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FGFR2 mutations are associated with poor outcomes in endometrioid endometrial cancer: An NRG Oncology/ Gynecologic Oncology Group study

Yvette W. Jeske[a,†], **Shamshad Ali**[b], **Sara A Byron**[c], **Feng Gao**[d], **Robert S Mannel**[e], **Rahel G Ghebre**[f], **Paul A DiSilvestro**[g], **Shashikant B Lele**[h], **Michael L Pearl**[i], **Amy P Schmidt**[j], **Heather A Lankes**[b], **Nilsa C Ramirez**[k], **Golnar Rasty**[l], **Matthew Powell**[j], **Paul J Goodfellow**[m], and **Pamela M Pollock**[a,c,*]

[a]Queensland University of Technology (QUT) at the Translational Research Institute, Brisbane, Australia

[b]NRG Oncology Statistics and Data Management Center, Roswell Park Cancer Institute, Buffalo, NY, USA

[c]Cancer and Cell Biology Division, Translational Genomics Research Institute, Phoenix, AZ, USA

[d]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St Louis, MO, USA

[e]Gynecologic Oncology, The Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

[f]University of Minnesota Medical Center – Fairview, Minneapolis, MN, USA

[g]Gynecologic Oncology, Women and Infants Hospital, Providence, RI, USA

[h]Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY, USA

[i]Obstetrics and Gynecology, Stony Brook University Hospital, Stony Brook, NY, USA

[j]Department of Obstetrics and Gynecology, Washington University School of Medicine, St Louis, MO, USA

[k]GOG Tissue Bank/NRG Oncology Biospecimen Bank – Columbus, Biopathology Center, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA

[l]Department of Laboratory Medicine, University of Toronto, ON, M5G2C, CANADA

[m]Department of Obstetrics and Gynecology, The Ohio State University and James Comprehensive Cancer Center, Columbus, OH, USA

[*]Corresponding author at: Institute of Health and Biomedical Innovation, Queensland University of Technology at TRI, 37 Kent St, Brisbane 4102, Queensland, Australia. pamela.pollock@qut.edu.au (P.M. Pollock).

[†]Deceased.

Conflicts of interest

Drs. Pollock and Goodfellow are listed as inventors of two patents involving the detection of FGFR2 mutations for diagnostic or prognostic purposes in endometrial cancer. Drs. Pollock and Powell have received compensation as a member of a scientific advisory board for Novartis and Eisai respectively. The remaining authors declare no conflicts of interests.

Abstract

Purpose—Activating *FGFR2* mutations have been identified in ~10% of endometrioid endometrial cancers (ECs). We have previously reported that mutations in *FGFR2* are associated with shorter disease free survival (DFS) in stage I/II EC patients. Here we sought to validate the prognostic importance of *FGFR2* mutations in a large, multi-institutional patient cohort.

Methods—Tumors were collected as part of the GOG 210 clinical trial "Molecular Staging of Endometrial Cancer" where samples underwent rigorous pathological review and had more than three years of detailed clinical follow-up. DNA was extracted and four exons encompassing the FGFR2 mutation hotspots were amplified and sequenced.

Results—Mutations were identified in 144 of the 973 endometrioid ECs, of which 125 were classified as known activating mutations and were included in the statistical analyses. Consistent with FGFR2 having an association with more aggressive disease, *FGFR2* mutations were more common in patients initially diagnosed with stage III/IV EC (29/170;17%) versus stage I/II EC (96/803; 12%; $p = 0.07$, Chi-square test). Additionally, incidence of progression (progressed, recurred or died from disease) was significantly more prevalent (32/125, 26%) among patients with *FGFR2* mutation versus wild type (120/848, 14%; $p < 0.001$, Chi-square test). Using Cox regression analysis adjusting for known prognostic factors, patients with *FGFR2* mutation had significantly ($p < 0.025$) shorter progression-free survival (PFS; HR 1.903; 95% CI 1.177–3.076) and endometrial cancer specific survival (ECS; HR 2.013; 95% CI 1.096–3.696).

Conclusion—In summary, our findings suggest that clinical trials testing the efficacy of FGFR inhibitors in the adjuvant setting to prevent recurrence and death are warranted.

Keywords

Endometrial cancer; FGFR2; Mutation; Outcome; Prognosis

1. Introduction

Endometrial cancer (EC) is responsible for ~76,000 deaths worldwide and has a higher incidence in developed countries due to its association with obesity [1]. The majority of ECs are detected early (75%) and have a relatively good prognosis. However, if a patient presents with metastatic disease, or recurs after initial surgery, their prognosis is very poor, with a median survival of 7–12 months [2]. Although the endometrioid histological subtype is associated with good prognosis compared to other subtypes, due to its prevalence it is still responsible for ~50% of all EC deaths. For a woman diagnosed with early stage EC, a combination of clinicopathological features is currently used to guide decision making as to whether the patient should receive adjuvant therapy following initial surgery. These features include age, stage, histological subtype, tumor grade, depth of myometrial invasion, and tumor cell invasion of lymphatic vessels (lymphovascular space invasion: LVSI) [3]. However, these clinicopathological biomarkers fail to capture the heterogeneity of EC [4].

A recent review summarized promising prognostic and predictive biomarkers in EC [4], however they are not widely applied in the community. The development of tumor specific prognostic markers that could be used for risk stratification and to inform subsequent

treatment options is clearly needed for early stage patients. This is especially true given that early stage patients include those patients that have not been surgically staged and for whom stage-specific prognosis is significantly worse. Identification of the most effective therapy for these higher risk patients (e.g. chemotherapy, radiation, or targeted therapy) is also a priority.

Fibroblast growth factor receptor 2 (*FGFR2)* has been shown to be activated in a number of cancers through a variety of mechanisms including gene amplification, translocations, and point mutations [5]. Our lab was the first to identify *FGFR2* mutations, predominantly in the endometrioid histological subtype, which was subsequently confirmed by other groups [6–8]. Preclinical in vitro and in vivo studies in EC cell lines suggest that *FGFR2* mutation status is predictive of response to anti-FGFR therapies [7,9,10]. An increasing number of FGFR inhibitors are entering clinical trials for breast, lung, and other cancers [5]. We previously reported that somatic activating *FGFR2* mutations were associated with reduced disease free survival (DFS; hazard ratio [HR] = 3.24; 95% confidence interval, [CI] 1.35–7.77; $p = 0.008$) and overall survival (OS; HR = 2.00; 95% CI 1.09–3.65; $p = 0.025$) in early stage endometrioid EC (386 stage I and II cases) [6]. In the current study, we sought to validate the prognostic importance of *FGFR2* mutations within the endometrioid subtype of EC in a large, multi-institutional cohort of patients with detailed clinical follow-up.

2. Materials and methods

2.1. Tumor samples and patient population

The GOG 210 clinical trial, “Molecular Staging of Endometrial Cancer,” was opened in 2003. In 2007 enrollment was limited to poor prognosis tumors and those occurring among non-obese and non-white patients. GOG 210 enrolled 6124 patients between 2003 and 2011. All participants provided written consent and specimens were prospectively collected at the time of surgery when all patients were comprehensively surgically staged (planned full pelvic and para-aortic lymph node dissection) based on the 1988 FIGO (International Federation of Gynecology and Obstetrics) staging system. Each case was reviewed for eligibility with respect to histological diagnosis and adequate surgical staging; 256 patients were deemed ineligible. Of the remaining 5869 eligible cases, 3713 (63.3%) enrolled during the unrestricted enrollment period. Of these, 2814 patients from 55 institutions had endometrioid histology. Patients in GOG-210 that had been previously analyzed as part of the WUSM cohort [6] were excluded from this study such that it comprises an independent cohort. The GOG Tissue Bank reviewed 1673 cases for tumor quality. All late stage cases (III/IV) and early stage (I/II) cases that recurred ($n = 152$) plus 841 random samples from early stage cases that did not recur and that had at least 3 years of follow-up were distributed for testing. Where available frozen specimens were used ($n = 794$). To ensure no bias was introduced by the inclusion of formalin fixed paraffin embedded (FFPE) samples, multiple age, grade, and stage matched samples that did not recur were included for every FFPE case that did recur. DNA extraction was successful from all samples; however, mutation analysis was unsuccessful in 20 samples. As such the patient cohort was comprised of 803 early stage patients (stage I, II) and 170 late stage (stage III/IV) patients. Institutional review boards at Washington University (St Louis, MO, USA), the Translational Genomics Research Institute

(Phoenix, AZ, USA), and the Queensland University of Technology (Brisbane, Australia) approved this study.

2.2. Central pathology review

Pathologic diagnoses were made at participating GOG institutions and then reviewed centrally by the GOG Pathology Committee where there was at least two reviewers and structured adjudication of differences of opinion. Surgical stage was determined post-operatively and coded according to FIGO 1988 Staging criteria.

2.3. FGFR2 mutation analysis

Frozen tumor and matched normal tissues were reviewed to identify tumor specimens with high neoplastic cellularity (>60%) and normal myometrium (uninvolved by cancer). DNA was extracted from frozen samples (n = 794) as previously described [6]. For those cases for which FFPE tissues were used (n = 199), areas containing >60% tumor cellularity were manually macrodissected or microdissected (Arcturus PixCell II LCM instrument) prior to DNA extraction using the semi-automated Maxwell® 16 instrument (Promega). Matched normal tissues were similarly dissected and DNAs prepared using the Maxwell® 16 instrument (Promega).

PCR amplification of four exons (7, 10, 13, 15) of *FGFR2* corresponding to the location of hotspot mutations was performed using M13 tailed primers. Exon 8 was also sequenced in 300 cases. Additional primers, which amplified smaller fragments, were used to amplify *FGFR2* from the FFPE samples (primers available upon request). PCR fragments were then sent to Functional Biosystems (USA) at room temperature where they were cleaned up using an Exo/Sap protocol and sequenced in both directions using Sanger sequencing. Data was analyzed using Sequencher (v 4.0, Gene Codes). An independent PCR reaction was sequenced to validate each mutation. Confirmation of somatic status by sequencing the matched germline DNA was performed for all novel mutations and the majority of cases with hotspot mutations (~65%), and all mutations assessed were indeed somatic.

2.4. Statistical analyses

The relationship between gene mutation and covariates was assessed using Chi-square test, Fisher's exact test, or Student's t-test as appropriate. Endometrial cancer specific survival (ECS) was defined as the time from date of entry to death due to disease. Cause of death was based on confirmed death records and where necessary the site nurse and/or CRA queried for resolution on cause of death. All patients with documented relapse who died had confirmed cause of death due to endometrial cancer. Patients who did not die of disease were censored at the date of last contact. Progression-free survival (PFS) was defined as the time from surgery to time of first documented evidence of recurrence or progression. Based on the study protocol, recurrence was defined as discovery of disease not previously present by clinical, radiographic, and/or laboratory means. Progression was defined as 50% or greater increase in the product from any documented lesion, however, histologic confirmation of suspected progressive disease was left to the judgment of the attending physician. Kaplan-Meier product limit method was used to estimate PFS and ECS. Differences in PFS and ECS by mutation status were evaluated by using the log-rank test [11]. Univariate and

multivariate Cox proportional hazard models were fitted to assess the effects of known covariates and mutation status on ECS and PFS. Clinically accepted prognostic factors that were significant on univariate analysis were included in the model including age, stage, and tumor grade. All analyses were two-sided and significance was set at a *p*-value of 0.05. Statistical analyses were performed using SAS 9.3.

3. Results

3.1. Characteristics of the GOG 210 patient cohort

The clinicopathologic characteristics of this GOG 210 patient cohort are consistent with the published literature for the general population. The majority of patients analyzed (83%) presented with early stage disease. The median age at diagnosis was 62 years (IQR: 55–69 years) with the majority of the women diagnosed between 50 and 70 (see Table 1). The distribution of patients across different age groups was consistent with the previously reported SEER data [12]. The patient cohort had a median follow up time of 68 months (IQR: 49–105 months). Thirteen percent of women had a BMI <25 (underweight and normal), 20% had a BMI between 25 and 30 (overweight) and 67% had a BMI above 30 (obese).

3.2. Prevalence and spectrum of FGFR2 mutations

FGFR2 mutations were identified in 144/973 (15%) tumors investigated. Although the majority occurred at known mutational hotspots, the remaining mutations presumably include a proportion of “passenger” mutations attributable to the higher mutational load found in ECs with microsatellite instability (MSI) or carrying a somatic POLE mutation [8]. As such, the mutations have been characterized into those that are “known activating,” “putatively activating” and variants of unknown significance (VUS) where patients with the latter mutations were not included in the outcome analyses (Table 4).

Known activating mutations include all those mutations that occurred at codons previously identified as mutation “hotspots” [6,7] (Table 4). Many of these mutations have been functionally studied to determine how they result in receptor activation. The G385R mutation was included in this category of “known activating” mutations as this mutation has been reported in a patient with sporadic craniosynostosis [34], and the homologous mutation in *FGFR3* has been identified in a multiple myeloma cell line where functional studies showed it was weakly activating [30]. The majority of sequence changes (125/144; 87%) occurred at one of these seven codons.

Another eight somatic mutations were defined as “putatively activating”. Although mutations were examined using mutation assessor and PolyPhen-2 (Table 4), it is difficult to determine with any certainty whether a particular missense change is likely to result in receptor activation, especially for those mutations in the transmembrane region where no structural data is available. As such we defined mutations as “putatively activating” if they had occurred in two independent cancer patients but there was either limited or no functional data. In some cases a mutation had been reported in another EC patient or in a patient with another cancer also characterized by FGFR2 activation (e.g. cholangiocarcinomas,

ameloblastomas). We included two mutations where the homologous mutation in *FGFR3* had been reported in bladder cancer, which is associated with FGFR3 activation. Also included in this category were two mutations associated with Bent bone dysplasia, which have been reported to show features associated with both loss and gain of receptor function [31] (Table 4).

Thirteen mutations were classified as VUS (Table 4). These included a nonsense mutation in the extracellular domain (R251*), a predicted loss of function missense mutation affecting the HRD consensus in the kinase domain (D627Y), two in-frame transmembrane deletions, and five other missense mutations for which no other data was available to support their role as potentially activating. Only two of these occurred in tumors with MLH1 methylation and MSI (Table 4). The remaining three mutations did not show a POLE mutation signature however they were designated VUS based on their low frequency and lack of functional data. This category included four additional novel mutations that were found in patients also carrying a known activating mutation (S252 W + V294 L, K660E + N653S, N550 K + L551I, and N550 K + L551F).

3.3. FGFR2 mutations are associated with poor outcomes

FGFR2 mutation showed a trend towards being more prevalent among advanced age (≥70 years) patients (16% vs. 12%, chi-square p value = 0.07). Consistent with FGFR2 having an association with more aggressive disease, *FGFR2* mutations were more common in patients initially diagnosed with stage III/IV EC (29/170; 17%) versus stage I/II EC, although this did not reach statistical significance (96/803; 12%; $p = 0.07$, Chi-square test) (Table 1).

Additionally, incidence of progression (progressed, recurred or died from disease) was significantly more prevalent (32/125, 26%) among patients with *FGFR2* mutations versus wild type (120/848, 14%), (Chi-square test $p < 0.001$). Consistent with previous studies [35] Cox proportional hazard regression analysis identified increasing age, later stage (III, IV), and higher tumor grade as unfavorable prognostic factors relative to PFS, as well as ECS (Table 2). In addition, univariate analysis demonstrated, activating mutations in *FGFR2* to be independently prognostic for worse outcome, that is shorter PFS (HR 1.867; 95% CI 1.264–2.758; $p = 0.002$) and ECS (HR 2.075; 95% CI 1.303–3.307; $p = 0.002$). Similar analyses were carried out including the additional 10 cases defined as putatively activating with similar results, albeit with a slight reduction in significance (Table 2). In multivariate analysis, adjusting for known prognostic factors age, stage, and grade, the relative risk of failure was significantly greater among patients with *FGFR2* mutation. Specifically, patients with *FGFR2* mutation had significantly ($p < 0.025$) shorter PFS (HR 1.584; 95% CI 1.063–2.361) and ECS (HR 1.665; 95% CI 1.032–2.687) (Table 2). The Kaplan Meier survival plot for ECS survival according to activating *FGFR2* mutation status is presented in Fig. 1. *FGFR2* mutations were significantly associated with shorter PFS (log rank test, $p = 0.001$) (data not shown) and decreased ECS (log rank test, $p = 0.004$) in the total cohort of 973 patients. In those patients with grade 3 disease recurrence/progression was seen in 54/140 (38%) patients with wildtype *FGFR2* and 11/24 (46%) patients with mutant *FGFR2*.

The utility of *FGFR2* mutation in early stage disease, where prognostic biomarkers are needed most, was evaluated (Table 3). Among patients with stage I/II disease, activating

mutations were shown to be independently associated with shorter PFS (HR 2.141; 95% CI 1.333–3.3439; $p = 0.002$) and ECS (HR 2.302; 95% CI 1.263–4.194; $p = 0.007$). Similar results were obtained when patients carrying “known + putative” activating mutations were analyzed (Table 3). The association between known activating mutations and poorer outcomes remained when multivariate analysis was performed, revealing that activating mutations were associated with shorter PFS (HR 1.903; 95% CI 1.177–3.076; $p = 0.009$) and ECS (HR 2.013; CI 95% 1.096–3.696; $p = 0.024$).

4. Discussion

Current risk stratification of EC patients is not ideal, with recurrences estimated to occur in ~15% of patients with grade 1/2 tumors who are often not offered adjuvant therapy, as well as significant morbidity in EC patients with grade 3 tumors who receive adjuvant therapy but carry a low risk of their tumor recurring. Molecular profiling of endome-trial cancer by TCGA has revealed that there are 3 subtypes within the endometrioid histological subtype of EC that differ in their somatic mutational load and have corresponding differences in their prognosis [8].

We have analyzed *FGFR2* from a large series of patients enrolled in the GOG 210 multi-institutional clinical trial focused on specimen banking for future molecular analyses. In addition to the large number of cases, several other characteristics of the study are notable including 1) samples were prospectively collected, 2) each sample underwent rigorous pathological review within the GOG Tissue Bank to confirm diagnosis and ensure it had sufficient tumor cellularity prior to DNA extraction, and 3) detailed follow-up for at least 3 years was available for all cases.

The most significant difference between the current analyses and that previously reported is that in the GOG 210 patient cohort, *FGFR2* mutations were found at a similar frequency across all three grades whereas in the WUSM cohort, they were significantly less common in grade 3 endometrioid endometrial cancers [6]. Although both patient cohorts were graded based on the 1988 FIGO grading system, it is well accepted that quantification of the percentage of solid growth is open to inter-observer variability near the diagnostic cut-points between grades, as is the qualitative scoring of nuclear atypia [36]. We suspect that this new finding of FGFR2 mutations in 15% of poorly differentiated ECs is due to differences in grading by the pathologists involved and we believe the multi-institutional cohort data is more reliable. The frequency of *FGFR2* hotspot mutations detected in the TCGA cohort with whole exome sequencing (22/248; 9%) was lower than we identified in this study, however this is likely due to differences in the patient population. The TCGA cohort was primarily composed of prospectively collected early stage patients whereas this cohort of GOG-210 patients had been enriched to include all late stage cases and those early stage cases that recurred.

One of the main advantages of the GOG 210 cohort is that detailed clinical follow-up is available which allows us to test for an association between *FGFR2* mutation status and ECS. Indeed, the current study found that patients carrying an activating *FGFR2* mutation were twice as likely to die from their disease compared to patients with wildtype *FGFR2*

(HR 2.075; 95% CI 1.303–3.307; $p = 0.002$), which remained significant when other poor prognosis features were taken into account in multivariate analysis (HR 1.67; 95% CI 1.03–2.69; $p = 0.037$). In the PORTEC 1/2 molecular risk stratification study where MSI and mutation status in 14 genes was assessed, *FGFR2* mutations were found almost exclusively in the MSI (9%) and copy number low/NSMP (no specific molecular profile) subtypes (12%) [37]. In the latter study, *FGFR2* mutation was not associated with recurrence or overall survival, whereas the presence of TP53 mutations (characteristically associated with the serous histological subtype) did predict recurrence and reduced overall survival, confirming the molecular subgroups proposed by TCGA. The GOG-210 cohort differs from the PORTEC 1/2 cohort in that tumors with mixed or serous histology were excluded and stage III/IV tumors were included. Given the finding within the PORTEC cohort that *FGFR2* mutations occur almost exclusively in the MSI and NSMP subtypes, the data presented herein suggests that *FGFR2* mutation status could possibly further stratify patients with poor prognoses within these latter subtypes. The findings described here are clinically relevant as EC patients often present with other comorbidities and it shows that patients diagnosed with *FGFR2* mutation positive EC are indeed dying due to their disease rather than from other comorbidities. This provides important clinical data supporting the testing of more specific FGFR inhibitors in this patient population.

A wide variety of in vitro and in vivo data support a role for FGFR2 signaling in driving cell migration. FGFR2 has been shown to be essential for keratinocyte migration both in vivo using conditional knockout mice as well as in vitro using keratinocytes derived from these mice [38]. FGF7 and FGF10, which only bind to FGFR2, have also been shown to drive migration and/or invasion in a variety of tissue types and our lab has also shown that FGF10 stimulation of FGFR2 in the Ishikawa endometrial cancer cell line drives migration and invasion (unpublished data). We therefore hypothesize that *FGFR2* mutation-positive EC have an increased ability to form micro-metastases outside the uterus, which results in the significantly shorter PFS seen in these patients following their initial surgical treatment.

Molecular biomarkers can either be diagnostic or prognostic and/or predictive of response to a certain therapy. There have been several studies showing that EC cell lines with *FGFR2* mutations are more sensitive to FGFR inhibition [7,9,10]. Dovitinib, a “first generation” multi-kinase inhibitor with anti-FGFR activity has been assessed in a Phase II trial in endometrial cancer patients with and without somatic *FGFR2* mutations [39]. Similar activity was seen in both arms suggesting the anti-angiogenic activity of dovitinib was responsible for these responses. Although longer lasting responses were seen in patients with *FGFR2* mutant tumors (~20 months) versus the non-mutant group (~9 months) this might reflect the different histological subtypes included within the two arms, rather than the FGFR activity of dovitinib, as more serous and clear cell EC were included in the non-mutant arm. This would be consistent with the lack of “on target” side effects including hyperphosphatemia and tissue calcification seen in the dovitinib trial. These side effects are characteristically seen with the “second generation” more specific FGFR inhibitors currently being evaluated in Phase I/II trials in multiple other FGFR-dependent malignancies [5]. Perhaps early signals of efficacy may come from “basket trials” open to patients with any solid malignancy with aberrations in FGFR1, FGFR2 or FGFR3, and where EC patients whose tumors carry *FGFR2* activating mutations may enroll.

Following the identification of the most effective and best tolerated FGFR inhibitor in patients with metastatic disease, we propose that administration of an FGFR inhibitor in the adjuvant setting following initial surgery might show a significant benefit with respect to ECS, reminiscent of trastuzumab in breast cancer [40]. Treating patients with *FGFR2* mutation positive EC with anti-FGFR agents at this earlier stage is expected to be more effective due to the reduced burden of tumor cells in the patient and less tumor heterogeneity, resulting in a decrease in the emergence of acquired resistance. We propose the following approach to assess the efficacy of FGFR inhibition to reduce the risk of recurrence of high-risk EC: 1) identify an effective FGFR inhibitor in the metastatic setting (perhaps, even in other FGFR dependent cancers); 2) combine FGFR inhibition with contemporary radiation protocols and compare to radiation therapy alone; 3) stratify by MSI and copy number low/NSMP molecular subtypes. Given the frequency of these cases, this is likely to require an international multi-site clinical trial in order to facilitate recruitment.

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HIGHLIGHTS

- FGFR2 mutations are more common in patients with late stage endometrioid EC.
- FGFR2 mutations are more common in patients with recurrent endometrioid EC.
- FGFR2 mutations are associated with shorter PFS and EC specific death.

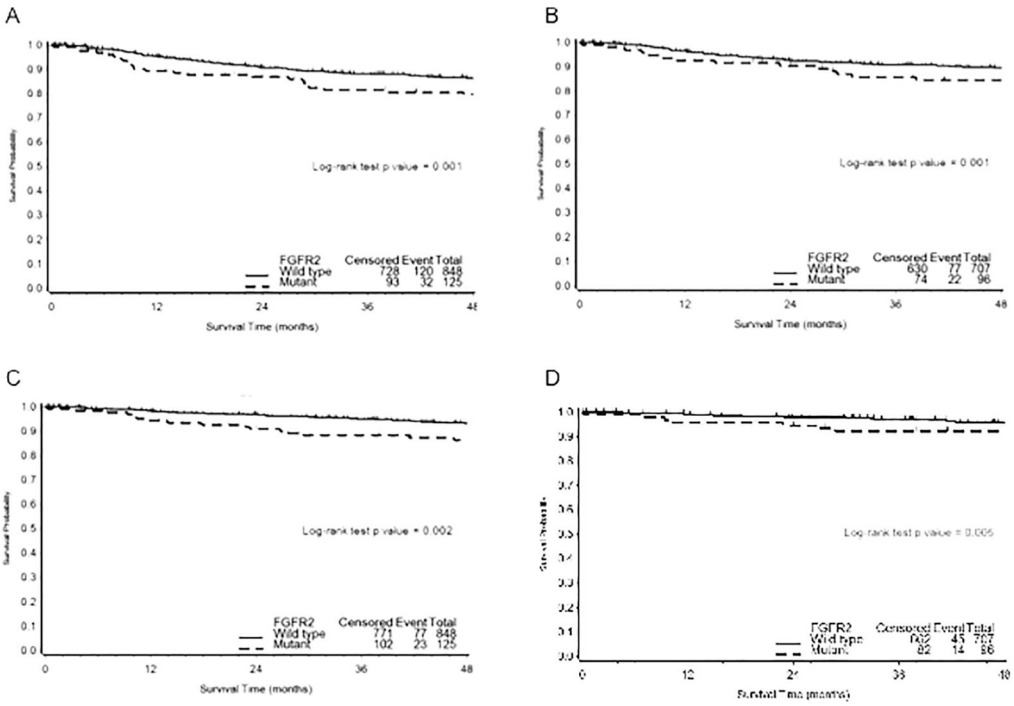

Fig. 1. Kaplan-Meier curves for survival by *FGFR2* mutation status

A–B. Progression-free survival (PFS) and endometrial specific survival (ECS) by *FGFR2* status (known activating mutation versus wild type) in the cohort of 973 endometrioid patients. C–D. Progression-free survival (PFS) and endometrial specific survival (ECS) by *FGFR2* status (known activating mutation versus wild type) in the cohort of 803 early stage endometrioid patients. Vertical bars represent censored cases.

Table 1

Relationship between *FGFR2* mutation and clinic-pathological features.

Characteristic	Value	FGFR2 mutation status				*p* value[a]
		Wild type		Mutant		
		N	%	N	%	
Age (years)[b]	<70	646	88.3	86	11.8	0.07
	≥70	202	83.8	39	16.2	
BMI[c]	<25	109	83.9	21	16.2	0.22
	≥25	735	87.7	103	12.3	
Race	Black	51	96.2	2	5.5	0.10
	White	760	86.5	119	13.5	
	Other	37	90.2	4	9.8	
Stage (FIGO 1988)	Early (I or II)	707	88.0	96	12.0	0.07
	Late (III or IV)	141	82.9	29	17.1	
Grade[d]	1	336	87.3	49	12.7	0.71
	2	370	87.9	51	12.1	
	3	140	85.4	24	14.6	

[a] Chi-square test.

[b] Age cut-off of 70 years is based on previous data showing age > 70 is associated with poorer outcomes [6].

[c] BMI not available for 5 cases.

[d] Tumor not graded for 3 cases.

Table 2

Univariate and multivariate outcome analysis of all EC patients (n = 973).

Univariate analysis	**Disease-free survival (DFS)**			**EC survival (ECS)**		
	HR	**95% CI**	**P[a]**	**HR**	**95% CI**	***p*[a]**
Age (years.)	1.030	1.014–1.045	<0.001	1.031	1.012–1.050	0.001
Race (ref = white)						
Black	1.435	0.776–2.653	0.250	1.369	0.634–2.953	0.424
Other	0.972	0.429–2.203	0.947	1.005	0.369–2.738	0.992
Stage (ref = 1A/1B)						
IC or II	1.632	1.088–2.447	0.018	1.820	1.082–3.059	0.024
III or IV	3.343	2.313–4.832	<0.001	4.492	2.860–7.053	<0.001
Grade (ref = 1 Well)						
2 Moderate	1.623	1.077–2.444	0.021	1.791	1.033–3.107	0.038
3 Poor	3.736	2.434–5.736	<0.001	5.528	3.208–9.527	<0.001
FGFR2 (ref = Wild type)						
“known activating”	1.867	1.264–2.758	0.002	2.075	1.303–3.307	0.002
FGFR2 (ref = WT)						
“known activating + putative”	1.682	1.139–2.484	0.009	1.878	1.179–2.993	0.008
Multivariable analysis						
Age (years)	1.030	1.014–1.046	<0.001	1.032	1.012–1.052	0.002
Stage (ref = IA/IB)						
IC/II	1.333	0.883–2.011	0.171	1.443	0.852–2.442	0.172
III/IV	2.504	1.698–3.693	<0.001	3.125	1.940–5.034	<0.001
Grade (ref = 1 Well)						
2 Moderate	1.487	0.986–2.243	0.059	1.606	0.925–2.790	0.093
3 Poor	2.936	1.888–4.565	<0.001	4.061	2.319–7.112	<0.001
FGFR2[b] (ref = WT)						
”known activating”	1.584	1.063–2.361	0.024	1.665	1.032–2.687	0.0368

WT = wild type.

[a]Wald test.

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[b] Multivariate model adjusting for age, stage and tumor grade.

Table 3

Univariate and multivariate analysis for stage I/II EC patients (n = 803).

Univariate analysis	**Progression-free survival (DFS)**			**Endometrial Cancer survival (ECS)**		
	HR	**95% CI**	p^a	**HR**	**95% CI**	p^a
Age (years)	1.035	1.016–1.054	<0.001	1.036	1.011–1.061	0.004
Race (ref = white)						
Black	1.787	0.900–3.549	0.097	1.963	0.844–4.567	0.117
Other	0.528	0.130–2.146	0.372	0.130	–	–
Stage (ref = IA/IB)						
IC or II	1.634	1.090–2.451	0.018	1.823	1.084–3.064	0.024
Grade (ref = 1 Well)						
2 Moderate	1.302	0.834–2.033	0.245	1.136	0.618–2.085	0.682
3 Poor	2.028	1.167–3.524	0.012	2.973	1.545–5.724	0.001
FGFR2 (ref = WT)						
”known activating”	2.141	1.333–3.439	0.002	2.302	1.263–4.194	0.007
FGFR2 (ref = WT)						
“known activating + putative”	1.927	1.200–3.095	0.007	2.077	1.140–3.785	0.017
Multivariable analyses						
Age (years)	1.032	1.013–1.051	0.001	1.032	1.008–1.057	0.001
Stage (ref = IA/IB)						
IC/II	1.359	0.898–2.057	0.147	1.465	0.861–2.492	0.159
Grade (ref = 1 Well)						
2 Moderate	1.257	0.805–1.964	0.314	1.068	0.581–1.963	0.832
3 Poor	1.882	1.078–3.285	0.026	2.755	1.422–5.338	0.003
FGFR2[b] (ref = WT)						
“known activating”	1.903	1.177–3.076	0.009	2.013	1.096–3.696	0.024

[a] Wald test.

[b] Multivariate model adjusting for age (>70), stage (IC/II) and tumor grade (grade 3).

Table 4

Mutations Identified In Endometrial Cancer Patients.

FGFR2 Mutation	# cases	Germline Syndrome	Functional data References	Species conserv[n]	FGFR conserv[n]	Mutation Assessor	PolyPhen2	Reported as somatic in a cancer associated with FGFR dependence
Known Activating								
S252W[a]	64	FGFR2	[7,13–15]	Y	Y	Medium	Prob. Damaging	[6–8]
N550K [b,c]	20	FGFR2/3	[7,16]	Y	Y	Neutral	Prob. Damaging	[6,7,17–20]
N550H	4	FGFR2/3	[16]	Y	Y	Low	Prob. Damaging	[6,8]
N550T	2		[16]	Y	Y	Neutral	Prob. Damaging	
N550D	1			Y	Y	Low	Prob. Damaging	[20]
C383R	14	FGFR1	[7,21]	Y	Y	medium	Poss. Damaging	[6,7,18,19,22–25]
K660E[d]	7	FGFR3	[26]	Y	Y	low	Prob. Damaging	[6,8]
K660M	1	FGFR3	[26]	Y	Y	low	Prob. Damaging	[7]
K660R	1		[26]	Y	Y	neutral	Prob. Damaging	
Y376C	6	FGFR1/2/3	[27,28]	Y	Y	medium	Prob. Damaging	[6,22,29]
P253R	4	FGFR2	[7,13–15]	Y	Y	Low	Benign	[6–8]
G385R	1	FGFR2	[30]	Y	Y	medium	Prob. Damaging	[30]
Putative Activating								
F276E	1	FGFR2		Y	Y	High	Poss. Damaging	[22]
A380S	1			Y	N	low	Poss. Damaging	
A380T	1			Y	N	low	Poss. Damaging	
Y382D	1	FGFR2	[31]	Y	Y	Medium	Prob. Damaging	[32]
M392R	2	FGFR2	[31]	Y	1/2	Medium	Poss. Damaging	[6]
V396D	2			N	1/2/3	Medium	Prob. Damaging	[6,18]
I548V	1			Y	Y	Neutral	Poss. Damaging	[6]
D651Y	1			Y	Y	low	Prob. Damaging	[33]
Variants of unknown Significance								
R251X	1			Y	Y	Truncation	Truncation	
V274I	1			Y	Y	low	Prob. Damaging	
V294M [e]	1			Y	N	low	Poss. Damaging	

FGFR2 Mutation	# cases	Germline Syndrome	Functional data References	Species conserv[n]	FGFR conserv[n]	Mutation Assessor	PolyPhen2	Reported as somatic in a cancer associated with FGFR dependence
V311I [e]	1			Y	N	low	Benign	
p.E378_C383delInsR	1					In/del	In/del	
p.I388_M391Idel	1					In/del	In/del	
D627Y	1			Y	Y	High	Prob. Damaging	
A629E	1			Y	Y	High	Prob. Damaging	
E637K	1			Y	Y	neutral	Prob. Damaging	
L551I [b]	1			Y	Y	low	Prob. Damaging	
L551F [c]	1			Y	Y	low	Prob. Damaging	
V294L [a]	1			Y	N	neutral	Benign	
N653S [d]	1			Y	N	neutral	Benign	

[a] One tumor carried a S252W and V294L mutation.

[b] One tumor carried a N550K and L551I mutation.

[c] One tumor carried a N550K and L551F mutation.

[d] One tumor carried a K660E and N653S mutation.

[e] MSI with MLH1 methylation.