La gestione del paziente metastatico

Lucia Lombardi Oncologia Medica IRCSS CROB

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Metastatic Squamous Cell Carcinoma of the Anus

Early-stage disease (T1/T2 N0) is associated with a good prognosis
5 year relative survival rate 70-80%

Regional disease (T2/T4 N1-3)
5 year relative survival rate 60%

Metastatic disease (M1)
5 year relative survival rate 20%*
The prognosis for patients with distant metastases is generally poor, although documented median survival rates vary from 8 to 34 months.

*The SEER database reports 5-year survival rates of 10% in men and 20% in women between 1973 and 2000

Prognostic Factors

1. SEX (male)
2. AGE (over 65 years)
3. RACE
4. NODAL INVOLVEMENT
5. POORLY DIFFERENTATIED HISTOLOGY
6. STAGE

5-years observed survival for anal cancer		
Stage	**Squamous cancers**	**Non-squamous cancer**
I	71%	59%
II	64%	53%
IIIA	48%	38%
IIIB	43%	24%
IV	21%	7%

Five-year OS,DFS,LF and DM by TN Category in Anal Carcinoma

Category	N° patients	Five-year OS	Five-year DFS	Loco-regional failure	Distant metastasis
NODE NEGATIVE					
T2N0	303	81%	69%	19%	12%
T3N0	115	75%	63%	22%	14%
T4N0	31	59%	40%	50%	21%
NODE POSITIVE					
T2N1-3	95	66%	40%	40%	31%
T3N1-3	47	44%	26%	58%	32%
T4N1-3	25	48%	34%	64%	17%

L Gunderson et al ASCO GI 2010 #285

Sites of anal cancer metastasis

Pelvic disease:

Local-relapse (10-30%)
Regional lymph nodes

Extrapelvic disease:

Liver (45%)
Extrapelvic lymph nodes (41%)
Lung (25%)
Bones (15%)
Brain (8%)

AG Renehan et al Br J Surg 2005;
C. Eng et al ASCO 2012 # 4060

Standard Treatment options

Palliative surgery

Palliative radiation therapy

Palliative combination chemotherapy and radiotherapy

Chemotherapy

Clinical trials

Palliative care

Pelvic Disease

Locally persistent, progressive or recurrente

Salvage surgical treatment

Abdominal-perineal excision

Posterior or total pelvic exenteration with multi-visceral resections

Persistent or progressive disease in inguinal lymph nodes

Radical groin dissection (may be flap reconstruction)

RT ?

Extra- Pelvic Disease

Chemotherapy

The choice of chemotherapy:

Previous treatment for early disease

Disease-free interval

Performance status of patient

Chemotherapy

CISPLATINO + 5FU

19 patients: 3 males, 16 females, have been treated with a combination of 5 fluorouracil (5FU) and cisplatinum. The FUP combination gave a high response rate with an acceptable toxicity in patients with metastatic anal cancer
The response rate was 66%; The actuarial survival was 62.2% at 1 year and 32.2% at 5 years and the median survival was 34.5 months.
Three patients are still alive at 4, 5 and 7 years and benefited from additional local treatment

Faivre et al: Bulletin du Cancer 1999, 86(10):861-865

Phase II chemotherapy trials of metastatic squamous cell carcinoma of the anus

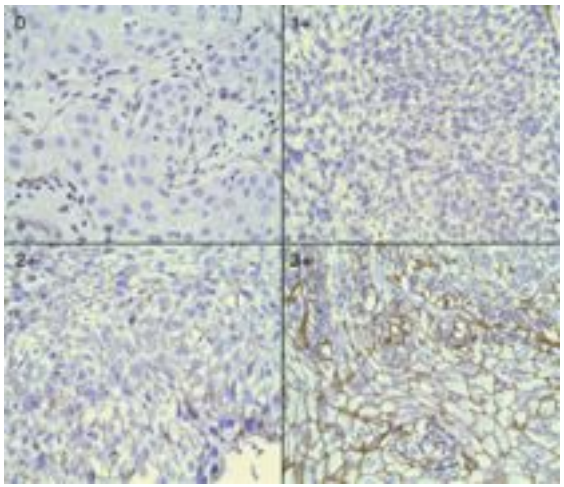
Author	Number of patients	Agents	Response rate	Median PFS (Months)	OS(Months)
Wilking et al	15	Vincristine,Bleomicyn and high dose of Methotrexate	3/12(25%)	2	NR
Hiansworth et al	60 (7 with anal cancer)	Paclitaxel, Carboplatin and infusional 5FU	65%overall 4/7 (57% anal cancer)	35 overal (26 anal cancer)	NR
Jhawer et al	20	Mitomycin, Adriamycin, Cisplatin and Bleomycin-CCNU	12/20(60%)	8	15

Case Reports of single-agent chemotherapy in metastatic squamous cell carcinoma of the anus

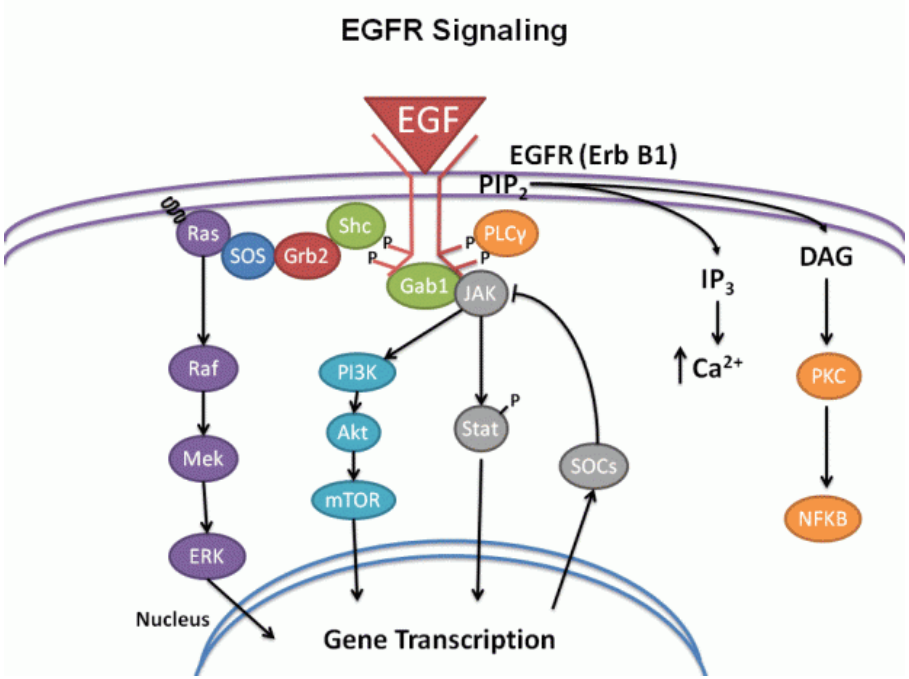
Author	Number of patients	Agents	Response	Median PFS (Months)	OS(Months)
Evans et al	1	Carboplatin	Partial	9	NR
Fischer et al	1	Doxorubicin and Cisplatin	Major	NR	NR
Zimm and Wampler	1	Semustine	Partial	15	NR
Golub et al	3	TIP	Complete 3/3	4,6,36	NR
Grifalchi et al	1	Irinotecan	Partial	NR	NR

Squamous cell carcinoma of the anus commonly over-expresses EGFR

positive EGFR: 55-90%
no EGFR gene amplification



Paliga et al Journal of Oncology 2011
Lè et al Journal of Clinical Pathology 2005



KRAS and PIK3CA gene mutations were found in 4 (5%) and 13 patients (16%), respectively. No mutations were found in the BRAF gene. *(Martin Journal Histopathology 2014)*

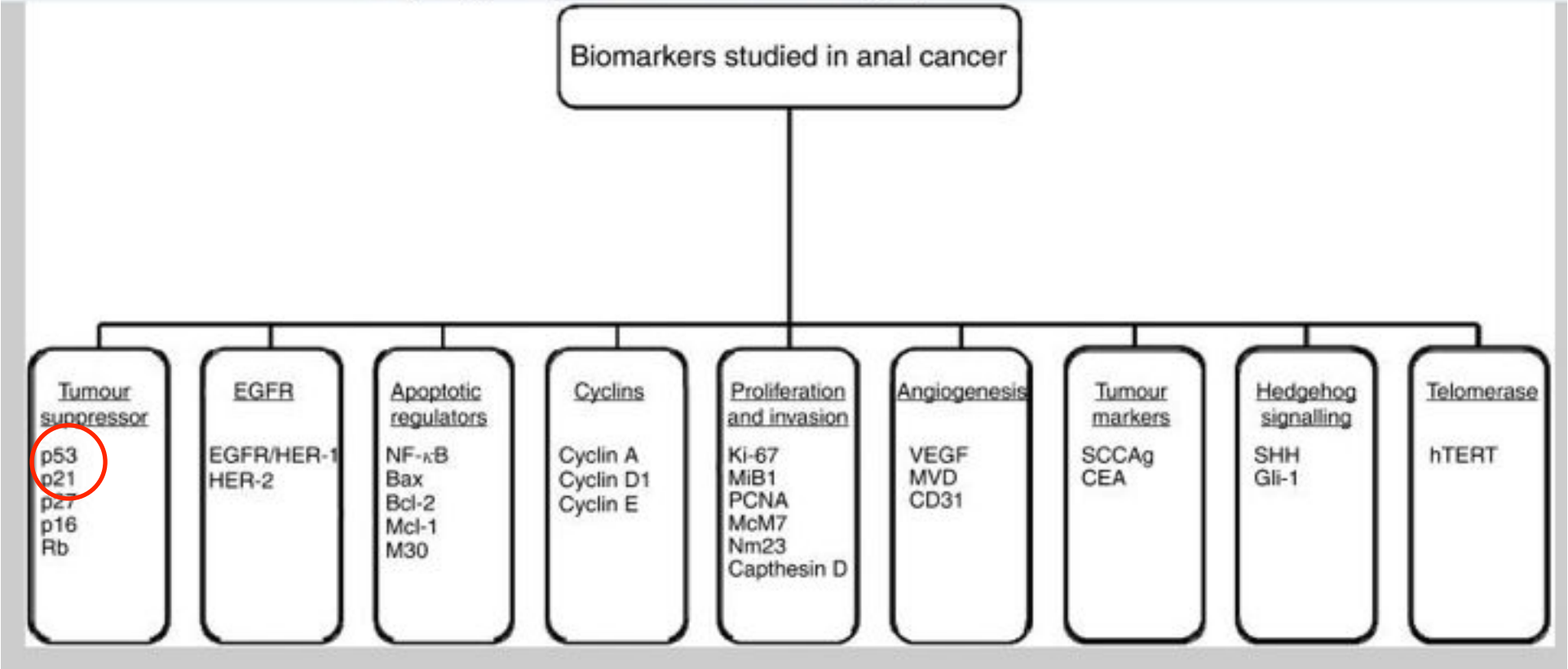
All tumors expressed wild-type status at codons 12 and 13 of the KRAS gene, and at codon 600 of the BRAF gene. Data show the absence of KRAS and BRAF mutations in anal SCC . *(L. Evesque ASCO GI 2010 #326)*

Studies of Cetuximab in metastatic squamous cell carcinoma of the anus

Author	Number of patients	Agents	Response rate	Median PFS (Months)	OS(Months)
De Dosso et al	1	Irinotecan and Cetuximab	Partial	Patient died of PE on treatment	NR
Lukan et al	7	Irinotecan and Cetuximab	5/7 response (3* partial, 1minor and 1 stable)	6	NR
Phan and Hoff	1	Irinotecan and Cetuximab	Partial	NR	NR

* All five responders were KRAS WT

Prognostic biomarkers in squamous cell carcinoma of the anus



T Lampejo et al British Journal of Cancer 2010

Localised Therapies

- Liver metastases: hepatic resection
  - median disease free survival: 9.6 months
  - overall survival: 22.3 months
- Palliative surgery
- Palliative radiotherapy

ClinicalTrials.gov

Study	Condition	Schedule	Phase	Primary outcome	Status
NCT0095524	Locally-advanced	***RT+DDP+5FU+ Cetuximab***	Phase II	Best overall Response Rate	unknown
NCT0068744	Locally-advanced	***RT+MMC+DDP or 5FU***	Phase II	Best overall Response Rate	terminated
NCT0251868	Advanced	***CDDP+5FU vs CBDCA+Paclitaxel***	Phase II	Best overall Response Rate	recruiting
NCT0162127	Locally-advanced	***RT+5FU+MMC +Cetuximab***	Phase I	Maximum tolerable dose	recruiting
NCT0065416	Advanced cancer	***FOLFIRI***	Phase II	Maximum tolerable dose	active, not recruiting
NCT0001910	Advanced cancer	***Vaccines from PPV***	Phase I		terminated
NCT0158184	Locally-advanced	***RT+5FU+Panitumumab***	Phase II	Complete response	recruiting

clinical practice guidelines

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Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Glynne-Jones[1], P. J. Nilsson[2], C. Aschele[3], V. Goh[4], D. Peiffert[5], A. Cervantes[6] & D. Arnold[7]*

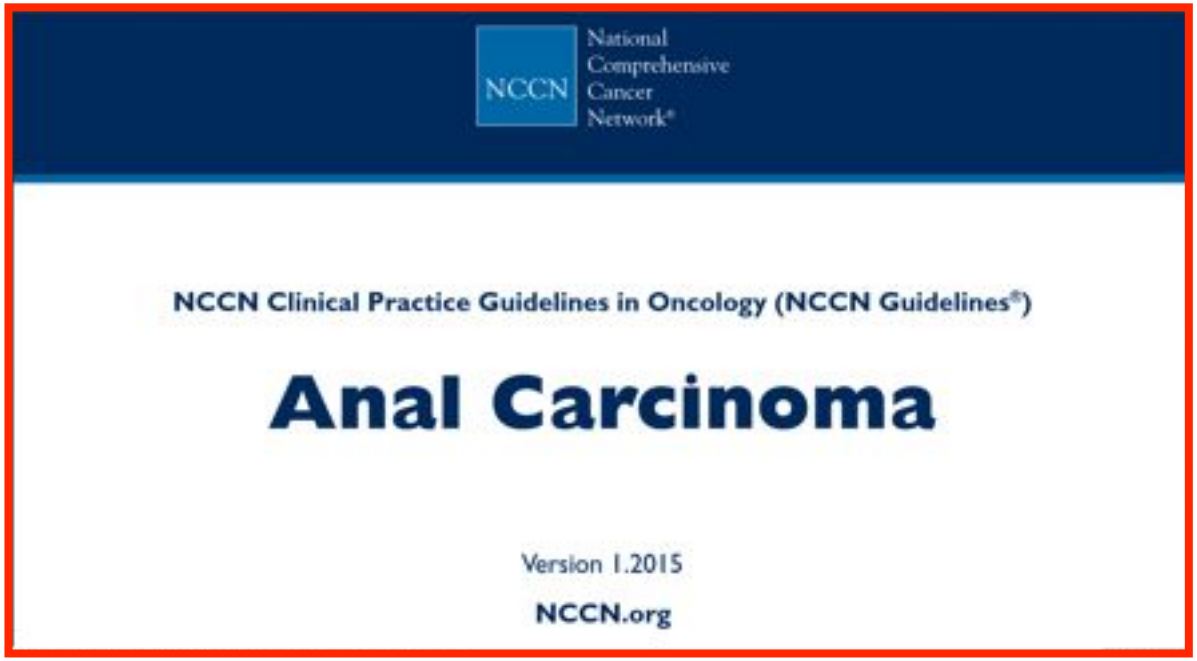
[1]Centre for Cancer Treatment, Mount Vernon Hospital, Northwood, Middlesex, UK; [2]Department of Molecular Medicine and Surgery, Karolinska Institutet and Center for Surgical Gastroenterology, Karolinska University Hospital, Stockholm, Sweden; [3]Medical Oncology and Hematology, Felettino Hospital, La Spezia, Italy; [4]Division of Imaging Sciences and Biomedical Engineering, King's College London, London, UK; [5]Department of Radiotherapy, Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France; [6]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; [7]Klinik für Tumorbiologie, Freiburg, Germany

1. There is no consensus on the standard chemotherapy treatment

2. Fit patients with symptomatic metastatic or recurrent disease not amenable to surgery should be considered for chemotherapy

3. Should be considered for chemotherapy, usually with a combination of cisplatin and 5-FU; activity is also reported for carboplatin, doxorubicin, taxanes and irinotecan ± cetuximab—or combinations of these agents

4. Currently, the international rare cancers initiative, which is a consortium of international investigators from the UK, US, Europe and Australia, has developed a multicentre international trial testing the role of CBDCA/paclitaxel vs 5-FU/cisplatin



. Treatment reccomendations for patients with a distant metastasis should be individualized, but metastatic disease is usually treated with cisplatin-based chemotherapy

2. Enrollment in a clinical trial is another option

3. Palliative RT with 5-FU based chemotherapy with platinum agent can also be given to patients with metastatic disease for local control in the case of symptomatic bulky primary

Conclusions

- No standard chemotherapy for metastatic disease
- Reported median survival varies, 8-34.5 months
- Guidelines currently recommendations
- Clinical trials incorporating tissue collection for biomarkers (targets other than EGFR:hedgehog inhibitor and mTOR inhibitor)
- International collaboration in global clinical trial is imperative and could improve outcomes in this setting

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