Uterine Carcinosarcoma (UC)

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I have no disclosures!

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Case

67 years old patient underwent TAH + BSO + pelvic & para-aortic LNE

Histology:

Carcinosarcoma (both malignant epithelial & mesenchymal elements)

>50% myometrial invasion

Node negative (18 pelvic + 8 para-aortic)

Radiological exam (PET-CT): no evidence of metastases.

What is the post-operative management for this patient?

A: Observation only

B: External-Beam Radiotherapy (EBRT)

C: EBRT + chemotherapy

D: Chemotherapy alone

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- Origin/molecular genetics
- prognosis

- Adjuvant radiotherapy
- Adjuvant chemotherapy
- Combination of adjuvant radiotherapy & chemotherapy
- Advanced/metastatic disease

- Suggestions for our case
- Future directions

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ORIGIN / MOLECULAR GENETICS

Histologically biphasic tumor, both malignant epithelial & mesenchymal elements

The histology of the metastatic component is more of an epithelial origin
Metastatic tumors shows 69% epithelial; 25% carcinosarcomatous; 6% sarcomatous

Immunohistochemical & molecular findings support that the carcinosarcomas represent metaplastic carcinomas

The molecular alterations seen in UCs are more akin to type II non-endometrioid type

Mutations/overexpressions:
P53; PI3K; KRAS; Abl; PDGF-R……

D'Angelo, et al. Best Pract Res Clin Obstet Gynaecol 2011;25:705-718; **Sreenan, et al.** Am J Surg Pathol 199519:666-678; **Gorai, et al.** Int J Cancer 1997;72:821-827; **Murray, et al.** Mutat Res 2010;686:68-73; **De Jong, et al.** Mol Pathol 2011;24:1368-1379; **Growdon et al.** Gynecol Oncol 2011;121:212-217**;** **Cimbulak, et al.** Gynecol Oncol 2007;105:138-144

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PROGNOSIS

Most cases present as advanced stage disease

Median Overall Survival: 8-26 months

Stage I UC has a “better prognosis”: 5-yr OS is 50%

Amant, et al. Gynecol Oncol 2005;98:274-280; **Garg, et al.** Int J Gynecol Cancer 2010;20:888-894

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ADJUVANT RADIOTHERAPY

Radiotherapy improves local control

Radiotherapy has NO impact on overall survival

	EORTC 55874 Reed et al.	SEER database Wright et al.	SEER database Clayton Smith et al.	SEER database Nemani et al.
Design	Phase 3 randomized	Non-randomized cohort	Non-randomized cohort	Non-randomized cohort
N Stage	224 (91) I-II	1819 I-II	2461	1855
Regimen	RT vs. none	RT vs. none	RT vs. none	RT vs. none
Local relapse	8% vs. 16% *P=0.004*			
Disease-Specific Survival	NS			
OS	NS	21% reduction in death (non LNE)	5 yr survival 5% vs. 2%	No difference

Reed, et al. Eur J Cancer;2008 44:808-818; **Wright, et al.** Am J Obstet Gynecol 2008;199:531-538; **Clayton Smith, et al.** Radiother Oncol 2008;88:227-232; **Nemani, et al.** Gynecol Oncol 2008;111:82-88

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ADJUVANT CHEMOTHERAPY

Chemotherapy has NO impact on local control

Chemotherapy MAY improve overall survival

	GOG Wolfson et al.	SARCGYN Pautier et al.	GOG232B Sutton et al.
Design	Randomized	Randomized	Non-randomized
N Stage	206 I-IV (complete resection)	81	65 I-II
Regimen	WART vs. Ifos-Cis x 3	RT +/- Doxo-Ifos-Cis	Ifos-Cis x 3
Local relapse Distant relapse	44 vs. 42 *NS* 25 vs. 23 *NS*		
PFS		DFS at 3 yrs: 55% vs 41%	54% at 7 yrs
OS	29% lower death in chemo arm *NS*	NS	52% at 7 yrs

Wolfson, et al. Gynecol Oncol 2007;107:177-185; **Pautier, et al.** Ann Oncol 2013;24:1099-1104; **Sutton, et al.** Gynecol Oncol 2005;96:630-634

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ADJUVANT RADIATION & CHEMOTHERAPY

Only retrospective studies including pelvic RT and chemotherapy

Different chemotherapy regimen: Cis-Ifos; Tax-Ifos; Carbo-Tax

Combined approach may be better than RT alone:

Retrospective analysis of 49 patients (stage I-IV)

RT alone vs RT + CT (mainly carbo-tax)

3 yrs PFS: 9% vs 35%

3 yrs OS: 34% vs. 66%

Makker, et al. Gynecol Oncol 2008;111:249-254;

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ADVANCED / METASTATIC DISEASE

	GOG Sutton et al.	GOG 161 Homesley et al.	Cochrane Galaal et al.	GOG Powell	BCCA Hoskins
Design	Randomized	Randomized	Randomized Meta-analysis	Phase 2	Phase 2
N	194	179	579	55	40
Regimen	Ifos +/- Cis	Ifos +/- Taxol	Ifos vs. Ifos-Cis	Carbo-Tax	Carbo-Tax
Response Rate	54% vs 36%	45% vs 29%		54% (13% CRs)	60%
PFS	6 vs 4 months	5.8 vs 3.6 months	HR 0.75		
OS	NS	13.5 vs 8.4 months	HR 0.72		

Sutton, et al. Gynecol Oncol;2000;79: 147-153; **Homesley, et al.** J Clin Oncol 2007;25:526-531; **Galaal, et al.** Cochrane Syst Rev 2013;2:CD006812; **Powell, et al.** J Clin Oncol 2010;28:2727-2731; **Hoskins, et al.** Gynecol Oncol 2008;108:58-62

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Targeted Therapy, Ongoing Trials

	ENGOT-EN1 NSGO	PazoDoble AGO-NOGGO
Design	Randomized	Randomized
N	148	87 (20)
Regimen	Carbo-Tax +/- Nintedanib	Pazopanib +/- Gem

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TREATMENT SUGGESTION FOR OUR CASE

67 years old patient underwent TAH + BSO + pelvic & para-aortic LNE

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Node negative (18 pelvic + 8 para-aortic)

Radiological exam (PET-CT): no evidence of metastases.

What is the post-operative management for this patient?

Chemotherapy alone (carboplatin-taxol)

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FUTURE DIRECTIONS

UC must be included in mainstream endometrial cancer trials

Prospective clinical trials: randomized or well-designed non-randomized trials

Research in Targetable genetic & molecular signaling pathways

Trials shall incorporate molecular-targeted therapies

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Thank You!

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