical staging of low-risk Stage IA endometrioid endometrial cancers". *Eur. J. Gynaecol. Oncol.*, 2017, 38, 80.
- [3] Kölbl A.C., Schlenk K., Behrendt N., Andergassen U.: "The importance of hCG in human endometrial adenocarcinoma and breast cancer". *Int. J. Biol. Markers*, 2018, 33, 33.
- [4] Roli L., Pecoraro V., Trenti T.: "Can NGAL be employed as prognostic and diagnostic biomarker in human cancers? A systematic review of current evidence". *Int. J. Biol. Markers*, 2017, 32, e53.
- [5] Liotta L.A., Kohn E.C.: "The microenvironment of the tumour-host interface". *Nature*, 2001, 411, 375.
- [6] Grivennikov S.I., Greten F.R., Karin M.: "Immunity, inflammation, and cancer". *Cell*, 2010, 140, 883.
- [7] Li H., Fan X., Houghton J.: "Tumor microenvironment: the role of the tumor stroma in cancer". *J. Cell. Biochem.*, 2007, 101, 805.
- [8] Najafi M., Farhood B., Mortezaee K.: "Contribution of regulatory T cells to cancer: A review". *J. Cell. Physiol.*, 2019, 234, 7983.
- [9] DeLeeuw R.J., Kost S.E., Kakal J.A., Nelson B.H.: "The prognostic value of FoxP3+ tumor-infiltrating lymphocytes in cancer: a critical review of the literature". *Clin. Cancer Res.*, 2012, 18, 3022.
- [10] Ibrahim E.M., Al-Foheidi M.E., Al-Mansour M.M., Kazkaz G.A.: "The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis". *Breast Cancer Res. Treat.*, 2014, 148, 467.
- [11] Yeong J., Thike A.A., Lim J.C., Lee B., Li H., Wong S.C., et al.: "Higher densities of Foxp3+ regulatory T cells are associated with better prognosis in triple-negative breast cancer". *Breast Cancer Res. Treat.*, 2017, 163, 21.
- [12] Stang A.: "Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses". *Eur. J. Epidemiol.*, 2010, 25, 603.
- [13] Workel H.H., Komdeur F.L., Wouters M.C., Plat A., Klip H.G., Eggink F.A., et al.: "CD103 defines intraepithelial CD8+ PD1+ tumour-infiltrating lymphocytes of prognostic significance in endometrial adenocarcinoma". *Eur. J. Cancer*, 2016, 60, 1.
- [14] Kübler K., Ayub T.H., Weber S.K., Zivanovic O., Abramian A., Keyver-Paik M.D., et al.: "Prognostic significance of tumor-associated macrophages in endometrial adenocarcinoma". *Gynecol. Oncol.*, 2014, 135, 176.
- [15] de Jong R.A., Leffers N., Boezen H.M., ten Hoor K.A., van der Zee A.G., Hollema H., Nijman H.W.: "Presence of tumor-infiltrating lymphocytes is an independent prognostic factor in type I and II endometrial cancer". *Gynecol. Oncol.*, 2009, 114, 105.

- [16] Giatromanolaki A., Bates G.J., Koukourakis M.I., Sivridis E., Gatter K.C., Harris A.L., Banham A.H.: "The presence of tumor-infiltrating FOXP3+ lymphocytes correlates with intratumoral angiogenesis in endometrial cancer". *Gynecol. Oncol.*, 2008, *110*, 216.
- [17] Kosmaczewska A., Ciszak L., Potoczek S., Frydecka I.: "The significance of Treg cells in defective tumor immunity". *Arch. Immunol. Ther. Exp. (Warsz.)*, 2008, *56*, 181.
- [18] Tanaka A., Sakaguchi S.: "Regulatory T cells in cancer immunotherapy". *Cell Res.*, 2017, *27*, 109.
- [19] Que Y., Xiao W., Guan Y.X., Liang Y., Yan S.M., Chen H.Y., et al.: "PD-L1 Expression Is Associated with FOXP3+ Regulatory T-Cell Infiltration of Soft Tissue Sarcoma and Poor Patient Prognosis". *J. Cancer*, 2017, *8*, 2018.
- [20] Shen Z., Zhou S., Wang Y., Li R.L., Zhong C., Liang C., Sun Y.: "Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer". *J. Cancer Res. Clin. Oncol.*, 2010, *136*, 1585.
- [21] DeLeeuw R.J., Kost S.E., Kakal J.A., Nelson B.H.: "The prognostic value of FoxP3+ tumor-infiltrating lymphocytes in cancer: a critical review of the literature". *Clin. Cancer Res.*, 2012, *18*, 3022.
- [22] Rashid T., Young-Pierce J.L., Garrett-Mayer E., Graybill W., Neal S., Spruill L.S.: "CD8, FoxP3, and CD45RO+ Lymphocytic Infiltrates in Type I and Type II Endometrial Cancers in African American and European American Females". *Int. J. Gynecol. Pathol.*, 2017, *36*, 540.

Corresponding Author:
XING-HAI TONG, M.D.
Department of Obstetrics and Gynecology
Shanghai Changning Maternity & Infant Health Hospital
No.773 Wuyi Road
Shanghai, 200051 (China)
e-mail: zbh513@sina.com