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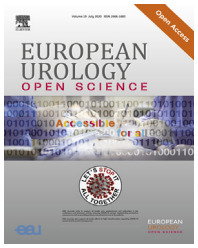

European Association of Urology

Urothelial Cancer

Fibroblast Growth Factor Receptor 3 Mutation as a Prognostic Indicator in Patients with Urothelial Carcinoma: A Systematic Review and Meta-analysis

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Article info

Article history:
Accepted August 26, 2020

Associate Editor:
Guillaume Ploussard

Keywords:
Fibroblast growth factor receptor 3 mutation
Muscle invasive
Non-muscle invasive
Progression-free survival
Recurrence-free survival
Urothelial carcinoma

Abstract

Background: Fibroblast growth factor receptor 3 (FGFR3) mutations have been implicated in urothelial tumorigenesis. FGFR3 inhibitors are being explored in clinical trials.

Objective: We aimed to study the association between FGFR3 mutations and survival in urothelial carcinoma.

Design, setting, and participants: We performed a systematic literature search of PubMed, Cochrane, Ovid, and Web of Science from January 1985 to October 2018. The search terms were as follows: targeted therapies, FGFR and its subtypes, urothelial, bladder, and cancer. We included case-control or cohort studies of FGFR3 mutations in urothelial carcinoma. We included studies reporting hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes comparing FGFR3 mutations with FGFR3 wild type. Two reviewers performed article selection.

Outcome measurements and statistical analysis: We assessed heterogeneity among study-specific HRs using I^2 statistic. We used a random effect model to obtain HR and 95% CI for event-free survival (EFS), composed of recurrence-free and progression-free survival. Statistical tests were two sided.

Results and limitations: Eleven studies (seven retrospective and four prospective) comprising 2162 patients were included. Analysis was performed for two groups. The first group included 1651 patients with non–muscle-invasive (NMI) urothelial carcinomas (886 [53.6%] had FGFR3 mutations). Compared with FGFR3 wild type, FGFR3 mutation did not influence EFS (HR = 0.99, CI = 0.77–1.28, p = 0.96). There

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http://dx.doi.org/10.1016/j.euros.2020.08.008

was no significant heterogeneity (I^2 = 25%). The second group included 511 patients with NMI and muscle-invasive (MI) urothelial carcinomas (151 [30%] had FGFR3 mutations). FGFR3 mutation was not prognostic (HR = 1.54, CI = 0.41–5.81, p = 0.52). There was heterogeneity (I^2 = 91%).
Conclusions: There is no association between FGFR3 mutation and EFS in NMI urothelial carcinoma, and in NMI and MI urothelial carcinoma groups.
Patient summary: Fibroblast growth factor receptor 3 (FGFR3) mutation is not associated with a worse survival outcome in urothelial carcinoma. This is important as FGFR inhibitors are emerging as a new treatment option.

1. Introduction

The treatment of urothelial carcinoma is continually evolving. Multiple therapies have shown efficacy in urothelial carcinoma, which include chemotherapy, immunotherapy, and targeted therapies. As newer effective treatment options come forth, there is a need for biomarkers for the diagnosis, risk stratification, monitoring of treatment modalities, and prognosticating.

The biomarker profile of urothelial carcinomas can be mapped and used to guide treatment with targeted therapies. Urothelial carcinoma subtypes, non–muscle invasive (NMI) and muscle invasive (MI), have distinct molecular pathways of urothelial tumorigenesis and progression. In the NMI type, the bladder epithelial cells can have mutation in RAS, fibroblast growth factor receptor 3 (FGFR3), or PIK3CA. Loss of heterozygosity of chromosome 9q has been associated with high-grade transformation of superficial papillary urothelial carcinoma. Loss of CDKN2A is associated with invasive carcinoma. Invasive transformation is associated with chromosome 9p and 9q loss of heterozygosity, TP53 mutation, and RB1 loss. As more mutations accumulate, urothelial carcinoma becomes more invasive and acquires metastatic potential [1].

FGFR alterations are among the earliest changes detected in urothelial carcinogenesis and may play a role in malignant transformation. FGFR3 mutations are found in 80% of stage Ta tumours and 10–20% of ≥ stage T2 tumours. Five mechanisms could occur: (1) FGFR3 point mutation that activates the RAS-MAPK pathway and phospholipase Cγ; (2) switch of FGFR3-IIIb isoform to FGFR3-IIIc isoform leading to autocrine or paracrine signalling; (3) Altered splicing by introduction of a single nucleotide polymorphism in the intron of the FGFR3 gene; (4) chromosomal translocations that can generate FGFR3 fusion proteins that are highly oncogenic; or (5) upregulation of FGFR3 expression [2].

Hence, alterations in FGFR3 are potentially important in urothelial carcinoma tumorigenesis. Currently, clinical trials are underway to study the effects of FGFR3 inhibitors in urothelial carcinomas. Considering that FGFR3 mutation is one of the molecular targets for treatment, here, we aimed to determine the impact of FGFR3 mutations on outcomes in urothelial carcinoma.

2. Patients and methods

2.1. Databases and searches

An electronic search of PubMed, Cochrane, Ovid, and Web of Science was performed from January 1985 to October 2018. The search was limited to English-language articles. The search terms included targeted therapies, FGFR and its subtypes, urothelial, bladder, and cancer. The citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy.

2.2. Study selection

The inclusion criteria included studies on NMI and MI urothelial cancers with recurrence or progression-free survival outcomes. There was no restriction based on study methodology. The exclusion criteria included studies on metastatic disease and duplicate publications. One reviewer (S.K.) evaluated the titles and abstracts identified by the search strategy, and all potentially relevant publications were retrieved as complete pdf documents. Two independent reviewers (S.K. and J.E.) then assessed the articles for study eligibility, and their disagreement was resolved by consensus.

2.3. Endpoints of interest

The recurrence-free and progression-free survival outcomes were the studies' endpoints of interest. Recurrence-free and progression-free survival outcomes were defined interchangeably between the studies; hence, we combined the two for our analysis and used the term event-free survival (EFS).

2.4. Data extraction

Data were extracted from the full-text articles. The following variables were collected: number of participants, sex, mean age, disease stage (NMI and MI), tumour grade, FGFR3 mutation positive or negative, FGFR3 mutation testing and company, duration of follow-up, treatment, and hazard ratio (HR) and 95% confidence interval (CI) for EFS. Outcome data were collected from the tables or figures where available; otherwise, they were estimated from Kaplan-Meier curves. We collected and analysed the data in two groups. One of the groups was NMI. The other group consisted of both NMI and MI, as the studies combined both of them together when presenting the results. We also conducted an analysis after combining all the studies and their outcomes.

2.5. Statistical analysis

Data were presented as means and proportions. Differences between groups were tested using χ^2 test. The prognostic value of FGFR3-mutated

compared with wild-type tumours was presented as HR with 95% CI. Data were combined into a meta-analysis using RevMan 5.3 analysis software (2014; Cochrane Collaboration, Copenhagen, Denmark). Estimates of HR were weighted and pooled using generic inverse variance and the random effect model. Statistical heterogeneity was assessed using the Cochran's Q and I^2 statistics. All statistical tests were two sided, and statistical significance was defined as $p < 0.05$. The random effect model was used due to heterogeneity between the studies. A funnel plot was used to determine publication bias.

3. Results

3.1. Study screening

The initial search yielded 828 titles. After reviewing the titles and abstracts, we excluded 649 as they did not contain data on FGFR mutation. Of the remaining 179 abstracts, 103 were excluded as they were not original articles or were animal or preclinical studies. An additional 63 articles were excluded as the inclusion criteria of NMI and MI with recurrence-free and progression-free survival outcomes were not met. Some of these studies did not analyse progression-free or recurrence-free survival, some included other diagnostic methods such as urine testing for recurrence, and some incorporated other mutations as part of their analysis, for example, CDKN2A and TP53. An additional two studies were excluded as they contained duplicate data. Consequently, 11 studies were selected for analysis. The flow diagram for the literature review is illustrated in Fig. 1.

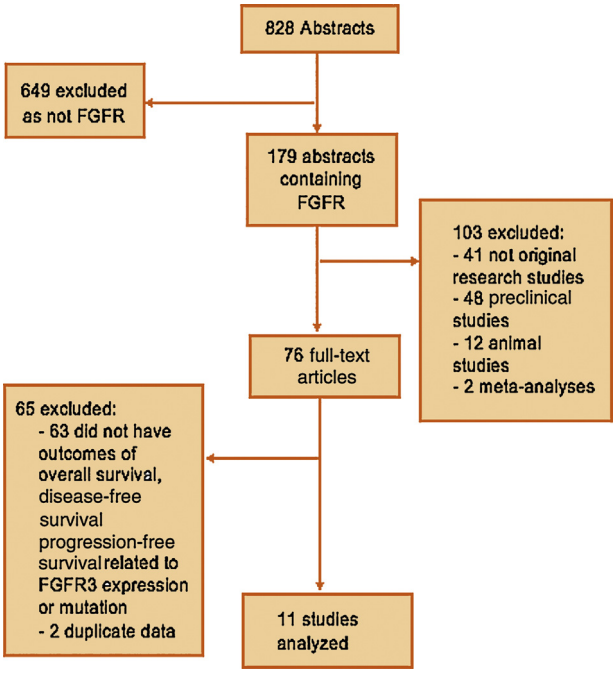

Fig. 1 – Flow diagram of included studies. FGFR = fibroblast growth factor receptor.

3.2. Study characteristics and meta-analysis results

Characteristics of the included studies are shown in Table 1 [3–13]. The studies comprised a total of 2162 patients. The cohort of NMI urothelial cancer comprised 1651 patients. The mean age was 68 yr, 80% were male patients, and 27% had a high tumour grade. FGFR3 mutation was positive in 886 (53.6%). The median follow-up period ranged from 28 to 101 mo. FGFR3 mutation in NMI urothelial carcinomas was not associated with EFS (HR = 0.99, 95% CI = 0.77–1.28, $p = 0.96$). There was no evidence of statistically significant heterogeneity between the studies (Cochran's Q $p = 0.25$, $I^2 = 25\%$; Fig. 2A).

The second group included 511 patients with both NMI and MI urothelial carcinomas. The mean age was 69 yr, 79% were male patients, and 62% had a high tumour grade. FGFR3 mutation was present in 151 (30%). The median follow-up period ranged from 1.7 to 68 mo. FGFR3 mutation was associated with nonsignificantly worse EFS (HR = 1.54, 95% CI = 0.41–5.81, $p = 0.52$; Fig. 2B). There was evidence of statistically significant heterogeneity between studies (Cochran's Q $p = <0.001$, $I^2 = 91\%$). This could suggest clinical heterogeneity due to the combination of NMI and MI groups, and different treatments that were utilised. In the outliers, Bertz et al's [9] study consisted mainly of NMI tumours and Lim et al's [12] dataset comprised mainly MI tumours, which received more extensive treatments that impacted outcomes.

We also conducted a combined analysis of the two groups, in which FGFR3 mutation was not associated with a worse EFS outcome (HR = 1.15, 95% CI = 0.70–1.86, $p = 0.59$). There is statistically significant heterogeneity between studies (Cochran's Q $p = <0.00001$, $I^2 = 83\%$).

3.3. Publication bias

A funnel plot depicted a consistent distribution of the studies, suggesting a lack of publication bias (Fig. 3).

4. Discussion

After reviewing 11 studies, which included 2162 patients, our meta-analysis shows that FGFR3 mutation compared with FGFR3 wild type did not influence EFS in NMI urothelial carcinoma. A nonsignificant association with worse outcome was observed in an analysis of a mixed cohort of NMI and MI urothelial carcinomas. These findings support that FGFR3 mutation does not lead to worse outcomes.

FGFR3 mutation may be able to serve as a biomarker for urothelial cancers to help with diagnosis, treatment, and prognostication. Robertson et al [14] examined the molecular characterisation of 412 urothelial carcinomas—MI high grade, and noted that urothelial cancers have one of the highest mutation rates compared with other cancers. Of these, in luminal papillary tumours, FGFR3 mutations occurred in 42/57. The FGFR3 mutations were more frequent in lower stages and had better survival. Through

Table 1 – Study characteristics.

Study	Sample size	FGFR3+	FGFR3+ analysis	Mean age (yr)	Sex	Disease stage	Grade	Treatment	Median follow-up (mo)
NMI									
Burger (2008) [3]	221	141	SNaPshot	68	Male 77%	NMI	WHO (1973):	TUR	35
							G1–86 (39%), G2–110 (50%), G3–25 (11%)		
							WHO (2004):		
							PUNLMP–49 (22%), low grade–119 (55%), high grade–50 (23%)		
Hernandez (2006) [4]	764	385	PCR and direct sequencing	66	Male 87%	NMI	WHO (2004):	TUR–306 (40%)	63
							LMPN–43 (6%), TaG1–251 (33%), TaG2–239 (31%), TaG3–88 (11%), T1G2–24 (3%), T1G3–119 (15%)	TUR + BCG–201 (26%)	
								TUR + chemotherapy–179 (23%)	
								TUR + BCG + chemotherapy–43 (6%)	
								Other–24 (3%)	
Mhawech-Fauceglia (2006) [5]	254	151	IHC	69	Male 79%	NMI	WHO (1973):	TUR–193 (76%)	28
							G1–82 (32%), G2–105 (41%), G3–67 (26%)	TUR + BCG–28 (11%)	
								Partial cystectomy–2 (0.8%)	
								Radical cystectomy–4 (1.6%)	
								Therapy unknown–27 (11%)	
Van der Aa (2005) [6]	53	17	PCR–T7 sequence v2.0	68	Male 79%	NMI	WHO (1973):	TUR, then 42 (79%) treated with immunotherapy or chemotherapy by intravesical instillation at the time of progression	55
							G1–2 (4%), G2–24 (45%), G3–27 (51%)		
							WHO/ISUP (1998):		
							Low grade–14 (26%), high grade–39 (74%)		
van Rhijn (2010) [7]	230	155	SNaPshot	65	Male 76%	NMI	WHO (1973):	TUR–72 (31%)	101
							G1–88 (38%), G2–108 (47%), G3–34 (15%)	TUR + chemotherapy–58 (25%)	
							WHO (2004):	TUR + BCG–58 (25%)	
							PUN-LMP–82 (36%), LG-PUC–80 (35%), HG-PUC–68 (29%)	TUR + BCG + chemotherapy–42 (19%)	
van Rhijn (2012) [8]	129	37	SNaPshot	69	Male 81%	NMI	WHO (1973):	TUR + BCG–106 (82%)	78
							G2–55 (43%), G3–74 (57%)	TUR + BCG + chemotherapy–23 (18%)	
							WHO (2004):		
							Low grade–26 (20%), high grade–103 (80%)		
NMI + MI									
Bertz (2014) [9]	56	28	SNaPshot	71	Male 80%	NMI, MI	WHO (1973):	TUR	53
							G1–11 (18%), G2–31 (51%), G3–19 (31%)		
							WHO (2004):		
							Low grade–25 (41%), high grade–36 (59%)		
Eltze (2008) [10]	154	61	SNaPshot	68	Male 72%	NMI, MI	WHO:	TUR	68
							G1–47 (31%), G2–43 (28%), G3–64 (42%)		

Table 1 (*Continued*)

Study	Sample size	FGFR3+	FGFR3+ analysis	Mean age (yr)	Sex	Disease stage	Grade	Treatment	Median follow-up (mo)
Kim (2015) [11]	109	22	MSK-IMPACT assay	68	Male 75%	NMI, MI	High grade	Radical cystectomy + neoadjuvant chemotherapy—42 (39%) Radical cystectomy—67 (61%)	1.7
Lim (2016) [12]	98	14	IHC	70	Male 84%	NMI, MI	High grade	Cystectomy—51 (52%) Cystectomy + adjuvant chemotherapy—47 (48%)	34
Mhawech-Fauceglia (2007) [13]	94	26	IHC	70	Male 84%	NMI, MI	WHO (2003): Low grade—36 (80%), high grade—9 (20%)	TUR—32 (71%) TUR + BCG—7 (16%) Cystectomy—6 (13%)	12

BCG = bacillus Calmette–Guérin; FGFR3 = fibroblast growth factor receptor 3; HG-PUC = high-grade papillary urothelial carcinoma; IHC = immunohistochemistry; ISUP = International Society of Urological Pathology; LG-PUC = low-grade papillary urothelial carcinoma; LMPN = low malignant potential neoplasm; MI = muscle invasive; NMI = non–muscle invasive; PCR = polymerase chain reaction; PUN-LMP = papillary urothelial neoplasm of low malignant potential; TUR = transurethral resection; WHO = World Health Organization.

next-generation sequencing, urothelial tumours were analysed for FGFR aberrations: 15% had activating FGFR3 somatic mutations, 7% had FGFR1 amplifications, 6% had gene fusions, and 3% had FGFR3 amplifications [15]. Hence, FGFR mutations might play an important role in guiding treatment. Furthermore, FGFR mutation status can be combined with known biomarkers to determine treatment efficacy. As programmed cell death (PD)-1/PD-ligand 1 (PD-L1) inhibitors are approved for treating urothelial carcinoma, some real-world evidence data suggested that FGFR alterations had higher positivity rates in early stages, and lower PD-L1 expression was observed in patients with FGFR mutation [16]. This highlights that a different treatment option could be followed for patients with FGFR mutations. Additional studies are required to determine whether FGFR mutation could be utilised as a predictive or prognostic biomarker.

Our meta-analysis did not suggest a significant effect of FGFR3 mutations on outcomes. However, in clinical trials, FGFR3 mutation is an actionable target for targeted therapies, as specific intervention can impact survival outcomes in urothelial carcinomas. Recent clinical studies have shown promising results for FGFR inhibitors in urothelial carcinoma with FGFR3 mutations. In a phase II trial, erdafitinib was administered to patients with locally advanced, surgically unresectable, or metastatic urothelial carcinoma. Objective tumour response occurred in 40% (3% complete and 37% partial response) with erdafitinib [17]. Additionally, in another phase II trial, BCGJ398, a selective pan-FGFR, was administered to patients with metastatic urothelial carcinoma and the overall response rate was 25.4%, with disease stabilisation in 38.8% of patients [18]. Based on these results, erdafitinib received accelerated Food and Drug Administration approval [19]. In a phase I study, rogaratinib, an oral pan-FGFR inhibitor, was administered to patients with urothelial, and head and neck squamous and non–small-cell lung cancers. Of 100 patients, 15 (15%) achieved an objective response, and 10 of these15 (67%) patients had FGFR mRNA overexpressing tumours [20]. In the phase I expansion cohort in urothelial carcinoma, rogaratinib was studied further. A total of 219 patients with urothelial carcinoma were prescreened for FGR1–3 mRNA expression levels and FGFR3 activating mutations, 45% of whom were FGFR positive. Of these FGFR-positive patients, 87% were positive for FGFR3 mRNA and 5% for FGFR1 mRNA, and 8% were double FGFR mRNA positive; 7% had FGFR3 mutation. The objective response rate was 24%. In addition, 10 FGFR-positive urothelial carcinoma patients progressed on immunotherapy, and after treatment with rogaratinib, the objective response rate was 30% and the disease control rate was 80%. This supports that rogaratinib had response and disease control rates in urothelial patients who were refractory to previous immunotherapy [21].

As FGFR inhibitors are being studied in various cancers and have shown efficacy, phase III trials are being conducted to assess them further. A phase III clinical trial is underway to study erdafitinib compared with vinflunine or docetaxel or pembrolizumab in locally advanced urothelial cancer

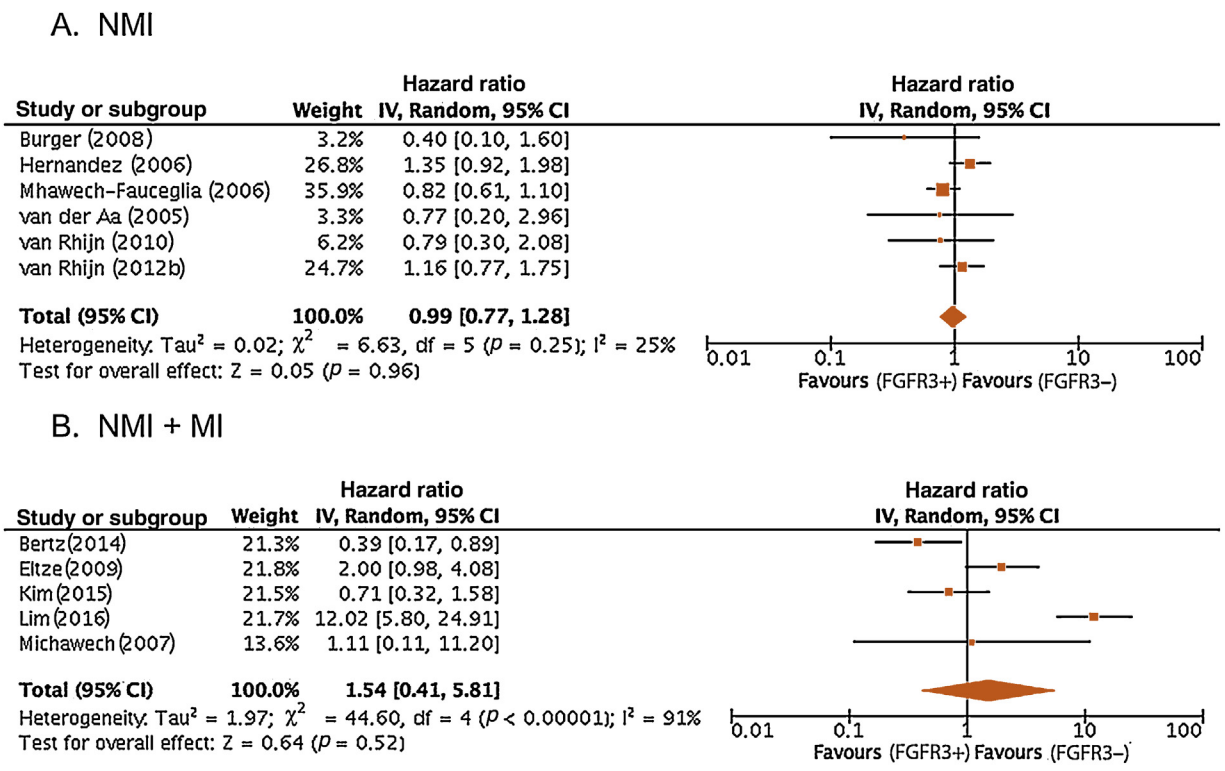

Fig. 2 – Forest plots displaying HR in FGFR3-positive and FGFR3-negative groups for EFS: (A) NMI and (B) NMI + MI. CI = confidence interval; EFS = event-free survival; FGFR3 = fibroblast growth factor receptor 3; HR = hazard ratio; IV = inverse variance; MI = muscle invasive; NMI = non–muscle invasive.

with FGFR aberrations [22]. Likewise, FGFR inhibitors are being used in combination with immunotherapy to improve response rates and survival outcomes. BISCAY, a randomised, multidrug, biomarker-directed, multicentre, multiarm phase 1b study in patients with MI urothelial cancer, who were platinum refractory and immune therapy naïve, were divided into four cohorts through DNA analysis and next-generation sequencing. In arm A, patients had FGFR 1, 2, and 3 mutations/fusions, and were given AZD4547 or AZD4547 + durvalumab. In arm B, patients with *ATM*, *BRCA* 1/2, and *HRR* gene mutations were assigned to olaparib + durvalumab. In arm C, patients with RICTOR, TSC1, and TSC2 mutations were assigned to receive vistusertib + durvalumab. In arm D, no mutations were detected and the patients were given durvalumab. The objective response rates in these arms were as follows: arm A with AZD4547—20% and with AZD4547 + durvalumab—28.6%, arm B—35.7%, arm C—24.1%, and arm D—27.6%. It was concluded that AZD4547 monotherapy had similar response rates to the combination of AZD4547 and durvalumab [23]. Furthermore, IMvigor130 phase III clinical trial studied atezolizumab with or without platinum-based chemotherapy in untreated metastatic urothelial carcinoma. The interim analysis results stated a clinically meaningful benefit in overall survival in the arm that consisted of atezolizumab with platinum and gemcitabine, but it did not cross the prespecified interim efficacy boundary, and a follow-up analysis is pending [24]. As immune therapy has a role in urothelial cancer, trials are underway to study the combination of immune therapy with FGFR inhibitors.

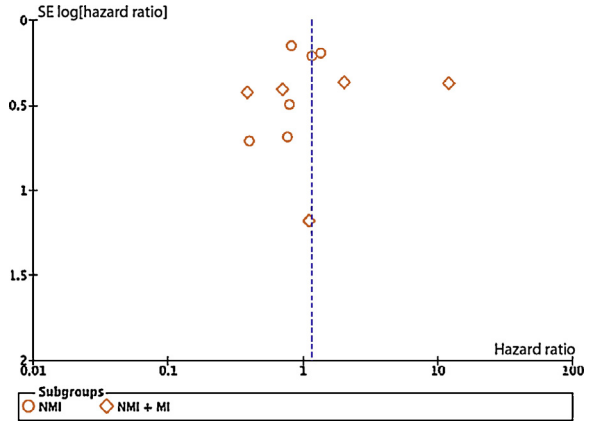

Fig. 3 – Funnel plot of the studies. MI = muscle invasive; NMI = non–muscle invasive; SE = standard error.

Additionally, to further study the effects of combination therapy, a phase 1b/2 study, FIDES-02, is being conducted with a pan-FGFR kinase inhibitor, derazantinib, in combination with the PD-L1 inhibitor atezolizumab in advanced urothelial cancer, including metastatic, surgically unresectable, and FGFR gene aberrations [25]. Preclinical models have also shown that the activity of pan-FGFR inhibitors in urothelial carcinoma is higher in PIK3CA wild type. Copanlisib, a pan class I PI3K inhibitor, when combined with rogaratinib had synergistic activity to reduce tumour

growth. Hence, a clinical trial with rogaratinib and copanlisib in FGFR cancers is on-going [26].

Our meta-analysis has limitations. Most of the selected studies included patients with NMI disease only, while a group of them combined both NMI and MI urothelial cancer patients for their analysis, and we were unable to differentiate between outcomes of these patient groups. There was clinical heterogeneity in the analysis. It is likely that this heterogeneity was driven by the combination of NMI and MI patients. We were unable to analyse the EFS for the advanced disease MI, as studies including MI patients only were not available. Data on overall survival was lacking; hence, overall survival was not analysed and EFS was utilised. In addition, we were unable to conduct a subgroup analysis according to grade for EFS, as the studies did not separate urothelial carcinoma into groups in their analysis. Furthermore, we were unable to analyse the EFS for upper tract and bladder urothelial carcinomas separately, as the selected studies did not analyse outcomes for these two particular groups. In our meta-analysis, we included studies in which patients tested positive for FGFR3 mainly through the immunohistochemistry or SNaPshot method. There is on-going research about which method to utilise in current practice to test for FGFR3 positivity, especially with the FGFR3 inhibitors as a therapeutic option [27,28]. The studies included in the meta-analysis are nonrandomised and can be related to a publishing bias.

5. Conclusions

Our meta-analysis shows that in the NMI urothelial carcinoma, and in the NMI and MI urothelial carcinoma groups, FGFR3 mutation status is not associated with a worse outcome. Several clinical trials are underway to study the effects of FGFR inhibitors on urothelial carcinomas with FGFR3 aberrations. As phase II clinical trials have resulted in better response rates, phase III clinical trials for FGFR inhibitors are on-going. Clinical trials comparing the efficacy of FGFR inhibitors, chemotherapy, and/or immunotherapy are also in progress. Studying FGFR3 in clinical trials is of utmost importance, as it could be a potential treatment option for patients with chemoresistant cancers or when immune therapy is not effective/contraindicated in urothelial carcinoma; therefore, embedded correlative studies for biomarker testing should be a priority in the design of these studies. Hence, in future, a pooled analysis for MI and metastatic urothelial cancers to assess survival outcomes could be conducted.

***Author contributions*:** Francisco E. Vera-Badillo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Vera-Badillo.
Acquisition of data: Vera-Badillo.
Analysis and interpretation of data: Vera-Badillo, Khalid, Emack.
Drafting of the manuscript: Vera-Badillo, Khalid.
Critical revision of the manuscript for important intellectual content: Vera-Badillo, Khalid, Emack, Basulaiman, Booth, Duran, Robinson, Berman, Smoragiewicz, Amir.
Statistical analysis: Vera-Badillo, Khalid.
Obtaining funding: Vera-Badillo.
Administrative, technical, or material support: Vera-Badillo.
Supervision: Vera-Badillo.
Other: None.

Financial disclosures: Francisco E. Vera-Badillo certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** This work was supported by Queen's University, Kingston, ON, Canada

***Acknowledgements*:** We thank Dr. Bas W.G. van Rhijn, from Division of Urology at Princess Margaret Hospital, Toronto, CA, and Dr. David B. Solit, from Medicine and Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, and Weill Medical College of Cornell University, New York, NY, for sharing non-published data. We also acknowledge Dr. Adrian Verdines, from the Department of Medicine, Instituto Mexicano del Seguro Social (IMSS) in Monterrey, Mexico, for conducting the systematic search.

CRediT authorship contribution statement

Sidra Khalid: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing. **Bassam Mohammed Basulaiman:** Conceptualization, Methodology, Validation, Resources, Investigation, Writing - review & editing. **Jeffrey Emack:** Validation, Investigation, Resources, Writing - review & editing. **Christopher M. Booth:** Validation, Data curation, Writing - review & editing. **Ignacio Duran:** Validation, Data curation, Writing - review & editing. **Andrew Robinson:** Validation, Data curation, Writing - review & editing. **David Berman:** Validation, Data curation, Writing - original draft, Writing - review & editing. **Martin Smoragiewicz:** Validation, Data curation, Writing - review & editing. **Eitan Amir:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Francisco E. Vera-Badillo :** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Supervision.

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