Appendix 3: Study of prognostic value of cytokines expression in cancer tissue

Cytokine (no. of studies)	Study author	Description of Effect						
		OS			PFS			cut off value
		effect	univariat	Multivariate	effect	univariat	multivariat	
VEGF (25)	Zhang et al., 2003	NS	NS	NS	VEGF overexpression (above median) was associated with significantly shorter DFI	(P 0.003).	NS	
	Ogawa et al., 2001	NS	NS	NS	positive VEGF was significantly associated with better PFS in stage I diseases, but not in stage III-IV diseases	p 0.005 (stage I-II), p = 0.767 (stage III-IV)	NS	
	Shen et al., 2000	The OS of patients with high VEGF expression (score >3) was significantly worse than that of patients with low and negative VEGF expression	p = 0.0004	p= 0.006	NS	NS	NS	
	Kuerti et al., 2017	The shorter OS is significantly associated with high VEGF-C expression	HR 2.02, (1.12-3.63) p=0.019	NS	There is no stastictically significant association between PFS and high VEGF-C expression	HR 1.44 (0.89-2.31) p=0.13	NS	

					compared to low expression			
	Masoumi-Moghaddam et al., 2015	high VEGF expression were associated with prolonged OS	HR = 0.46; 95% CI, 0.27-0.77; p:0.003)	(HR = 0.46; 95% CI, 0.27-0.79; p:0.005)	High VEGF- was not significantly associated with PFS	p = 0.512	NS	cut off point was INC score of 3.5 (using Classification and Regression Tree, CART algorithm)
	Duncan et al., 2008	higher VEGF expression were associated with shortened OS	HR = 1.59 (1.02-2.49) p =0.04	HR 1.78 (1.08-2.94) p = 0.023	NS	NS	NS	
	Li et al., 2009	positive VEGF-D expression were associated with shortened OS compared to negative VEGF expression	HR 105.424 (16.673–666.602) P<0.001	HR 24.721(2.172–281.347) P=0.01	positive VEGF-D expression were associated with shortened DFS compared to negative VEGF expression	HR 124.603 (16.305–952.221) P<0.001	HR 12.537 (1.247–126.052) P=0.032	
	Smerdel et al., 2009	high VEGF expression were associated with shortened OS compared to low VEGF expression	p=0.052	HR 2.205 (1.188-4.09) p 0.012	NS			
	Engels et al., 2009	positive VEGF-A expression were not significantly associated with prolonged OS	p=0.2251	0.612 (0.314 - 1.194) P 0.15	positive higher VEGF-A expression were associated with prolonged PFS	p=0.046	0.537 (0.291-0.992) P 0.047	
	Hata et al., 2011	higher VEGF expression were associated with shortened OS but not statistically significant	HR 1.198 (0.671-2.137) p 0.541 for all patients, HR 1.729 (95%CI 0.927 - 3.227) p 0.085 fpr stage III-IV	NS	NS	NS	NS	cut off value of 0.147 gene expression level was based on median value of gene expression

	van der Bilt et al., 2012	positve VEGF in tissue were not significantly associated with OS compared to negative VEGF	VEGF A HR 1.21 (0.59-2.48) p = NS VEGF B HR 0.11 (0.02.0.81) p= 0.03 . VEGF C HR 0.59 (0.40-0.87) p=0.01. VEGF D HR 0.65 (0.46-0.94) p= 0.02	VEGF B HR 0.19 (0.03-1.39) p = NS VEGF C HR 0.86 (0.54-1.37) p= NS VEGF D HR 0.86 (0.56-1.32) p= NS	positive VEGF expression in tissue were not significantly associated with PFS compred to negative VEGF	VEGF A HR 0.81 (047-1.42) p = NS VEGF B HR 0.10 (0.01.0.69) p= 0.02 . VEGF C HR 0.64 (0.44-0.91) p=0.01. VEGF D HR 0.73 (0.52-1.03) p= NS	VEGF B HR 0.15 (0.02-1.07) p = NS VEGF C HR 0.95 (0.64-1.42) p= NS	
	Huang et al. ,2011	positive VEGF-C expression were associated with shortened OS	HR= 6.198 (3.946-9.735) p<0.0001	HR 5.170 (3.035 - 8.807) P<0.0001	NS			
	Williams et al., 2012	higher VEGF expression (>100) were associated with shortened OS	log rank 7.5, p=0.006, 95 %CI 31.7-54.3	NS	VEGF expression in tissue were not significantly associated with PFS	p= 0.085 (combination with CA9)	NS	
	Chen et al., 2012	VEGF expression in tissue were not significantly associated with OS	p= 0.000	HR 0.709 (95% CI, 0.426-1.179), p 0.185	VEGF expression in tissue were not significantly associated with PFS	p 0.163	NS	
	Skirnisdottir et al., 2016	NS	NS	NS	VEGF-A expression in tissue were not significantly associated with DFS	HR 0.943 (0.427-2.083)	HR 1.404 (0.597-3.303) , p value = 0.436	
	Kassim et al., 2003	higher VEGF >120 pg/mg were associated with shortened OS	p= 0.023 (F = 5.45)	RR 5.6 p 0.02 Log rank 8.4	NS			Cut off value of 120 pg/mL was used to maximising the sum of sensitivity (835) and specificity (83.3%)

	Nishida et al., 2004	high expression of VEGF C and VEGF R2 was associated with shorter OS. High expression of VEGF A and VEGF R3 were not significantly associated with shorter OS.	VEGF A p= 0.46. VEGF C p = 0.0018, VEGF-R2 p= 0.019, VEGF R3 p= 0.99		high expression of VEGF A was associated with shorter PFS. High expression of VEGF C, VEGF R2 and VEGF R3 were not significantly associated with shorter PFS	VGEF A p= 0.47. VEGF C p = 0.25, VEGF R2 p= 0.0002, VEGF R3 p= 0.054	VEGF A OR 7.16 (1.719–29.826) p = 0.007. VEGF C OR 1.76 (0.531–5.843) p = 0.36, VEGF R2 OR 0.33 (0.068-1.593) p=0.17, VEGF R3 OR 0.22 (0.044 - 1.130) p=0.84	
	Raspollini et al., 2004	positive VEGF expression were associated with shortened OS	p<0.0001	HR 1.91 1.07—3.41 P 0.027	positive VEGF expression were associated with shortened OS and DFI	P=0.0033	HR 0.23 (0.78_2.67) p= 0.23	
	Yokoyama et al., 2003	Positive VEGF D were associated with reduced 10 years survival rates (carcinoma-specific survival). Positive VEGF C and VEGFR3 were not significantly associated with reduced 10 years survival rates.	VEGF D P<0.002. VEGF C P<0.046	VEGF D relative risk: 8.2, 95% CI: 2.33–83.33 P 0.004. VEGF C RR 2.7 (0.72-37.51) p 0.101	NS	NS	NS	
	Brustmann et al., 2003	NS	NS	NS	strong VEGF expression were associated with shortened DFS	P = 0.0052	NS	

	Rudlowsky et al., 2006	Serum VEGF levels were not correlated with OS	p= 0.09	NS	NS	NS	NS	
	Liu et al., 2012	strong VEGF expression were associated with prolonged OS	p= 0.048					
	O'Toole et al., 2006	higher VEGF expression were associated with shortened OS	p<0.0001	p<0.0001	higher VEGF expression were associated with shortened DFS	p<0.0001	p <0.05	
	Siddiqui et al., 2011	higher VEGF expression (score >3) were associated with poor OS	P <0.01	P <0.0001				score 3 was used as a cutoff
IL-6	Masoumi-Moghaddam et al., 2015	high VEGF expression had better mean and median value of OS but not significant	p = 0.646	NS	high VEGF expression had better mean and median value of DFS but not significant	p= 0.301		
TGF-α	D'Antonio et.al., 2002	NS	NS	NS	positive expression of TGF-α was correlated with better PFS	p = 0.04	p=0.002	
CSF-1	Chamber et al., 1997	expression of CSF-1 receptor and epithelial CSF-1 in metastatic lession of invasive stage III tumor were correlated to poorer DFS but this result was not significant		RR 1.82, p 0.062	expression of CSF-1 receptor and epithelial CSF-1 n metastatic lession of invasive stage III tumor were correlated to poorer DFS	NS	RR 2.31, p 0.007	
IL-10	Liu et al., 2012	IL-10 expression was not correlated to OS	p = 0.548	NS	NS	NS	NS	
TGF-β1	Liu et al., 2012	High TGF-β1 expression was correlated with poorer OS	p = 0.001	NS		NS	NS	cut off value was A= 0.358 based on log rank tets

IL-17	Droeser et al, 2013	positive IL-17 expression showed beteer OS but this result as not significant	p=0.05	NS	IL-17 expression had positive prognostic effect on RFS	0.01	NS	