Hematologic toxicity in anal cancer patients during combined chemo-radiation: a radiation oncologist perspective

Table 1. Acute hematologic toxicity in phase III randomized trials of anal cancer patients

Author	Year	Randomization	Pts	CHT	RT technique	Boost strategy	HT scoring scale	≥G3 HT
Flam et al.	1996	RT-CHT	145	5-FU	AP/PA	Sequential	NCI	G4-G5:
RTOG 8704/ECOG 1289		vs.						3%
		RT-CHT	146	5-FU/MMC				vs.
								18%
UKCCCR	1996	RT alone	290	None	AP/PA	Sequential	NA	No grading available
ACT I		vs.						WBC < 1,000/ul
		RT-CHT	295	5-FU/MMC	Boost: electrons, photons,			0% (RT) vs. 2% (RT-CHT)
					^{192}Ir implants			Plt< 25,000/µl
								0% (RT) vs. 2% (RT-CHT)
Bartelink et al.	1997	RT alone	52	None	AP/PA	Sequential	WHO	NA
EORTC 22861		vs.						
		RT-CHT	51	5-FU/MMC	Boost: electrons, photons,			
					^{192}Ir implants			
Ajani et al.	2008	RT-CHT	341	5-FU/MMC	AP/PA	Sequential	CTCAE v2.0	Overall:
RTOG 98-11		vs.			AP/PA + paired laterals			61%
		RT-CHT	341	5-FU/DDP	PA + laterals			vs.
					Direct perineal boost:			42%
					electrons, photons			
Peiffert et al.	2012	ICHT + RT-CHT (standard boost)	75	5-FU/DDP	AP/PA	Sequential	CTCAE v3.0	Overall:
ACCORD 03		vs.						
		ICHT + RT-CHT (intensified boost)	75	5-FU/DDP	Four-field box technique			29% (ICT arms)
		vs.						vs.
		RT-CHT (standard boost)	82	5-FU/DDP	Boost: electrons, photons,			19% (RT-CT arms)
		vs.			^{192}Ir implants			
		RT-CHT (intensified boost)	75	5-FU/DDP				
James et al.	2013	RT-CHT	246	5-FU/MMC	Four-field box technique	Sequential	CTCAE v3.0	Overall:
ACT II		vs.						
		RT-CHT	246	5-FU/DDP	Boost: 3DCRT			MMC group: 26%
		vs.						vs.

Author	Year	Randomization	Pts	CHT	RT technique	Boost strategy	HT scoring scale	≥G3 HT
		RT-CHT + maintenance CT	226	5-FU/MMC + 5FU/DDP				DDP group: 16%
		vs.						
		RT-CHT + maintenance CT	222	5-FU/DDP + 5FU/DDP				

pts: patients; CHT: chemotherapy; RT: radiotherapy; HT: hematologic toxicity; ICHT: induction chemotherapy; 5-FU: 5-fluorouracil; MMC: mytomicin C; DDP: cisplatin; AP/PA: anterior–posterior/posterior–anterior; ^{192}Ir: iriudium 192; 3DCRT: 3-dimensional conformal radiotherapy; NA: not available; NCI: National Cancer Institute; WHO: World Health Organization; CTCAE: Common Terminology Criteria for Adverse Effects; WBC: white blood cells; Plt: platelets; µl: microliter.

Table 2. Acute hematologic toxicity in IMRT series of anal cancer patients

Author	Year	Pts	IMRT technique	Boost strategy	BM opt	CHT	HT scoring scale	G3-G4 HT
Milano et al.	2005	17	Stating angle	Sequential	Yes (iliac BM)	5-FU/MMC	RTOG	Overall: 53%
			7-field class solution			5-FU		Leukopenia: 47%
								Thrombocytopenia: 18%
								Anemia: 12%
Salama et al.	2007	53	Static angle	Sequential	No	5-FU/MMC	CTCAE v 3.0	Leukopenia: 53%
			9-field class solution	SIB		5-FU/DDP		Thrombocytopenia: 28%
						5-FU		Anemia: 9%
Pepek et al	2010	47	NA	Sequential	Yes (iliac BM)	5-FU/MMC	CTCAE v 3.0	Overall: 24%
						Cape/MMC		Leukopenia: 24%
						Cape		Thrombocytopenia: 3%
								Anemia: 3%
Bazan et al.	2011	29	Static angle	Sequential	NA	5-FU/MMC	CTCAE v 3.0	Overall: 21%
						Cape/MMC		
						5-FU/DDP		
Vieillot et al.	2012	72	Static angle	Sequential	Yes (iliac BM)	5-FU/MMC	CTCAE v 3.0	Overall: 25%
			5–7 field class solution			5-FU/DDP		Neutropenia: 21%
								Thrombocytopenia: 9%
								Anemia: 6%
DeFoe et al.	2012	78	Static angle	Sequential	Yes (pelvic bones)	5-FU/MMC	CTCAE v 3.0	Overall: 43%
			5–9 field class solution			5-FU/DDP		Leukopenia: 36%
						Cape		Neutropenia: 39%
								Thrombocytopenia: 12%
								Anemia: 4%
Kachnic et al.	2012	43	Static angle	SIB	Yes (iliac BM)	5-FU/MMC	CTCAE v 3.0	Overall: 61%
			8–10 field class solution			5-FU/DDP		
						5-FU		
Kachnic et al.	2013	52	NA	SIB	Yes (iliac BM)	5-FU/MMC	CTCAE v 3.0	Overall: 58%
RTOG 0529								
Chuong et al.	2013	52	NA	Sequential	No	5-FU/MMC	CTCAE v 4.0	Leukopenia: 30%
				SIB		5-FU/DDP		Thrombocytopenia: 21%
								Anemia: 13%

Author	Year	Pts	IMRT technique	Boost strategy	BM opt	CHT	HT scoring scale	G3-G4 HT
Belgioia et al.	2015	41	Helical tomotherapy	SIB	Yes (pelvic bones)	5-FU/MMC	CTCAE v 3.0	Overall: 7%
						Cape		
Franco et al.	2016	39	VMAT	SIB	No	5-FU/MMC	CTCAE v 3.0	Leukopenia: 36%
								Neutropenia: 31%
								Thrombocytopenia: 13%
								Anemia: 0%
Call et al.	2016	152	Static angle	Sequential	Yes (iliac BM)	5-FU/MMC	RTOG	Overall: 41%
			7–9 field class solution	SIB		5-FU/DDP	CTCAE v 3.0	
						5-FU/MMC/DDP		
						5-FU/DDP/Cet		

Table 3. Dosimetric parameters with a correlation to hematologic toxicity in anal cancer series.

Author	Year	Pts	Technique	CHT	Bony regions	BM def	BM opt	HT scoring scale	End point	DP increasing HT risk
Mell et al.	2008	48	Static IMRT	5-FU/MMC	Pelvic bones	CT-based	Yes (some pts)	CTCAE v 3.0	WBC, ANC nadirs	PBM-$V_{5,}$-$V_{10,}$-$V_{15,}$-V_{20}
						WB contour				LSBM-$V_{10,}$-$V_{15,}$-V_{20}
Bazan et al.	2012	33	IMRT	5-FU/MMC	Pelvic bones	CT-based	No	CTCAE v 3.0	≥G3 overall HT	PBM-mean dose ≥30 Gy
				Cape/MMC		WB contour				
Cheng et al.	2014	32	IMRT	5-FU/MMC	Pelvic bones	CT-based	No	CTCAE v 3.0	≥G3 overall HT	LSBM-V_{10} > 80%
				Cape/MMC		WB contour				
Julie et al.	2015	108	Static IMRT	5-FU/MMC	Pelvic bones	CT-based	No	CTCAE v 4.0	≥G2 anemia	PBM-D_{max}>57 Gy
				Cape/MMC		WB contour			≥G2 overall HT	PBM-V_{10} > 87%
Robinson et al.	2015	40	3DCRT	5-FU/MMC	Pelvic bones	CT-based	No	CTCAE v 4.0	WBC, ANC nadirs	Several metrics of
			IMRT	Cape/MMC		WB contour				PBM, LSBM, IBM,LPBM
				MMC						
Rose et al.	2016	45	IMRT	5-FU/MMC	Pelvic bones	^{18}FDG-PET-based	Yes (iliac crests,	RTOG	ANC, WBC nadirs,	^{ACT}BM-EUD
						^{ACT}BM contour	femoral heads)		≥G3 overall HT	
Franco et al.	2016	50	Static IMRT	5-FU/MMC	Pelvic bones	CT-based	No	RTOG	≥G3 overall HT	LSBM-V_{40} ≥ 41%
			VMAT			WB contour				
Franco et al.	2016	44	Static IMRT	5-FU/MMC	Pelvic bones	^{18}FDG-PET-based	No	RTOG	WBC, ANC, Plt, Hb	LSBM-mean dose
			VMAT			^{ACT}BM contour			nadirs	LSBM-$V_{10,}$-$V_{20,}$-V_{30}
										IBM-V_{10}

pts: patients; CHT: chemotherapy; BM: bone marrow; def: definition; opt: optimization; HT: hematologic toxicity; DP: dosimetric parameters; IMRT: intensity-modulated radiotherapy; 3DCRT: 3-dimensional conformal radiotherapy; 5-FU: 5-fluorouracil; Cape: capecitabine; MMC: mytomicin C; CT-based: computed tomography-based; WB: whole bone; ^{18}FDG-based PET: ^{18}F-fluorodeoxyglucose-based positron-emission tomography;^{ACT}BM: active bone marrow; RTOG: Radiation Therapy Oncology Group; CTCAE: Common Terminology Criteria for Adverse Effects; WBC: white blood cells; ANC: absolute neutrophil count; Plt: platelets; Hb: hemoglobin; PBM: pelvic bone marrow; LSBM: lumbar–sacral bone marrow; IBM: iliac bone marrow; LPBM: lower pelvis bone marrow; EUD: equivalent uniform dose; V_x: volume receving the dose X Gy.

pts: patients; Cht: chemotherapy; BM: bone marrow; def: definition; opt: optimization; HT: hematologic toxicity; DP: dosimetric parameters; IMRT: intensity-modulated radiotherapy; 3DCRT: 3-dimensional conformal radiotherapy; 5-FU: 5-fluorouracil; Cape: capecitabine; MMC: mytomicin C; CT-based: computed tomography-based; WB: whole bone; ^{18}FDG-based PET: ^{18}F-fluorodeoxyglucose-based positron-emission tomography;^{ACT}BM: active bone marrow; RTOG: Radiation Therapy Oncology Group; CTCAE: Common Terminology Criteria for Adverse Effects; WBC: white blood cells; ANC: absolute neutrophil count; Plt: platelets; Hb: hemoglobin; PBM: pelvic bone marrow; LSBM: lumbar–sacral bone marrow; IBM: iliac bone marrow; LPBM: lower pelvis bone marrow; EUD: equivalent uniform dose; V_x: volume receving the dose X Gy.

Table 4. Dosimetric parameters with a correlation to hematologic toxicity in clinical series with tumors other than anal cancer.

Author	Year	Setting	Pts	Technique	CHT	Bony regions	BM def	BM opt	HT scoring scale	End point	DP increasing HT risk
Yang et al.	2014	Rectal cancer	120	3DCRT	5-FU	Pelvic bones	CT-based	No	CTCAE v 3.0	WBC, Hb nadirs	LSBM-V_{45}
				IMRT	Cape		WB contour				Coxal BM-V45
Wan et al.	2015	Rectal cancer	93	Static IMRT	Cape	Pelvic bones	CT-based	No	CTCAE v 4.0	≥G2 overall HT	LSBM-$V_{40} \geq 60\%$
							WB contour				
Wang et al.	2016	Rectal cancer	35	Static IMRT	Cape + Oxa	Pelvic bones	MR-based	Yes (pelvic bones)	RTOG	WBC, ANC, Plt nadirs	PBM-V_5
							^{ACT}BM contour				
Wang et al.	2016	Gastric cancer	25	Static IMRT	Cape	Based on the	MR-based	Yes	RTOG	WBC, ANC, Plt nadirs	PBM-$V_{5,}$-$V_{20,}$-V_{30}
						extent of PTV	^{ACT}BM contour				
Sini et al.	2016	Prostate cancer	121	Static IMRT	None	Pelvic bones	CT-based	No	CTCAE v 4.0	≥ G2 lymphopenia	PBM-$V_{40} > 94.6$ cc
				VMAT, Tomo			WB contour				
Deek et al.	2016	NSCLC	52	3DCRT	CBDCA + Pacl	D1-D10 vertebrae	CT-based	No	CTCAE v 4.0	≥G3 leukopenia	MVD>23.9 Gy
				IMRT		Ribs, clavicles	WB contour				TV-$V_{20} > 56\%$
						Scapulae, sternum					TV-$V_{30} > 52.1\%$
Mell et al.	2006	Cervical cancer	37	IMRT	Weekly DDP	Pelvic bones	CT-based	Yes (some pts)	RTOG	≥G2 leukopenia	PBM-$V_{10} > 90\%$
							WB contour			≥G2 neutropenia	PBM-$V_{20} > 75\%$
Albuquerque et al.	2011	Cervical cancer	40	3DCRT	Weekly DDP	Pelvic bones	CT-based	No	CTCAE v 3.0	≥G2 overall HT	PBM-$V_{20} > 80\%$
							WB contour				
Rose et al.	2011	Cervical cancer	81	IMRT	Weekly DDP	Pelvic bones	CT-based	No	RTOG	≥G3 leukopenia	PBM-$V_{10} > 95\%$
							WB contour				PBM-$V_{20} > 76\%$
Rose et al.	2012	Cervical cancer	26	IMRT	Weekly DDP	Pelvic bones	^{18}FDG-PET-based	Yes (pelvic bones)	RTOG	WBC, ANC, Plt, Hb	^{ACT}BM-mean dose
							^{ACT}BM contour			nadirs	
Zhu et al.	2015	Cervical cancer	102	IMRT	Weekly DDP	Pelvic bones	CT-based	Yes (pelvic bones)	NA	Weekly reduction in	PBM-$V_{20,}$-$V_{30,}$-V_{40}
							WB contour			WBC and ANC	

pts: patients; CHT: chemotherapy; BM: bone marrow; def: definition; opt: optimization; HT: hematologic toxicity; DP: dosimetric parameters; IMRT: intensity-modulated radiotherapy; 3DCRT: 3-dimensional conformal radiotherapy; VMAT: volumetric-modulated arc therapy; Tomo: tomotherapy; PTV: planning target volume; 5-FU: 5-fluorouracil; Cape: capecitabine; Oxa: Oxaliplatin; CBDCA: carboplatin; Pacl: paclitaxel; DDP: cisplatin; CT-based: computed tomography-based; MR-based: magnetic resonance based; WB: whole bone; ^{18}FDG-based PET: ^{18}F-fluorodeoxyglucose-based positron-emission tomography; ^{ACT}BM: active bone marrow; RTOG: Radiation Therapy Oncology Group; CTCAE: Common Terminology Criteria for Adverse Effects; WBC: white blood cells; ANC: absolute neutrophil count; Plt: platelets; Hb: hemoglobin; PBM: pelvic bone marrow; LSBM: lumbar–sacral bone marrow; TV: thoracic vertebrae; V_x: volume receving the dose X Gy; MVD: mean vertebral dose.