

Appendix 2: Study of prognostic value of cytokines level in serum

Cytokine and no. of studies	Study author	Prognostic value						cut off
		OS			PFS			
		effect	univariat analysis	multivariat analysis	effect	univariat analysis	multivariat analysis	
VEGF (12)	Hefler et al., 2006	higher serum VEGF were associated with a shortened OS. In stage I diseases, serum VEGF ≥ 380 pg/mL had an OR 8.2 (1.6 - 42.2, CI 95%) for experiencing cancer related death	p 0.001	1.8 (1.2–2.8) p 0.03	NS			cut off value of 380 pg/mL was based on previous study
	Harlozinska et al., 2004	higher serum VEGF (>750 pg/mL) was associated to shortened OS		OS: RR 2.35 (1.14 -4.84) p 0.0202	NS			cut off value based was on 95% percentile of reference group: 750 pg/mL
	Dobrzycka et al., 2015	higher VEGF was associated with poorer OS	HR 2.111 (1.188-4.943)	HR 2.340 (1.186–4.643)	higher VEGF was associated with poorer DFS	HR 2.189 (1.284-3.136)	HR 2.648 (1.142–3.663)	cut off value was based on median level of VEGF
			p <0.001	p <0.001		p <0.001	p <0.001	

Cooper et al., 2002	higher serum VEGF ≥ 380 pg/mL were associated with shortened OS	HR 2.13 (1.19-3.79)	HR 2.08 (1.10-3.95)	NS			cut off value of 380 pg/mL was used as this was the level to maximized the estimated hazard ratio
		p =0.009	p 0.002				
Chen et al., 1999	higher serum VEGF were associated with shortened OS		RR 4.47 (1.98-10.07)	higher serum VEGF were associated with shortened DFS		RR 3.34 (1.58-7.09)	(cut off level: 75% quartile)
		p = 0,001	p 0.001		p= 0.001	p 0.002	
Cheng et al., 2013	higher serum VEGF -C ≥ 10200 pg/mL were associated with shortened OS	p <0.0001	1.256-5.501 , p 0.01	NS	NS	NS	cut off level of ≥ 10200 pg/mL was based on median level of VEGFC
Liang et al., 2013	higher serum VEGF -C ≥ 9470 pg/mL were associated with shortened OS	P 0.001	HR 1.145-1.896 p= 0.025	NS	NS	NS	cut off level of ≥ 9470 pg/mL was based on median level of VEGFC
Sallinen et al., 2014	higher serum VEGF >0.43 ng/mL were associated with shortened OS	HR=2.6 (95%CI 1.390-4.745) p = 0.002	NS	higher serum VEGF were associated with shortened RFS	RFS(recurrence free survival) HR=2.1 (95% CI 1.98-3.846), p= 0.019	NS	cut off value of 0.43 ng/mL was based on median value

	Mahner et al., 2010	Poorer OS was associated significantly with higher VEGF-165 serum level after CTX, but not before surgery, before CTXm and during CTX	p = 0.302 (before surgery), 0.230 (before CTX), 0.496 (during CTX), and 0.023 (after CTX)	NS	Poorer PFS was associated significantly with higher VEGF-165 serum level before CTX and after CTX, but not before surgery and during CTX	p = 0.352 (before surgery), 0.043 (before CTX), 0.946 (during CTX), and 0.006 (after CTX)	NS	cut off level was defined using median value of each serum VEGF level: before surgery 171 pg/mL, after surgery 272 pg/mL, during CTX 139 pg/mL, after CTX 147 pg/mL
IL 6 (4)	Lambeck et al., 2007	higher serum IL-6 > 15.0 pg/mL were associated with shortened OS	HR 2.13 (1.39 - 3.27) p = 0.001	NS	higher serum IL-6 > 15.0 pg/mL were associated with shortened PFS	HR 1.91(1.25 - 2.93) p<0.001	NS	cut off level of 15 pg/mL pg/mL was based on median level of IL-6
	Matsuo et al., 2015 (PLASMA)	NS	NS	NS	higher IL-6 level \geq 10 pg/mL was not significantly associated with lower 2-year PFS rate	HR 1.40, 95%CI 0.97–2.03, P = 0.07).	NS	cut off value determination was not described
	Kumar et al., 2017	Serum IL-6 \geq 24 pg/mL was not significantly associated with 6 months and 12 months OS	p=0.57 (12 months) p= 0.14 (6 months)	NS	NS	NS	NS	cut off value of 24 pg/mL was based on previous study
	Tempfer et al., 1996	elevated serum IL-6 \geq 0.7 pg/mL before therapy were significantly correlated to poorer OS	P < 0.01	NS	elevated serum IL-6 \geq 0.7 pg/mL before therapy were significantly correlated to poorer DSF	P< 0.003	NS	cut off value of 0.7 pg/mL was based on 95% percentiles of control groups

	Scambia, 1995	OS was shorter for patient with higher level of IL-6	p = 0.009	p = 0.0081	NS	NS	NS	cut off value of 6 pg/mL was based on >95 percentile
IL-8	Aune, 2012	Serum IL-8 \geq 59 pg/mL was associated with poorer OS	p 0.007, HR 1.006 (95% CI 1.002 - 1.010)	p 0.029, HR 1.004 (95% CI 1.000 - 1.009)	NS	NS	NS	cut off value of 59 pg/mL was based on 2SD above the median value (previous study)