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REVIEW ARTICLE

Fibroblast Growth Factor Receptor Family Members as Prognostic Biomarkers in Head and Neck Squamous Cell Carcinoma: A Systematic Review

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Abstract
Background Since head and neck cancer is characterized by poor survival rates, there is a demand for novel therapeutic targets and prognostic biomarkers. An upcoming therapeutic target is the fibroblast growth factor receptor (FGFR) family. However, their prognostic role in head and neck cancer remains unclear.
Objective To systematically review current evidence on the prognostic value of FGFR family members in head and neck squamous cell carcinoma (HNSCC).
Methods A systematic search of PubMed, Embase, and the Cochrane Library was performed for publications up to 14 May 2014. Two reviewers screened all articles and included prognostic studies on the molecular biomarkers FGFR1-5 in any type of HNSCC. Relevant studies were assessed on risk of bias using the Quality in Prognostic Studies (QUIPS) tool. Data on FGFR aberrations and survival outcome were extracted from relevant studies. The prognostic value of FGFR aberrations was compared among studies.
Results The initial search yielded 1568 publications of which 12 fulfilled the inclusion criteria. Four studies reported *FGFR1* gene amplification (9.3–17.4 %) and FGFR1 protein overexpression (11.8 %) in HNSCC. FGFR1 protein expression by cancer-associated fibroblasts correlated with poor

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survival outcome in one study ($p<0.01$). Eight studies reported high rates of *FGFR4* Gly388Arg polymorphisms (32.5–54.2 %) and FGFR4 protein overexpression (16–35 %), with varying correlations with survival. So far, no studies assessed the prognostic role of FGFR2, FGFR3, or FGFR5 in HNSCC.
Limitations Significant risk of bias has been identified among included studies. Therefore, cautious interpretation of the results is recommended.
Conclusion In conclusion, evidence was found for prognostic value of FGFR1 expression in cancer-associated fibroblasts in HNSCC. Prognostic evidence on the other FGFR family members in HNSCC is limited and conflicting. This emphasizes the need for future well-conducted prognostic studies.

1 Introduction

With 350,000 deaths each year, head and neck cancer accounts for a significant part of global cancer mortality and is the sixth most common cancer worldwide, affecting more than 650,000 people each year [1]. The most common types of head and neck cancer are laryngeal, oral, and oropharyngeal cancer [2]. Although more than 95 % of these cancers are squamous cell carcinoma, clinical and molecular characteristics of these tumors are heterogeneous [3–5]. Frequently, head and neck squamous cell carcinoma (HNSCC) is detected at an advanced stage implying that the primary tumor has already metastasized to the neck. Advanced stage HNSCC is nowadays treated with varying combinations of radiation therapy, chemotherapy and surgery.

Current chemoradiation therapy regimens cause severe short- and long-term side-effects in more than 80 % of HNSCC patients [6]. Additionally, 5-year relative survival rates have slightly improved over the past three decades, but remain low at 65 %. Persisting poor survival rates of HNSCC with current treatment regimens have led to a search for novel therapeutic targets and prognostic biomarkers [6, 7]. The effort to resolve these problems has led to a quest for novel predictive and prognostic biomarkers with the intention to individualize treatment and reserve aggressive therapy for biologically aggressive tumors. As a result, molecular carcinogenesis has become a major focus of cancer research. Previous research endeavors in the pursuit of novel therapeutic targets have identified potential predictive and prognostic molecular biomarkers in HNSCC [3, 8]. One of them is the fibroblast growth factor receptor (FGFR) family [9].

FGFRs are upcoming promising therapeutic targets and possible prognostic biomarkers in multiple types of cancer, including HNSCC [9, 10]. The FGFR family comprises five (FGFR1–5) cell membrane-bound tyrosine kinase receptors linked to multiple intracellular downstream signaling pathways. FGFRs regulate tissue homeostasis in normal human tissues [11, 12]. In cancer cells, oncogenic aberrations in FGFR pathway-related genes dysregulate and constitutively activate the FGFR pathway, resulting in particular hallmark capabilities in cancer cells: to sustain proliferative signaling, resist cell death, induce angiogenesis, and activate invasion by cell migration [13–15]. These genomic aberrations include gene fusion, translocation, amplification, and somatic DNA mutations [9]. Because of their major role in cancer cell biology, FGFR family members provide promising opportunities for targeted therapies in a wide spectrum of solid tumors [9, 16, 17]. In addition, previous studies have identified a possible role of FGFRs as prognostic biomarkers, by which they could select patients for adjuvant systemic therapy [18, 19]. However, the prognostic value of FGFRs in HNSCC remains a subject of debate and has not yet been reviewed in this type of cancer. Therefore, the aim of this study was to systematically review current evidence on the prognostic value of FGFR1–5 in HNSCC and analyze it in a clinically relevant meta-analysis.

2 Materials and Methods

2.1 Eligibility Criteria and Information Sources

Studies were eligible for inclusion if they were English original articles and addressed the prognostic value of FGFRs in any type of HNSCC (i.e. overall survival, disease-specific survival, disease-free survival, recurrence-free survival, or progression-free survival). FGFR was required to be investigated as a molecular biomarker with laboratory techniques (protein expression, gene amplification, mutation, translation, polymorphism, or mRNA). Original articles were defined as primary research studies with new, unpublished results and written by the researchers who performed the study. Studies were excluded if they investigated fibroblast growth factor (FGF) instead of FGFR, had no prognostic study design, were repetitive studies on same samples, or were non-English. Also, animal studies, case reports, reviews, meta-analysis, and commentaries were excluded. A systematic search of PubMed, Embase, and the Cochrane Library was performed for publications up to 14 May 2014.

2.2 Search Strategy and Study Selection

The search terms ‘FGFR1–5’ and ‘head and neck cancer’ with all relevant synonyms were used (Online resource 1). Using predefined inclusion and exclusion criteria, two authors (NI and KL) independently screened all retrieved records on title and abstract and excluded duplicate titles to select potentially eligible articles. Subsequently, relevant articles were screened on full text, and a further selection of eligible articles was made on relevance of full text. Finally, review articles on this

topic and references of selected articles were manually screened for titles not identified by the initial search. Selection was based on consensus.

2.3 Data Collection and Data Items

Two authors independently (NI and KL) extracted all data of the selected studies using a standardized data extraction form. Discrepancies were resolved by discussion. The following information was extracted from each study: first author's name, year of publication, sample size, head and neck site, treatment, FGFR aberration investigated, type of survival outcome, patient material, laboratory techniques, statistical analysis, cut-off value (if applicable), prevalence of FGFR aberration, correlations with survival outcome, and length of follow-up.

2.4 Risk of Bias in Individual Studies

The methodological quality of the remaining eligible articles was independently assessed by two reviewers (NI and KL), using criteria of the Quality In Prognosis Studies (QUIPS) tool [20]. This tool has been evaluated in 43 groups reviewing prognostic studies and has been identified as a reliable and useful tool for systematic reviewers. Among nine review groups, inter-rater agreement statistic (kappa) varied between 0.56–0.82 [21]. According to the QUIPS tool, risk of bias was scored as low, moderate or high for the following six items; study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis, and reporting (Online resource 2). Studies scoring low risk of bias on three or more items were considered to be of 'high' methodological quality, while studies scoring high risk of bias on three or more items were considered to be of 'low' methodological quality. All other studies were of moderate quality. The use of proper positive and negative controls for laboratory techniques on FGFR and the use of well-defined scoring criteria for FGFR aberrations were also considered as methodological quality criteria. When there was disagreement on (certain items of) risk of bias of a study, two authors (NI and KL) discussed reasons for disagreement in order to mutually agree on final risk of bias score using the QUIPS tool (Online resource 2).

2.5 Synthesis of Results

Because of clinical and methodological heterogeneity of the included studies (study population, type of survival outcome, material, techniques, cut-off values, and applied statistical models), results were not quantitatively pooled. Therefore, a clinically relevant meta-analysis could not be performed. A forest plot was produced using Comprehensive Meta-Analysis Version 2.2.064 software (Biostat, Englewood, NJ, USA).

3 Results

3.1 Search and Selection

The initial search yielded 1568 unique articles (Fig. 1). One Chinese article could not be screened because no abstract or full text was available [22]. Therefore, 41 English language, full-text articles were evaluated in more detail, of which 12 original articles met our inclusion criteria. Cross-reference checking revealed no additional relevant publications. Of these 12 included articles, four determined the prognostic value of FGFR1 in HNSCC and eight determined the prognostic value of FGFR4 by laboratory techniques. Of all 12 studies, Choi et al. had the smallest study population of 24 patients [23]. Seven studies had a study population of mixed HNSCC types, and five studies had a study population of only one type of HNSCC. None of the studies included other types of cancer than HNSCC. In all studies patients were followed in time, but two did not specify the type of survival outcome measured nor the duration of follow-up. All studies accept one analyzed survival outcome using statistical methods such as Log-rank test or Cox proportional hazards model. Furthermore, repetitive studies on similar samples were not found. No articles assessed the prognostic value of FGFR2 or FGFR3 in HNSCC.

3.2 Quality Assessment

According to the QUIPS tool, the quality of included studies ranged from high to low. This was mainly because blinding of observers was absent, outcomes were not standardized, and Cox proportional hazard models to control for confounding factors were not performed (Table 1). Three studies did not use proper positive and negative controls for the laboratory techniques [19, 25, 27]. All studies used well-defined criteria for scoring FGFR aberrations. Two studies were of high quality [18, 29], four of moderate quality [19, 23, 25, 30], and six studies were of low quality [24, 26–28, 31, 32]. No studies were excluded based on methodological quality.

3.3 *FGFR1* Gene Amplification and FGFR1 Protein Overexpression as Prognostic Biomarkers

Altogether, four studies on FGFR1 included a total of 993 patients with sample sizes ranging from 61 to 555 samples. Three of them determined *FGFR1* gene copy number status and two FGFR1 protein expression (Table 2) [24–27]. Similar fluorescence in situ hybridization (FISH) and immunohistochemical (IHC) techniques were used to determine *FGFR1*

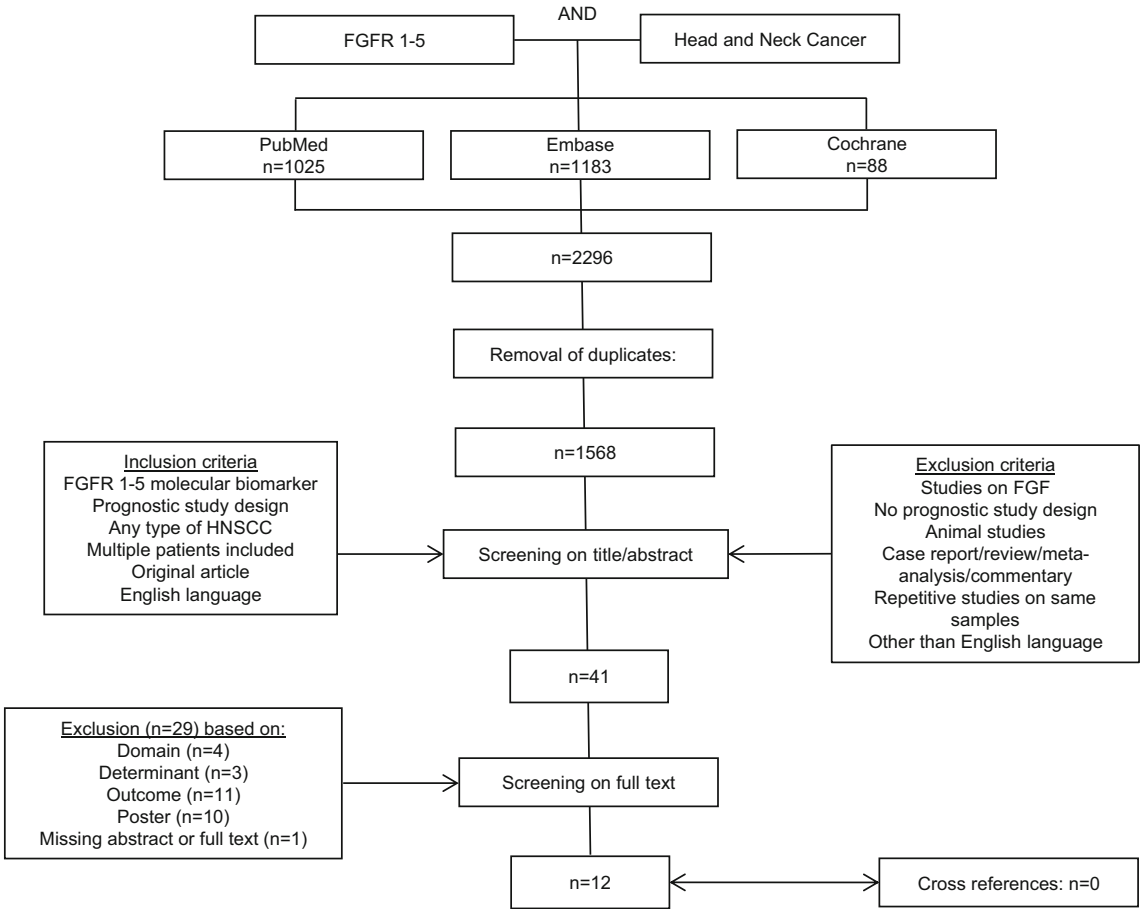

Fig. 1 Flowchart of study selection process (date of search: 14th of May, 2014). FGFR1–5, fibroblast growth factor receptor 1–5; FGF, fibroblast growth factor; HNSCC, head and neck squamous cell carcinoma

Table 1 Quality assessment of studies on the prognostic value of FGFR in HNSCC using the Quality In Prognosis Studies (QUIPS) assessment tool[a]

FGFR variant	Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
FGFR1	Göke (2013) [24]	◖	●	◖	●	●	●
	Young (2013) [25]	◖	◖	◖	○	●	●
	Freier (2007) [26]	●	◖	◖	●	●	●
	Hase (2006) [27]	◖	◖	◖	●	●	●
FGFR4	Farnebo (2013) [28]	◖	◖	○	●	●	●
	Dutra (2012) [18]	○	○	◖	○	◖	◖
	Choi (2012) [23]	◖	◖	○	○	●	●
	Azad (2012) [29]	◖	○	○	○	○	◖
	Tanuma (2010) [30]	◖	◖	○	●	◖	◖
	Ansell (2009) [31]	◖	◖	○	●	●	●
	Da Costa Andrade (2007) [19]	◖	◖	○	●	◖	◖
	Streit (2004) [32]	◖	◖	◖	●	●	●

Risk of bias: ○ = low risk; ◖ = moderate risk; ●high risk

FGFR, fibroblast growth factor receptor; FGFR1, fibroblast growth factor receptor 1; FGFR4, fibroblast growth factor receptor 4

[a] The included studies were assessed on items of methodological quality using the QUIPS assessment tool. An elaborate description of each QUIPS item is provided by Hayden et al. [20] and in Online source 2

Table 2 Characteristics of studies on the prognostic value of FGFR1 and FGFR4 in HNSCC

Study	Sample size	Head and neck site	Treatment	Prognostic biomarker	Survival outcome	Material	Technique	Statistical methods
FGFR1								
Göke (2013) [24]	555	OC, OP, HP, L, UP	S	*FGFR1* gene amplification	OS, RFS	FFPE	FISH	FE
Young (2013) [25]	107/123	Tongue	S S+ART S+ACRT CRT RT	*FGFR1* gene amplification	OS, PFS	FFPE	FISH	LR
Freier (2007) [26]	92/178	OC	?	*FGFR1* gene amplification FGFR1 protein expression	OS	FFPE	FISH IHC	LR
Hase (2006) [27]	61	OC	?	FGFR1 protein expression	Survival NOS	FFPE	IHC	LR
FGFR4								
Farnebo (2013) [28]	40	OC, HP, L	S+ART S+ACRT RT RT+S	*FGFR4* Gly388Arg SNP	OS	FS	PCR-RFLP	LR
Dutra (2012) [18]	125	OC, OP	S S+ART	*FGFR4* Gly388Arg SNP FGFR4 protein expression	DFS, DSS	PB FFPE	PCR-RFLP IHC	Wilcoxon signed-rank test, CPH
Choi (2012) [23]	24	OC	S S+ANOS	*FGFR4* Gly388Arg SNP	OS, DSS	FTT	PCR	LR
Azad (2012) [29]	531	OC, OP, HP, P, L	S S+ART	*FGFR4* Gly388Arg SNP	OS, DFS	PB	PCR	CPH
Tanuma (2010) [30]	150	OC	S	*FGFR4* Gly388Arg SNP	Survival NOS	PB FTT FFPE	PCR	LR, CPH
Ansell (2009) [31]	110	OC, P, L	S RT RT+S NT	*FGFR4* Gly388Arg SNP	OS	Cell lines FS	PCR-RFLP	LR
Da Costa Andrade (2007) [19]	75	HN NOS	S S+ART S+ACRT	*FGFR4* Gly388Arg SNP	OS	FFPE	PCR-RFLP	LR, CPH
Streit (2004) [32]	104	OC, OP	S	*FGFR4* Gly388Arg SNP FGFR4 protein expression	OS	FFPE	IHC PCR-RFLP	LR

?, not mentioned; ACRT, adjuvant chemoradiotherapy; ANOS, adjuvant therapy not otherwise specified; ART, adjuvant radiotherapy; CPH, Cox proportional hazards model; CRT, chemoradiotherapy; DFS, disease-free survival; DSS, disease-specific survival; FE, Fisher's exact test; FFPE, formalin-fixed and paraffin-embedded; FGFR, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; FS, frozen section; FTT, fresh tumor tissue; HN, head and neck; HP, hypopharynx; IHC, immunohistochemistry; L, larynx; LR, log-rank test; NA, not applicable; NOS, not otherwise specified; NT, no treatment; OC, oral cavity; OP, oropharynx; OS, overall survival; P, pharynx; PB, peripheral blood; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; PFS, progression-free survival; RFS, recurrence-free survival; RT, radiotherapy; S, surgery; SNP, single nucleotide polymorphism; UP, unknown primary

copy number changes and FGFR1 protein expression. Cut-off values for FGFR1 protein overexpression as well as *FGFR1* gene amplification varied among these studies (Table 3). In addition, different outcome measures, such as overall survival, progression-free survival, recurrence-free survival, and survival outcome not specified, were used in these studies. None used multivariable Cox proportional hazard models to control for confounding factors.

A high prevalence of *FGFR1* gene amplification (9.3–17.4 %) was found in HNSCC, and a high prevalence FGFR1 protein overexpression was found in oral SCC (11.8 %; Table 3) [24–27]. *FGFR1* gene amplification and FGFR1 protein expression in HNSCC were not significantly correlated to any measure of survival [24–26]. Overall survival and progression-free survival hazard ratios for FGFR1 amplification versus normal copy number pointed in the same direction (overall survival: HR=0.94; 95 % CI=0.37–2.39; progression-free survival: HR=0.79; 95 % CI=0.24–2.58; Fig. 2) [25]. However, one study found a significantly worse survival for FGFR1 protein expression in cancer-associated fibroblasts ($p<0.01$) [27].

3.4 *FGFR4* Gly388Arg Polymorphism and FGFR4 Protein Overexpression as Prognostic Biomarkers

Eight studies investigated the relationship between *FGFR4* Gly388Arg polymorphism and survival in HNSCC; two of them also determined FGFR4 protein expression in relation to survival (Table 2) [18, 19, 23, 28–32]. In total, these studies included 1159 patients with sample sizes ranging from 24 to 531. Study population, head and neck regions, materials and techniques, cut-off values to define protein overexpression, survival outcome measures, and length of follow-up varied considerably among all studies. Regarding statistical analysis, only four studies used a Cox proportional hazards model to control for confounding factors.

Overall, a high prevalence of the *FGFR4* Gly388Arg polymorphism (32.5-54.2 %) was found in HNSCC (Table 3). The Arg/Arg genotype occurred in fewer HNSCC cases (5–15.3 %), whereas wild type (Gly/Gly) occurred more frequently (37.5–67.5 %). Comparing overall survival outcome for the *FGFR4* Gly388Arg polymorphism, studies reported longer, equivalent, and even shorter survival rates [19, 23, 28–31]. One study found worse disease-specific survival while another study found no relationship with survival [18, 23]. Regarding disease-free survival, two studies reported no significant correlation with the *FGFR4* Gly388Arg polymorphism [18, 29]. Overall survival and progression-free survival hazard ratios for the *FGFR4* Arg388 allele pointed in opposite directions among different studies (Fig. 2). Because of non-symmetric lower and upper limit log values, findings on the *FGFR4* polymorphism found by Tanuma et al. could not be illustrated in the forest plot [30]. FGFR4 protein overexpression was related to worse overall survival in one study and to worse disease-free survival and disease-specific survival in another study [18, 32]. Other studies did not investigate the relation of FGFR4 protein expression to survival.

4 Discussion

During the past decade, multiple molecular biomarkers which play a role in tumor growth and metastatic spread have been identified. Molecular carcinogenesis has become a major field of cancer research and is driven by the need for novel targetable and prognostic molecular biomarkers. Among these are the FGFR family members [9]. There is increasing evidence for the therapeutic role of FGFRs in HNSCC, but their prognostic role remained unclear.

Herein, we present the first systematic review of currently available evidence on the prognostic value of FGFRs in HNSCC. All included articles were critically appraised using the QUIPS tool items [20]. Studies addressed the prognostic value of FGFR1 gene amplification, FGFR1 protein expression, FGFR4 genotype, and FGFR4 protein expression in 1870 HNSCC cases of various sites, including oral, oropharyngeal, hypopharyngeal, and laryngeal SCC. To date, 12 studies focused on the prognostic value of FGFRs in HNSCC [18, 19, 23–32]. While our extensive search retrieved multiple articles reporting on FGFR2 and FGFR3 in HNSCC, none of these studies assessed their prognostic value [33–39]. Therefore, only FGFR1 and FGFR4 could be assessed as prognostic biomarkers in HNSCC.

Current evidence suggests that *FGFR1* gene amplification and protein overexpression are not prognostic biomarkers of value in HNSCC. However, in one study, FGFR1 protein expression in cancer-associated fibroblasts of HNSCC was a prognostic biomarker which should be validated in a larger cohort [27]. Interestingly, evidence on the prognostic value of the *FGFR4* Gly388Arg polymorphism was conflicting [18, 19, 23, 28–32]. This could possibly be explained by differences in duration of follow-up time among studies with positive and negative results. In one study, differences in overall survival only occurred after 24 months of follow-up, while two out of three studies with negative results had a follow-up period of less than three years [23, 31, 32]. This in contrast to positive results in the other four studies with a follow-up time of more than 3 years [18, 19, 28, 30]. Remarkably, studies with statistically significant survival results used FFPE tissues, while studies without significant results used DNA from either fresh frozen tumor tissue, peripheral blood, or cell lines [18, 19, 23, 28–32]. Perhaps the

Table 3 Results of studies on the prognostic value of FGFR1 and FGFR4 in HNSCC patients

Study	Technique	Cut-off value		Prevalence		Survival		Follow-up (months)
		Definition	Value	Outcome	% (value)	Outcome	Value	
FGFR1								
Göke (2013) [24]	FISH	Nuclei amplified	≥20 %	Amplification	15 (68/452)	OS	p=0.71	Median: 26
		High level	> 9 signals			RFS	p=0.9	Median: 28
		Low level	2–9 signals					
Young (2013) [25]	FISH	Nuclei displaying>5 FGFR1 signals or FGFR1/chromosome 8 ratio>2	> 50 %	Amplification	9 (10/107)	OS	HR=0.94 95 % CI=0.37–2.39 p=0.90	Median: 61
						PFS	HR=0.79 95 % CI=0.24–2.58 p=0.70	
Freier (2007) [26]	FISH	Cells displaying> 6 signals	≥ 10 %	Amplification	17 (16/92)	OS	p>0.05	?
	IHC	High	Increased	High expression	12 (21/178)	OS	p>0.05	
		Not altered	Equal	Not altered	57 (102/178)			
		Low	Decreased or absent	Low expression	31 (55/178)			
Hase (2006) [27]	IHC	Positive	Complete or partial	Tumor cell expression	100 (61/61)			
				Fibroblast expression	67 (41/61)	NOS	p<0.01	?
FGFR4								
Farnebo (2013) [28]	PCR-RFLP	NA	NA	Wildtype Gly/Gly	68 (27/40)	OS	p=0.010	Mean: 30 Max: 76
				388Arg allele	32 (13/40)			
Dutra (2012) [18]	PCR-RFLP			Gly/Gly	54 (66/122)	DFS	HR=1.77 95 % CI=0.85–3.67 p=0.124	Min: 48
				Gly/Arg	39 (47/122)	DSS	HR=3.26 95 % CI=1.40–7.58 p=0.006	
				Arg/Arg	7 (9/122)			
	IHC	High	> 7	High expression	35 (26/75)	DFS	HR=3.26 95 % CI=1.44–7.37 p=0.005	
		Low	> 3 and<7	Low expression	65 (49/75)	DSS	HR=3.26 95 % CI=1.21–8.74 p=0.019	
		Negative	≤ 3	Negative	0 (0/75)			
	Risk profile	High	Low expression and 388Arg allele	High risk profile	24 (17/71)	DFS	HR=4.50 95 % CI=1.37–14.82 p=0.002	
		Intermediate	High expression and 388Arg allele *or* low expression and	Intermediate risk profile	61 (43/71)	DSS	HR=12.90 95 % CI=1.54–107.69 p<0.001	

Table 3 (continued)

Study	Technique	Cut-off value		Prevalence		Survival		Follow-up (months)
		Definition	Value	Outcome	% (value)	Outcome	Value	
			absence of 388 Arg allele					
		Low	High expression and absence of 388Arg allele	Low risk profile	15 (11/71)			
Choi (2012) [23]	PCR	NA	NA	Gly/Gly	38 (9/24)	OS	p=0.735	Median: 15 Range: 2–23
				Gly/Arg	54 (13/24)	DSS	p=0.848	
				Arg/Arg	8 (2/24)			
Azad (2012) [29]	PCR	NA	NA	Wild type Gly/Gly	61 (321/531)	OS	HR=0.90 95 % CI=0.72–1.13 p=0.37	Median: 110
				388Arg allele	39 (210/531)	DFS	HR=0.89 95 % CI=0.71–1.12 p=0.33	Median: 64
Tanuma (2010) [30]	PCR	NA	NA	Gly/Gly	46 (69/150)			60
				Gly/Arg	39 (58/150)	NOS	HR=1.15 95 % CI=0.58–2.49 p=0.048	
				Arg/Arg	15 (23/150)	NOS	HR=1.43 95 % CI=1.15–3.01 p=0.025	
Ansell (2009) [31]	PCR-RFLP	NA	NA	Wildtype Gly/Gly	56 (61/110)	OS	NS	Mean: 16 Range: 0–53
				388Arg allele	44 (49/110)			
Da Costa Andrade (2007) [19]	PCR-RFLP	NA	NA	Gly/Gly	56 (42/75)	OS	RR=2.18 95 % CI=1.05–4.55 p=0.037	Median: 36 Range: 0.4–76
				Gly/Arg	36 (27/75)			
				Arg/Arg	5 (4/75)			
Streit (2004) [32]	PCR-RFLP	NA	NA	Gly/Gly	43 (45/104)	OS	p>0.05	Median: 39
				Gly/Arg	43 (45/104)			
				Arg/Arg	13 (14/104)			
	IHC	High	No specification	High expression	16 (17/104)	OS	p>0.05	
		Intermediate		Intermediate expression	57 (59/104)			
		Low		Low expression	27 (28/104)			
			High FGFR4 expression and 388Arg allele	High risk profile			p=0.032	

, not significant; ?, unclear or not mentioned; 95 % CI, 95 % confidence interval; DFS, disease-free survival; FGFR, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, immunohistochemistry; NA, not applicable; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; RR, relative risk

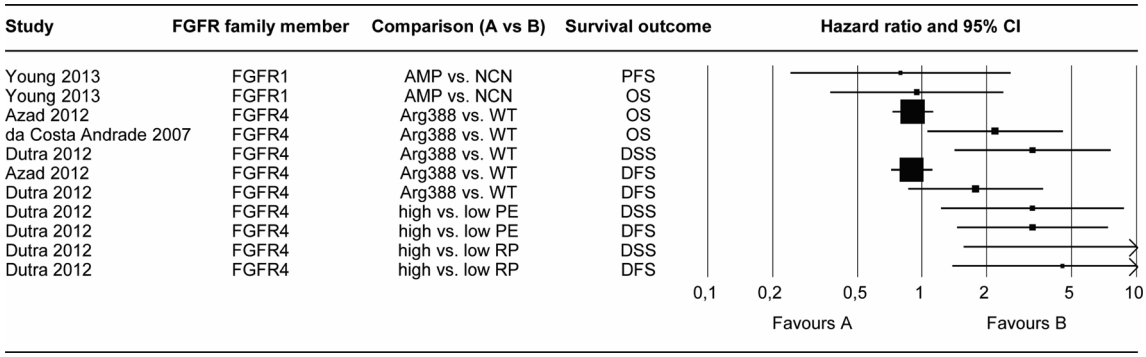

Fig. 2 Forest plot of HNSCC survival grouped by FGFR family member and comparison. AMP, amplification; Arg388, FGFR4 Arg388 allele; CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; FGFR, fibroblast growth factor receptor; HR, hazard ratio; NCN, normal copy number; NOS, not otherwise specified; OS, overall survival; PE, protein expression; PFS, progression-free survival; RP, risk profile; WT, wild type. Hazard ratios are illustrated as squared boxes and corresponding 95 % confidence intervals are illustrated as error bars

type of study material may influence the PCR techniques used to detect the *FGFR4* Gly388Arg polymorphism. Differences in tumor localization of HNSCC might explain the conflicting results on DFS related to the *FGFR4* Gly388Arg polymorphism found by Azad et al and Dutra et al [18, 29]. Azad et al also included hypopharyngeal and laryngeal tumors besides oral and oropharyngeal tumors. HNSCC from different anatomical locations show different clinical and molecular characteristics and are acknowledged as different entities. As such, tumor localization might affect patient outcome. Other differences in study populations or patient treatment could not explain the conflicting results. However, none of the studies were non-randomized controlled trials.

The prognostic value of FGFR has been investigated in numerous other types of cancer. Our findings are in agreement with studies on other types of cancer that also showed conflicting results. For example, studies on *FGFR1* gene amplification and *FGFR4* Gly388Arg polymorphism in lung SCC [40–46] and breast cancer [47–49] reported conflicting results on overall survival and disease-free survival. Only studies on *FGFR3* mutations in bladder cancer are in agreement with each other; nearly all studies found correlations with better progression-free survival and disease-specific survival [50]. For all other FGFRs in cancer, evidence on their prognostic value is limited or absent and therefore inconclusive, which is similar to HNSCC.

This review focusses on the prognostic value of FGFR aberrations in HNSCC. These prognostic associations do not necessarily predict the response to FGFR-inhibitor therapy as the latter is mainly, yet exclusively, predicted by the underlying aberration itself. For example, previous clinical studies in breast and lung cancer showed that FGFR-inhibitor therapies were only effective in FGFR-amplified or FGFR-mutated tumors [51, 52]. The *FGFR* genes are frequently aberrated in HNSCC, *FGFR1* is amplified in 10 % of HPV-negative HNSCC and *FGFR3* is aberrated in 11 % of HPV-positive HNSCC [53]. As such, HNSCC patients with *FGFR*-aberrated tumors may benefit from FGFR-inhibitor therapies as these tumors may be sensitive. In addition, targeting FGFR family members has shown to enhance radiotherapy and chemotherapy sensitivity of cancer cells. Radiotherapy resistant cancer cells upregulate FGFR3 protein and chemoradiotherapy resistant cancer cells upregulate FGFR4 protein. Targeting FGFR3 in resistant HNSCC cells restored sensitivity to radiotherapy and targeting FGFR4 restored sensitivity to chemoradiotherapy [54–56].

The probative value of the present review depends on methodological quality of included studies to some extent. All included studies have their specific strengths but the methodological quality is questionable in many. Poor description of study populations and incomplete data in two studies might have introduced selection bias [24, 25]. Six studies had a mean/median follow-up time less than three years [23, 24, 26–28, 31]. Risk of information bias is present in all included studies as none of them provided information on blinding of investigators for the current vital status of patients. Survival rate was only standardized in one study [25]. In all other studies, the definition and assessment of the specific survival outcomes were unclear. Some articles have relatively low sample sizes and did not use multivariable statistical methods, such as multivariable Cox proportional hazard models. Because of risk of bias among included studies, cautious interpretation of results is recommended.

5 Conclusion

In conclusion, high quality evidence regarding the prognostic role of FGFR in HNSCC patients is largely lacking. Current

evidence on FGFR1 in HNSCC is limited to only very few studies. This limited evidence suggests that *FGFR1* gene amplification and FGFR1 protein expression are not of value as prognostic biomarkers in HNSCC. However, FGFR1 protein expression in HNSCC-related fibroblasts holds promising prognostic value, but evidence is too limited to draw conclusions yet. The evidence on *FGFR4* Gly388Arg polymorphisms in HNSCC is conflicting and inconclusive. FGFR4 protein overexpression may serve as a prognostic biomarker, but evidence is also too limited to draw conclusions yet. Future research should determine the prognostic value of FGFR1-5 in HNSCC and clarify conflicting results concerning the FGFR4 Gly388Arg polymorphism in HNSCC.

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