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ORIGINAL RESEARCH

The Prognostic Significance and Co-Expression of Fibroblast Growth Factor Receptor 2 and c-Met in Endometrial Cancer

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Objective: We sought to study the expression of FGFR2 and c-Met and evaluate the correlation between the two proteins in a series of endometrial cancer patients as well as the prognostic significance of the two markers in endometrium carcinoma.

Methods: Patients who were diagnosed with endometrial cancer and had undergone surgical treatment in Beijing Chao-Yang Hospital, Capital Medical University from November 2004 to June 2011 were included in this study. Tissue microarray construction, immunohistochemical staining and scoring were employed to study the expression of FGFR2 and c-Met. SPSS version 22.0 was used to evaluate the correlation between FGFR2 and c-Met expression and the prognosis prediction value of the two markers.

Results: In total, 109 patients were included in this study. The median age was 56 years (ranges, 30–79). The most common histologic tumor subtype was adenocarcinoma (86.2%). The five-year survival rate was 87.2%. Significantly different FGFR2 expression was observed among patients with different disease stages ($p < 0.001$), depths of myometrial invasion ($p = 0.001$) and lymph node status ($p < 0.001$). C-Met expression was also increased in tissues from patients with advanced stage disease, deep myometrial invasion and lymph node metastasis ($p < 0.001$, $p = 0.031$ and $p < 0.001$, respectively). The expression of FGFR2 and c-Met was increased in the group with poorer prognosis (overall survival < 5 years) ($p = 0.002$ and $p = 0.023$, respectively). Moreover, a strong positive correlation was observed between FGFR2 and c-Met expression ($p < 0.01$, $r = 0.656$). FGFR2 was a significant factor that influence the FIGO stage.

Conclusion: Higher expression of FGFR2 and c-Met is associated with more advanced stage, deeper myometrial invasion and lymph node metastasis in endometrial cancer and poorer prognosis. In addition, high expression of FGFR2 is correlated with high c-Met expression.

Plain language summary: This study found that higher levels of two proteins, FGFR2 and c-Met, are linked to more advanced and aggressive forms of endometrial cancer, as well as poorer outcomes for patients. Additionally, the presence of one protein often indicates the presence of the other, suggesting they may work together in the progression of this cancer.

Keywords: endometrial cancer, FGFR2, c-Met, expression and correlation

Introduction

Endometrial cancer (EC) is one of the most common gynecologic malignancies, and its incidence is increasing. In the United States, 61380 estimated new cases of EC and 10920 estimated EC-related deaths are expected in 2017.[1] Most EC patients are diagnosed at an early stage (FIGO stage I or II) with localized disease, and the 5-year overall survival (OC) is 74–91%; however, the survival of patients with FIGO stage III or IV is dismal and ranges from 20% to 66%.[2] Besides traditional histological features, TCGA molecular prognostic groups have been integrated into the WHO[3] and FIGO[4] endometrial cancer staging systems in recent years, but still majority of EC patients are defined as 'intermediate prognosis' by current EC staging system, which highlights the need for additional potential markers for EC prognosis prediction and more precise treatment option choosing.[5]

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FGFR2 is a type of fibroblast growth factor receptor (FGFR) and belongs to the family of receptor tyrosine kinases (RTKs) that are well known for their role in tumorigenesis.[6] Deregulation of FGFR signaling is observed in a subset of many tumors, such as breast cancer, lung cancer and EC.[7] FGFR2 mutations have been identified in 12% of all EC cases and are associated with poor outcomes in EC,[8,9] but it is still not clear whether the abnormal expression of FGFR2 is also related to prognosis. C-Met protein, encoded by the oncogene c-Met, is also a member of the RTK family. It is the only known receptor of hepatocyte growth factor (HGF). The alteration of HGF/c-Met signaling is involved in oncogenesis and cancer aggressiveness.[10] In addition, FGFR and Met were reported to interact with each other in some cancers to promote cell growth or acquisition of resistance to inhibitors.[11,12]

In recent years, precision medicine and personalized treatment have gradually become the research focus of cancer diagnosis and treatment. Typing and treatment decisions based on the molecular characteristics of tumors are considered the core development direction of future cancer nursing.[13,14] At present, emerging fields such as epigenetics, molecular subtyping, and non coding RNAs (ncRNAs) have been widely applied in cancer diagnosis and treatment research and have shown significant potential in various malignant tumors including endometrial cancer.[15,16] The synergistic effect of FGFR2 and c-Met in endometrial cancer suggests that it may become an important complement to molecular targets and prognosis prediction, especially in promoting personalized therapy and highly innovative diagnostic technologies. However, current research on the synergistic expression and prognostic value of FGFR2 and c-Met in endometrial cancer is still limited, especially in terms of how they adapt to the precision medicine framework, which lacks in-depth exploration.

In our previous study, FGFR2 and c-Met were both identified as hub proteins in EC.[17] Based on this, the aim of this study is to clarify the expression characteristics and correlation of FGFR2 and c-Met in endometrial cancer, explore their association with disease progression (including tumor staging, depth of muscle infiltration, and lymph node metastasis), and evaluate their prognostic value for overall survival rate of patients. Meanwhile, this study also aims to further elucidate the clinical significance of FGFR2 and c-Met in the context of precision medicine, and promote their application as potential targets in personalized therapy. These studies not only provide new scientific basis for the diagnosis and treatment of endometrial cancer but also open up new research directions for the development of highly innovative diagnostic and prognostic strategies under the framework of precision medicine.

Materials and Methods

Patient Selection and Tissue Microarray Construction

Tissue paraffin blocks from 109 patients who were diagnosed with EC and had undergone surgical treatment in Beijing Chao-Yang Hospital, Capital Medical University from 2000 to April 2011 were included in this study. Data on clinicopathological characteristics, including age, surgical stage, histologic type, grade, depth of myometrial invasion and lymph node metastasis, were collected from patient medical records. The tumors were staged according to the international FIGO 2009 staging system.[18] OS was defined as the period from the date of diagnosis by histology to the date of death or the last date of follow-up in April 2016. All procedures were approved by the Ethics Committee for Human Experiments of the Capital Medical University.

After a review of the slides by two pathologists to locate and mark the cancer tissues on paraffin blocks, appropriate areas from the tumors were selected for tissue microarray (TMA) construction. Using a Quick Ray Manual Tissue Microarrayer (SRstar Instruments Ltd., Shanghai, China), 1.0-mm-diameter tissue cores were punched from each donor block, and then inserted into a recipient block, which consisted of 10 × 12 arrays. Four-micrometer serial sections from the tissue microarray blocks were cut for immunohistochemical staining.

Immunohistochemical Staining and Scoring

Anti-FGFR2 (mouse, No. ab58201) and anti-Met (c-Met) antibodies (rabbit, No. ab51067) were purchased from Abcam (Cambridge, United Kingdom), and secondary antibodies (peroxidase-conjugated goat anti-mouse, rabbit IgG) were purchased from DingGuo ChangSheng Biotechnology CO., Ltd (Beijing, China). Immunohistochemistry was performed by a two-step method. After deparaffinization in xylene and alcohol, sections were boiled for 10 minutes in citrate buffer (pH = 6.0) for antigen retrieval. The sections were incubated in 3% hydrogen peroxide for 30 minutes and rinsed 3 times,

3 min each, in phosphate-buffered saline (PBS, pH 7.4). Then, 5% goat serum was used to block the nonspecific binding. The sections were then incubated for 1 hour at room temperature with the primary antibodies (FGFR2, 1:50; Met, 1:100). After washing 3 times with PBS, 3 min each, the sections were incubated with the secondary antibody at room temperature for 60 min, and 3.3′-diaminobenzidine (DAB) was used for developing the signal. Finally, the sections were dehydrated with xylene, alcohol and counterstained with hematoxylin for 2 min. Photomicrographs were captured under a microscope (BA400, Motic China Group Co., Ltd, Xiamen, China). Mean optical density (MOD) was analyzed by Image-Pro Plus V6.0 Program (Media Cybernetics, MD, USA) to quantify the expression of target proteins.

Statistical Analysis

Categorical data are presented as the medians with the associated ranges or proportions. Immunohistochemical staining intensity (or MOD), continuous variable, is presented as the mean ± standard deviation (SD) and compared between groups using *t*-tests. Survival data were estimated using Kaplan-Meier curves. Correlation between the expression of FGFR2 and c-Met was estimated by the Pearson correlation test. Cox regression proportional hazard model was used to explore the prognostic significance of FGFR2 and c-Met to overall survival (OS) when adjusted with FIGO stage, histological grading and histological type, multiple linear regression model was used to explore the prognostic significance of FGFR2 and c-Met to FIGO stage when adjusted with age and histologic grading and type. $P < 0.05$ was defined as the threshold for statistical significance. All statistical analyses were conducted with SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

The characteristics of the 109 patients with EC are presented in Table 1. The median age was 56 years (range, 30–79). Stages I and II (78.9%) were categorized as early stage, whereas stages III and IV represented advanced stage disease (21.1%). Twenty-eight (25.7%) patients exhibited invasion in ≥1/2 of the myometrium. The most common histologic

Table 1 Clinico-Pathologic Characteristics of Patients

Variable	Ec Patients (n=109)
Age, median (range)	56 (30–79)
Stage (%)	
I	73 (67.0)
II	13 (11.9)
III	19 (17.4)
IV	4 (3.7)
Myometrial invasion (%)	
<1/2	81 (74.3)
≥1/2	28 (25.7)
Histology (%)	
Adenocarcinoma	94 (86.2)
Others	15 (13.8)
Grade (%)	
1	40 (36.7)
2	55 (50.5)
3	14 (12.8)
Lymph node metastasis (%)	
Yes	14 (12.8)
No	95 (87.2)
Overall survival (%)	
≥5 years	95 (87.2)
<5 years	14 (12.8)

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tumor type was adenocarcinoma (86.2%). G1, G2 and G3 tumors accounted for 36.7%, 50.5% and 12.8% of cases, respectively. The risk of lymph node metastasis was 12.8%.

The overall staining on the tissue microarray for FGFR2 and c-Met is shown in Figure 1. FGFR2 staining was mainly localized to the cell membrane as well as to the cytoplasm in glandular cells in EC tissues (Figure 1A and B). The differences in expression of FGFR2 and c-Met were correlated with various clinicopathological characteristic of EC patients. Significantly different expression of FGFR2 was observed among patients with different disease stages ($p < 0.001$) and depths of myometrial invasion ($p = 0.001$) (Table 2). Higher expression of FGFR2 was associated with higher stage and deeper myometrial invasion. In addition, staining for FGFR2 was significantly higher in tissues of patients with lymph node metastasis than in tissues of patients without lymph node metastasis ($p < 0.001$). C-Met staining was localized to both the cell membrane and cytoplasm (Figure 1C and D). C-Met expression was also increased in tissues from patients with advanced stage disease, deep myometrial invasion and lymph node metastasis ($p < 0.001$, $p=0.031$, and $p < 0.001$, respectively) (Table 2). However, the staining for FGFR2 and c-Met was not significantly different between the two types of histology ($p = 0.122$ and $p = 0.220$, respectively) and different grades ($p = 0.562$ and $p = 0.329$, respectively).

The Kaplan–Meier curves are shown in Figure 2, and the five-year survival rate was 87.2%. The expression of FGFR2 and c-Met was lower in the group with poorer prognosis (OS ≥ 5 years) than in the group with better prognosis (OS < 5 years) ($p = 0.002$ and $p = 0.023$, respectively). Moreover, a strong positive Pearson's correlation was observed between FGFR2 and c-Met expression ($p < 0.01$, $r = 0.656$) (Figure 3). FGFR2 expression was significantly higher among cases with high c-Met expression than in cases with low c-Met expression.

Cox regression analyses for the associations between FGFR2, c-Met and OS when adjusted with Age, FIGO stage, Histological grading and Histological type are presented in Table 3. Neither FGF2 nor c-Met was significant independent predictor of worse OS ($p = 0.748$ and 0.692 respectively).

Table 4 shows the coefficients of the MLR model, which was used to analyse the associations between FGFR2, c-Met and cancer FIGO stage when adjusted with Age, FIGO stage, Histological grading and Histological type. The p-value was less than 0.05 for the FGFR2 ($p = 0.009$) while more than 0.05 for c-Met ($p = 0.362$), which means FGFR2 is an independent positive predictor to endometrium cancer stage but c-Met is not.

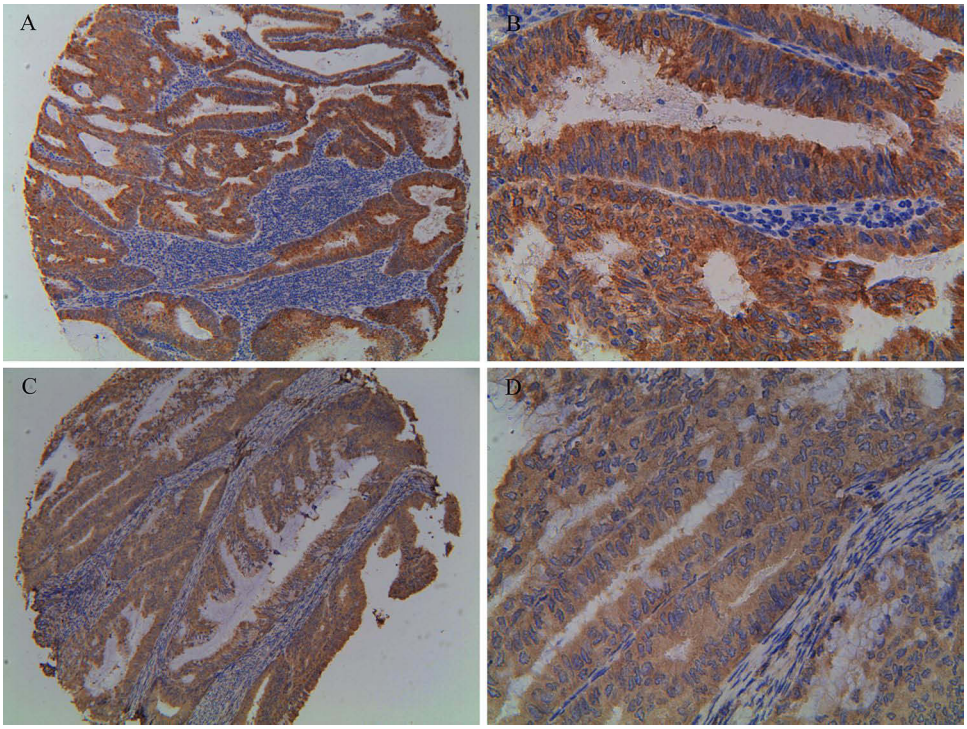

Figure 1 Overall staining For FGFR2 (**A** and **B**) and c-Met (**C** and **D**) on the tissue microarray.

Table 2 Correlation Between Clinicopathological Parameters and FGFR2 and c-Met Expression

Variable	FGFR2	*P*	c-Met	*P*
Stage		<0.001*		<0.001**
I+II	0.1899±0.039		0.1985±0.033	
III+IV	0.2329±0.035		0.2349±0.035	
Myometrial Invasion		0.001*		0.031*
<1/2	0.1914±0.039		0.2017±0.036	
≥1/2	0.2210±0.043		0.2192±0.036	
Histology		0.122		0.220
Adenocarcinoma	0.1965±0.040		0.2044±0.036	
Others	0.2146±0.049		0.2171±0.041	
Grade		0.562		0.329
1	0.1994±0.038		0.2050±0.036	
2	0.1960±0.045		0.2035±0.033	
3	0.2096±0.037		0.2199±0.049	
Lymph node metastasis		<0.001*		<0.001**
Yes	0.1922±0.039		0.2005±0.035	
No	0.2450±0.032		0.2444±0.028	
Overall survival		0.002*		0.023*
≥5 years	0.1943±0.041		0.2031±0.035	
<5 years	0.2309±0.043		0.2271±0.046	

Notes: *P<0.05, **P<0.01.

Discussion

We performed this study to determine the effect of FGFR2 and c-Met expression on the outcomes of EC patients including overall survival and FIGO stage and, more specifically, to focus on the correlation between FGFR2 and c-Met

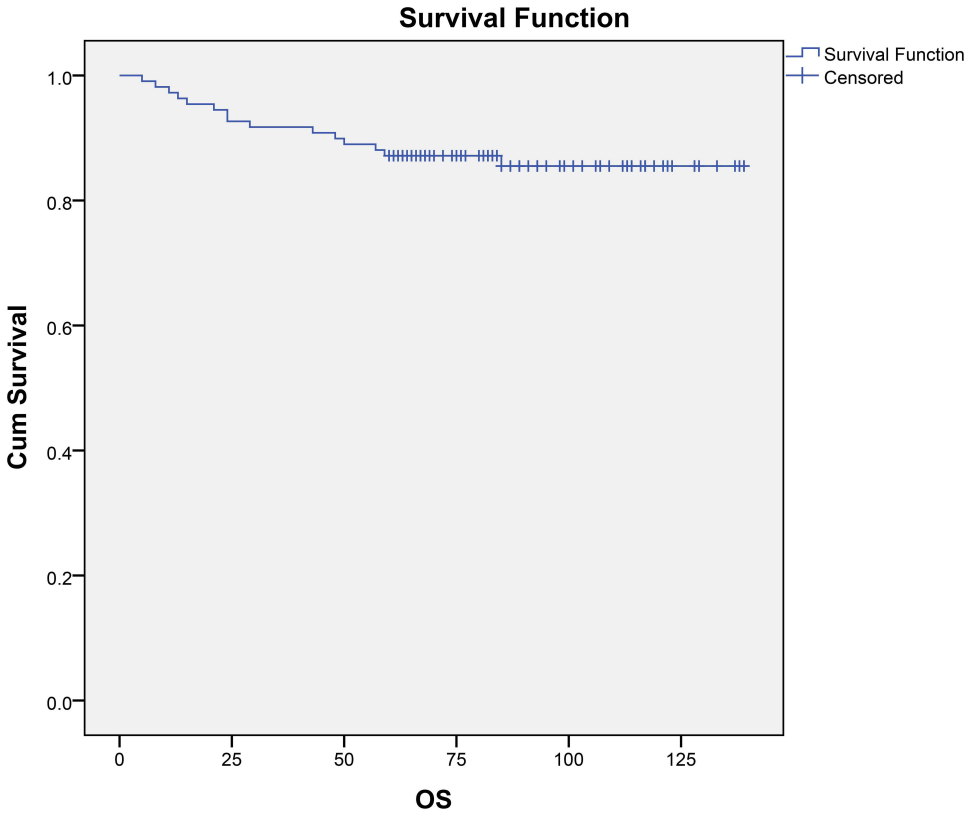

Figure 2 The Kaplan-Meier OS curves.

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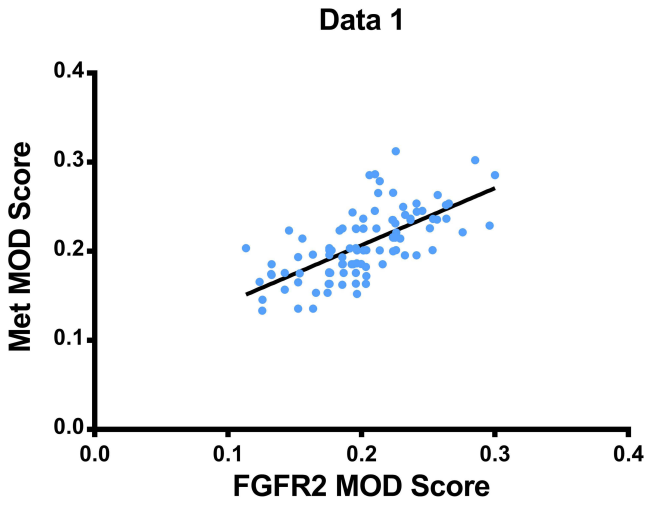

Figure 3 The Pearson's correlation between FGFR2 and c-Met expression.

expression. FGF and FGFR proteins are expressed in many tissues and are involved in the biological processes such as cell growth, wound healing and angiogenesis by activating multiple downstream pathways including the RAS/MAPK and PI3K/AKT pathways.[19] Deregulation of FGFR signaling is observed in a subset of many cancers, through a variety of mechanisms including gene amplification, translation, and point mutations. Mutations in FGFR2 have been shown to be associated with EC. Sara et al detected mutations in the FGFR2, KRAS, CTNNB1 and PIK3CA genes in 466 patients with EC and found that the mutations in FGFR2 and KRAS were more common and significantly correlated with prognosis.[20] Recently, a Gynecologic Oncology Group (GOG) study in 2017 identified FGFR2 mutations in 144 out of 973 tumors investigated (15%) and showed that patients with FGFR2 mutations had significantly more aggressive disease and shorter progression-free survival and EC- specific survival than did patient without FGFR2 mutations.[9] Only one previous study had investigated the role of FGFR2 protein expression in EC. In this study by Gatius et al, the authors stained 2 tissue microarrays containing 157 EC samples and showed that FGFR2 protein was localized to the cytoplasm

Table 3 Results of Multivariate Cox Regression Analysis

Variables	HR	95% CI
Age	1.094	0.997 ~ 1.201
FIGO stage	1.714	1.338 ~ 2.197
Histological grading	1.594	0.701 ~ 3.623
FGFR2	21.955	0.000 ~ 3,283,808,695.888
MET	96.891	0.000 ~ 631,962,322,048.062
Histological type: 2 vs 1	0.898	0.256 ~ 3.144

Table 4 Results of the Multiple Linear Analysis

	Unstandardized Coefficients		Standardized Coefficients	t	*P*
	β	Std. error	β		
Intercept	−1.746	0.662	–	−2.638	0.010**
Histological type	0.541	0.231	0.203	2.342	0.021*
Histological grading	0.415	0.12	0.299	3.453	0.001**
FGFR2	7.326	2.732	0.309	2.682	0.009**
MET	2.594	2.83	0.106	0.916	0.362
Age	0	0.008	0.003	0.034	0.973

Notes: * p<0.05 ** p<0.01.

and nucleus and that its expression was correlated with stage, histological type and grade.[21] However, the authors did not examine the relation between FGFR2 expression and survival outcomes. In this study, we have shown that a higher expression of FGFR2 is associated with more advanced stage when adjusted with age, histologic grading and type. Higher FGFR2 patient group shows deeper myometrial invasion, lymph node metastasis, and shorter survival. Activated FGFR seems a highly promising potential therapeutic target based on current finding and multiple preclinical studies.

C-Met is expressed at high levels in numerous malignant tumors and contributes to oncogenesis, invasion and metastasis of tumors.[22] Overexpression of c-Met is common in EC and associated with poor prognosis. Felix examined the expression of c-Met in all histologic types of EC and found that the staining intensity was not significantly related to any of the clinicopathological factors including survival outcomes.[23] Conversely, Bishop reported that patients with stronger c-Met staining had shorter OS than patients with weaker staining in uterine serous carcinoma.[24] In the present study, higher c-Met expression was observed in more advanced stage, patients with deeper invasion, wider lymph node metastasis and shorter OS it showed non-significance on OS and FIGO stage in multivariate Cox model and MLR. C-Met may play a role in the progression of EC but seems not as significant as FGFR2 does.

In this study, we also observed a significant correlation between FGFR2 and c-Met expression. FGFR and c-Met have been recently reported to interact with each other to promote cell growth or acquisition of resistance to specific inhibitors in some cancer cell lines. Harbinski reported that after being inhibited by MET inhibitors, the growth and survival of MKN-45 gastric cancer cells can be rescued by several members of the FGF family and that cell growth and survival was inhibited again in response to cotreatment with FGFR inhibitors. In addition, c-Met inhibitors can also deregulate the expression of FRS2, which is a substrate of FGFR.[25] In a recent study, strong overexpression and activation of Met was found in a lung cancer cell line resistant to two kinds of FGFR inhibitor.[26] In EC, a previous study examined the stimulatory effects of various factors on HGF gene expression in isolated endometrial stromal cells and showed that bFGF induced an increase in HGF transcription, which indicated that the aberrant expression of bFGF in tumor cells may act as a paracrine factor to stimulate HGF expression.[27] However, in the study by Felix, no significant association was observed between bFGF and c-Met expression in EC, which is different from our results.[23] However, the combined use of FGFR and c-met inhibitors has been shown to significantly inhibit cell proliferation in some cancer cells.[26,28]

In recent years, significant progress has been made in the molecular classification and genomic analysis of endometrial cancer, particularly with the Cancer Genome Atlas (TCGA) project proposing four molecular subtypes: POLE hypermutation, microsatellite instability (MSI), low copy number, and high copy number. These subtypes exhibit significant differences in prognosis and treatment response and have been incorporated into clinical practice to guide individualized treatment strategies.[29] In addition to the TCGA classification framework, an increasing number of novel molecular markers are considered to have potential prognostic and diagnostic value. L1 cell adhesion molecule (L1CAM), as a potential prognostic marker, has gradually attracted attention in the study of endometrial cancer. The high expression of L1CAM has been found to be associated with higher tumor invasiveness and poorer survival prognosis.[30] In addition, the expression of L1CAM is also associated with higher levels of FIGO grading and older age, suggesting its potential value as an adjuvant therapy in certain subgroups of patients.[31]

This study found that high expression of FGFR2 and c-Met is associated with the progression and poor prognosis of endometrial cancer, suggesting that these two molecules may play a key role in the invasiveness and progression of the disease. In the context of precision medicine, understanding the expression patterns of these molecules can help develop new diagnostic biomarkers and therapeutic targets. For example, inhibitors targeting FGFR2 and c-Met may provide new therapeutic options for patients with high expression of these molecules. Research has shown that the FGFR2 targeted drug BGJ-398 can significantly inhibit the metastasis of ascites tumor cells.[32] At the same time, FGFR inhibitors show significant tumor growth inhibition in xenografts with high/moderate FGFR2c expression and significantly prolong survival in four-fifths of the models.[33] The above content provides a theoretical basis for targeting FGFR2 pathway activated metastatic tumors.

In addition, ncRNA plays an important role in the occurrence and progression of cancer and has been applied as a tool for cancer diagnosis and treatment.[15] Research has shown that CircNOLC1 can attenuate colorectal cancer cell proliferation, migration, and liver metastasis by interacting with AZGP1 and inducing miR-212-5p upregulation of c-Met expression.[34] Therefore, further research on the interaction between ncRNA and FGFR2 and c-Met may provide new ideas for the treatment of endometrial cancer. In summary, this study emphasizes the importance of FGFR2 and c-Met in endometrial cancer and

provides a foundation for the development of new diagnostic and treatment strategies in the context of precision medicine in the future. Incorporating these molecular markers into existing molecular classification systems, combined with other biomarkers such as ncRNA, will help achieve more precise patient stratification and personalized treatment, improving patient prognosis.

In this study, all patients participated on the basis of informed consent, and the research procedure has been approved by the Ethics Committee of Capital Medical University. However, with the deepening of molecular biomarker research, ethical issues related to patient privacy and data use have become increasingly complex. Especially in precision medicine and personalized treatment, how to balance patients' right to know and research needs is an ethical issue that needs further exploration. Ethical and regulatory considerations are equally important in molecular biomarker research and personalized therapy. Molecular diagnosis and treatment strategies without sufficient discussion and guidance may lead to patient privacy breaches, data abuse, and improper treatment choices, thereby triggering potential medical legal issues and medical malpractice lawsuits. Therefore, researchers must strictly adhere to ethical standards when conducting such studies, ensuring the confidentiality of patient information and the legality of data use. At the same time, medical institutions should establish clear guidelines to regulate the use of molecular markers and avoid legal disputes caused by improper treatment choices. This not only safeguards the rights of patients but also enhances the credibility and sustainability of medical research.

It is particularly important to provide consultation and support on fertility preservation for EC patients who still have fertility. In recent years, the development of fertility preservation technology has provided more treatment options for young cancer patients, but the ethical and psychological support during its implementation still needs to be strengthened. Research has shown that appropriate fertility preservation strategies can not only help patients maintain their fertility but also significantly improve their quality of life and mental health.[35,36] Therefore, when formulating treatment plans, the patient's fertility needs should be comprehensively considered, and personalized fertility preservation plans should be provided to achieve the best balance between treatment effectiveness and quality of life.

Because FGFR2 and c-Met appear to play a critical role in the tumorigenesis and prognosis of EC, as well as demonstrating a strong correlation with each other, their combinatorial role warrants further exploration in the context of targeted therapy and biomarker-driven management strategies. The findings of this study suggest that FGFR2 and c-Met could serve as important molecular targets for therapeutic interventions and as predictive markers for disease progression. This relevance extends beyond individual patient care, as these molecular markers could contribute to the development of risk-stratified treatment protocols that reduce overtreatment and improve resource allocation in healthcare systems. However, one limitation of this study is the reliance on a single immunohistochemical technique to evaluate the expression of FGFR2 and c-Met in EC tissues. This approach, while providing valuable insights, does not fully capture the dynamic functional interactions between these proteins or their regulatory mechanisms. Future studies employing complementary methodologies, such as cell culture, transcriptomic analysis, and animal models, are necessary to validate these findings and to unravel the molecular pathways underlying their synergistic effects. Such efforts could further clarify their potential as therapeutic targets, particularly in the context of combination therapies.

Conclusions

Higher expression of FGFR2 and c-Met is associated with more advanced disease stages, deeper myometrial invasion, lymph node metastasis, and poorer prognoses in EC patients. Moreover, FGFR2 expression was found to be independently associated with disease stage, and a strong correlation was observed between FGFR2 and c-Met expression. These findings underscore the potential clinical utility of FGFR2 and c-Met as prognostic markers and therapeutic targets in EC. Importantly, the implications of this study extend beyond the molecular level, highlighting the potential for FGFR2 and c-Met to influence cancer care and public health. Integrating these markers into existing diagnostic frameworks could improve patient stratification and enable more precise, individualized treatment strategies, aligning with the principles of precision medicine. Furthermore, their role in cancer progression and prognosis underscores the need for further investment in large-scale studies and the development of accessible diagnostic tools. This approach could ultimately enhance early detection, refine therapeutic decisions, and contribute to better patient outcomes, while also addressing the broader public health challenge of optimizing cancer care delivery.

Data Sharing Statement

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee for Human Experiments of the Capital Medical University. Informed consent was obtained from all the participants. All methods were carried out in accordance with Declaration of Helsinki.

Consent for Publication

All the authors confirming that WRITTEN INFORMED consent was obtained from all subjects and/or their legal guardian(s).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared that they have no conflicts of interest regarding this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2017;67:7–30. doi:10.3322/caac.21387
2. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. *Lancet*. 2016;387:1094–1108. doi:10.1016/s0140-6736(15)00130-0
3. Cree IA, White VA, Indave BI, et al. Revising the WHO classification: female genital tract tumours. *Histopathology*. 2020;76(1):151–156. doi:10.1111/his.13977
4. Berek JS, Matias-Guiu X, Creutzberg C, et al. FIGO staging of endometrial cancer:2023. *J Gynecol Oncol*. 2023;34(5):e85. doi:10.3802/jgo.2023.34.e85
5. Werner HM, Salvesen HB. Current status of molecular biomarkers in endometrial cancer. *Curr Oncol Rep*. 2014;16:403. doi:10.1007/s11912-014-0403-3
6. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. *Nat Rev Cancer*. 2017;17(5):318–332. doi:10.1038/nrc.2017.8
7. Helsten T, Elkin S, Arthur E, et al. The FGFR landscape in cancer: analysis of 4853 tumors by next-generation sequencing. *Clin Cancer Res*. 2016;22:259–267. doi:10.1158/1078-0432.ccr-14-3212
8. Salvesen HB, Haldorsen IS, Trovik J. Markers for individualised therapy in endometrial carcinoma. *Lancet Oncol*. 2012;13:e353–e361. doi:10.1016/s1470-2045(12)70213-9
9. Jeske YW, Ali S, Byron SA, et al. FGFR2 mutations are associated with poor outcomes in endometrioid endometrial cancer: an NRG oncology/gynecologic oncology group study. *Gynecol Oncol*. 2017;145(2):366–373. doi:10.1016/j.ygyno.2017.02.031
10. Maroun CR, Rowlands T. The met receptor tyrosine kinase: a key player in oncogenesis and drug resistance. *Pharmacol Ther*. 2014;142:316–338. doi:10.1016/j.pharmthera.2013.12.014
11. Jo J-C, Choi EK, Shin J-S. Targeting FGFR pathway in human hepatocellular carcinoma: expressing pFGFR and pMET for antitumor activity. *Mol Cancer Ther*. 2015;14(11):2613–2622. doi:10.1158/1535-7163.MCT-14-0780
12. Kataoka Y, Mukohara T, Tomioka H, et al. Foretinib (GSK1363089), a multi-kinase inhibitor of MET and VEGFRs, inhibits growth of gastric cancer cell lines by blocking inter-receptor tyrosine kinase networks. *Invest New Drugs*. 2012;30:1352–1360. doi:10.1007/s10637-011-9699-0
13. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes [published correction appears in nature. 2023 feb;614(7948):E39. doi: 10.1038/s41586-022-05598-w]. *Nature*. 2020;578(7793):82–93. doi:10.1038/s41586-020-1969-6
14. Giampaolino P, Cafasso V, Boccia D, et al. Fertility-sparing approach in patients with endometrioid endometrial cancer grade 2 stage IA (FIGO): a qualitative systematic review. *Biomed Res Int*. 2022;2022:4070368. doi:10.1155/2022/4070368
15. Piergentili R, Basile G, Nocella C, et al. Using ncRNAs as tools in cancer diagnosis and treatment-the way towards personalized medicine to improve patients' health. *Int J mol Sci*. 2022;23(16):9353. doi:10.3390/ijms23169353
16. León-Castillo A, de Boer SM, Powell ME, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. *J Clin Oncol*. 2020;38(29):3388–3397. doi:10.1200/JCO.20.00549
17. Gao H, Zhang Z. Systematic analysis of endometrial cancer-associated hub proteins based on text mining. *Biomed Res Int*. 2015;2015:615825. doi:10.1155/2015/615825

18. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009;105:103–104. doi:10.1016/j.ijgo.2009.02.012
19. Katoh M, Nakagama H. FGF receptors: cancer biology and therapeutics. *Med Res Rev*. 2014;34:280–300. doi:10.1002/med.21288
20. Byron SA, Gartside M, Powell MA, et al. FGFR2 point mutations in 466 endometrioid endometrial tumors: relationship with MSI, KRAS, PIK3CA, CTNNB1 mutations and clinicopathological features. *PLoS One*. 2012;7(2):e30801. doi:10.1371/journal.pone.0030801
21. Gatius S, Velasco A, Azueta A, et al. FGFR2 alterations in endometrial carcinoma. *Mod Pathology*. 2011;24:1500–1510. doi:10.1038/modpathol.2011.110
22. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. *Nat Rev Mol Cell Biology*. 2003;4:915–925. doi:10.1038/nrm1261
23. Felix AS, Edwards RP, Stone RA, et al. Associations between hepatocyte growth factor, c-Met, and basic fibroblast growth factor and survival in endometrial cancer patients. *Br J Cancer*. 2012;106:2004–2009. doi:10.1038/bjc.2012.200
24. Bishop EA, Lengyel ER, Yamada SD, Montag A, Temkin SM. The expression of hepatocyte growth factor (HGF) and c-Met in uterine serous carcinoma. *Gynecol Oncol*. 2011;121:218–223. doi:10.1016/j.ygyno.2010.11.031
25. Harbinski F, Craig VJ, Sanghavi S, et al. Rescue screens with secreted proteins reveal compensatory potential of receptor tyrosine kinases in driving cancer growth. *Cancer Discov*. 2012;2:948–959. doi:10.1158/2159-8290.CD-12-0237
26. Kim SM, Kim H, Yun MR, et al. Activation of the met kinase confers acquired drug resistance in FGFR-targeted lung cancer therapy. *Oncogenesis*. 2016;5:e241. doi:10.1038/oncsis.2016.48
27. Yoshida S, Harada T, Iwabe T. Induction of hepatocyte growth factor in stromal cells by tumor-derived basic fibroblast growth factor enhances growth and invasion of endometrial cancer. *J Clin Endocrinol Metabol*. 2002;87(5):2376–2383. doi:10.1210/jcem.87.5.8483
28. Kentsis A, Reed C, Rice KL, et al. Autocrine activation of the MET receptor tyrosine kinase in acute myeloid leukemia. *Nat Med*. 2012;18:1118–1122. doi:10.1038/nm.2819
29. van den Heerik ASVM, Horeweg N, de Boer SM, Bosse T, Creutzberg CL. Adjuvant therapy for endometrial cancer in the era of molecular classification: radiotherapy, chemoradiation and novel targets for therapy. *Int J Gynecol Cancer*. 2021;31(4):594–604. doi:10.1136/ijgc-2020-001822
30. Vizza E, Bruno V, Cutillo G, et al. Prognostic role of the removed vaginal cuff and its correlation with L1CAM in low-risk endometrial adenocarcinoma. *Cancers*. 2021;14(1):34. doi:10.3390/cancers14010034
31. Giannini A, D'Oria O, Corrado G, et al. The role of L1CAM as predictor of poor prognosis in stage I endometrial cancer: a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2024;309(3):789–799. doi:10.1007/s00404-023-07149-8
32. Cavazzoni A, Salamon I, Fumarola C, et al. Synergic activity of FGFR2 and MEK inhibitors in the treatment of FGFR2-amplified cancers of unknown primary. *Mol Ther*. 2024;32(10):3650–3668. doi:10.1016/j.ymthe.2024.07.011
33. Sengal AT, Bonazzi V, Smith D, et al. Endometrial cancer PDX-derived organoids (PDXOs) and PDXs with FGFR2c isoform expression are sensitive to FGFR inhibition. *NPJ Precis Oncol*. 2023;7(1):127. doi:10.1038/s41698-023-00478-6
34. Yuan M, Zhang X, Yue F, et al. CircNOLC1 promotes colorectal cancer liver metastasis by interacting with AZGP1 and sponging miR-212-5p to regulate reprogramming of the oxidative pentose phosphate pathway. *Adv Sci*. 2023;10(33):e2205229. doi:10.1002/advs.202205229
35. Zaami S, Stark M, Signore F, Gullo G, Marinelli E. Fertility preservation in female cancer sufferers: (only) a moral obligation? *Eur J Contracept Reprod Health Care*. 2022;27(4):335–340. doi:10.1080/13625187.2022.2045936
36. Mutlu L, Manavella DD, Gullo G, McNamara B, Santin AD, Patrizio P. Endometrial cancer in reproductive age: fertility-sparing approach and reproductive outcomes. *Cancers*. 2022;14(21):5187. doi:10.3390/cancers14215187