University of Ljubljana
Veterinary Faculty

Zdravljenje tumorjev z elektrokemoterapijo in genskim elektroprenosom pri psih

Nataša Tozon
Veterinarska fakulteta, Univerza v Ljubljani

Veterinary and Comparative Oncology
Original Article
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Efficacy and safety of electrochemotherapy combined with peritumoral IL-12 gene electrotransfer of canine mast cell tumours

M. Cemazar[1,2], J. Ambrozic Avgustin[3], D. Pavlin[4], G. Sersa[1], A. Poli[5], A. Krhac Levacic[3], N. Tesic[2], U. Lampreht Tratar[1], M. Rak[2] and N. Tozon[4]

[1]Department of Experimental Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[2]Faculty of Health Sciences, University of Primorska, Isola, Slovenia
[3]Biotechnical Faculty, University of Ljubljana, Ljubljana, Slovenia
[4]Veterinary Faculty, University of Ljubljana, Ljubljana, Slovenia
[5]Department of Veterinary Science, University of Pisa, Pisa, Italy

“obstaja le ena medicina” – eno zdravje (One health)

(La Rue)

- Veterinarska onkologija = pomemben del v raziskavah humane onkologije: živali veljajo za odličen model v raziskovanju potencialnih etioloških dejavnikov, saj delijo skupni življenjski prostor, podoben je razvoj bolezni in samo zdravljenje.

Klinične študije – onkologija /vse: 125/232

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mačke: 32
konji: 11
eksoti/divje ž.: 4
Ekonomske kategorije ž.: 4

AMERICAN SOCIETY of GENE & CELL THERAPY

The Vector

The Official e-Newsletter of the ASGCT

Volume 6, Issue 5: September 2017

Inside This Issue

President's Message

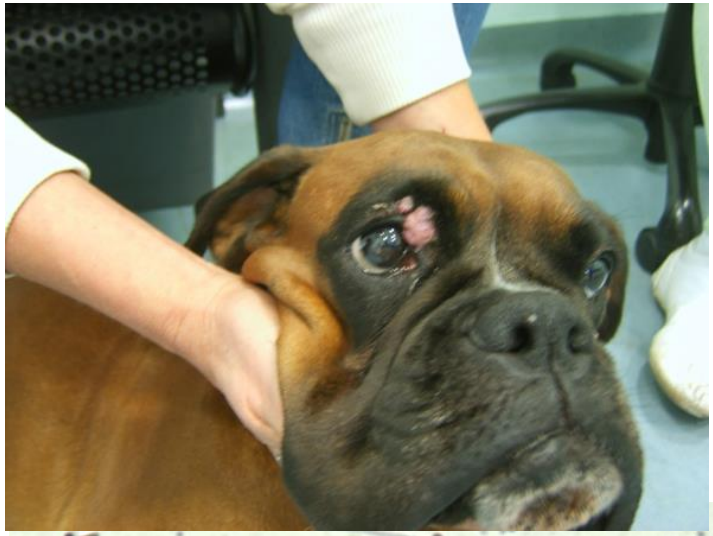
Dear Colleagues,

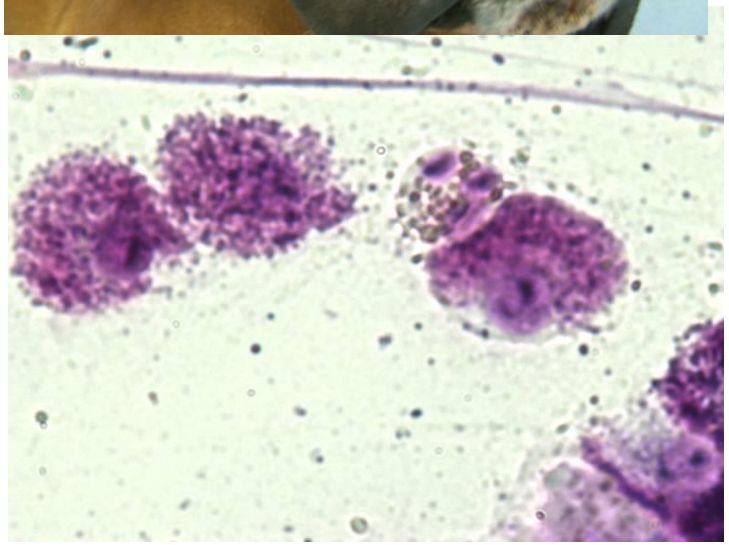
Gene and cell therapy is entering a new and exciting era. Last week, the FDA approved the first in class CAR T-cell therapy CTL019 (tisagenlecleucel, marketed under the name Kymriah). The approach is the result of more than 20 years of research and the collective efforts of many ASGCT members. As patients benefit from the approval and commercialization of this therapy, it will undoubtedly have a lasting impact on our field driving growth and innovation.

Along with these rapid advances and the new therapeutics that will become

Mastocitom (Mast cell tumours - MCTs):

- Najpogostejši kožni tumor psov, 16 – 21% vseh kožnih tumorjev.
- zelo raznolik glede na klinični izgled in biološko obnašanje, kar predstavlja poseben izziv v diagnostiki in še psebej zdravljenju.
- Zdravljenje moramo prilagoditi histološki stopnji malignosti in kliničnemu stadiju: široki varnostni robovi z/brez radio/ kemoterapijo





Veterinary and Comparative Oncology

Original Article

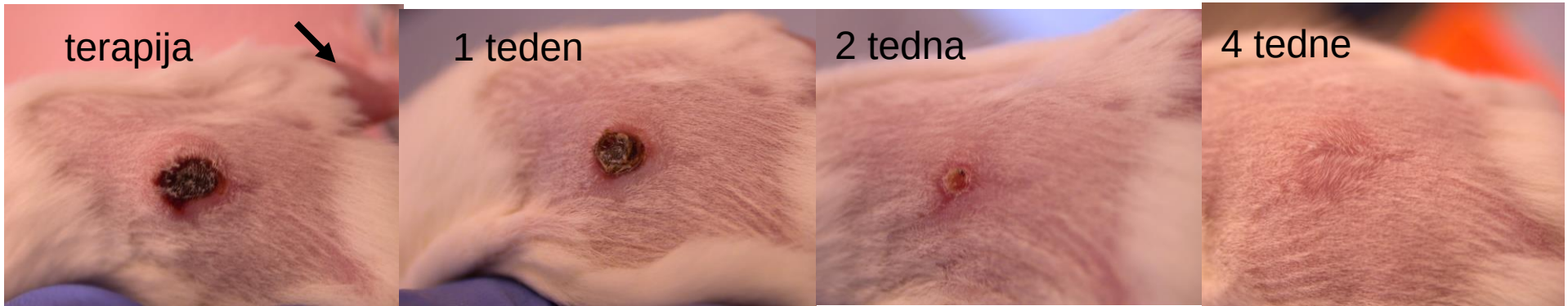
DOI: 10.1111/j.1476-5829.2012.00341.x

European consensus document on mast cell tumours in dogs and cats

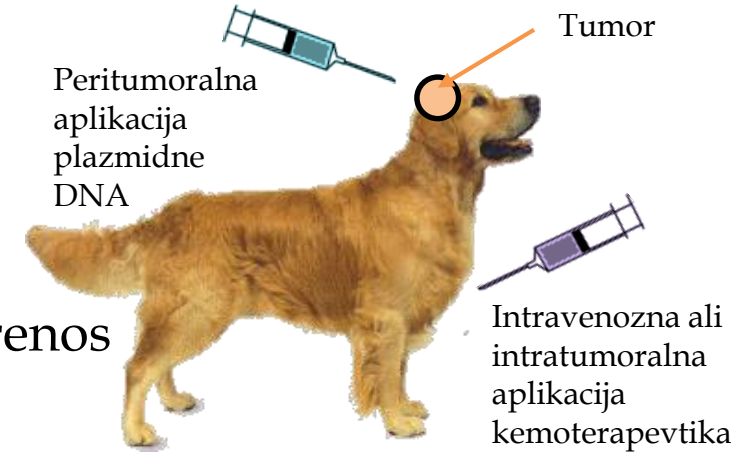
L. Blackwood[1,†], S. Murphy[2,†], P. Buracco[3], J. P. De Vos[4], P. De Fornel-Thibaud[5], J. Hirschberger[6], M. Kessler[7], J. Pastor[8], F. Ponce[9], K. Savary-Bataille[10] and D. J. Argyle[11]

Protitumorska učinkovitost EGT z IL-12

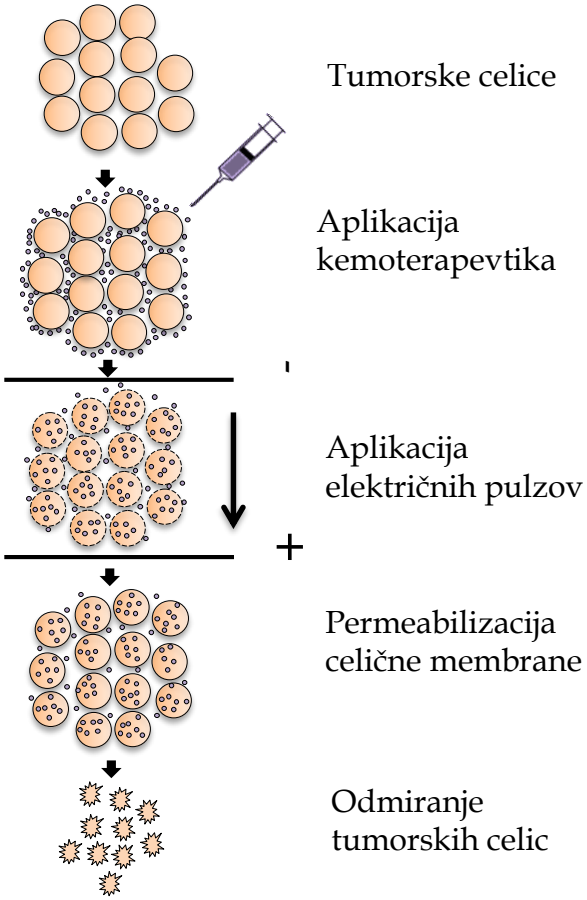
- Eksperimentalni modeli različnih tumorjev:
  - melanom, sarkom, različni karcinomi, limfom
- Protitumorski učinki EGT z IL-12 se izražajo kot:
  - upočasnitev rasti oz. popolna regresija tumorjev
  - dolgotrajna protitumorska zaščita (živali odporne na ponovno izrast tumorjev pri ponovitvi apl. tumorskih celic)
  - zmanjšanje števila pljučnih metastaz
  - podaljšanje življenjske dobe zdravljenih živali
  - brez pomembnih sistemskih stranskih učinkov



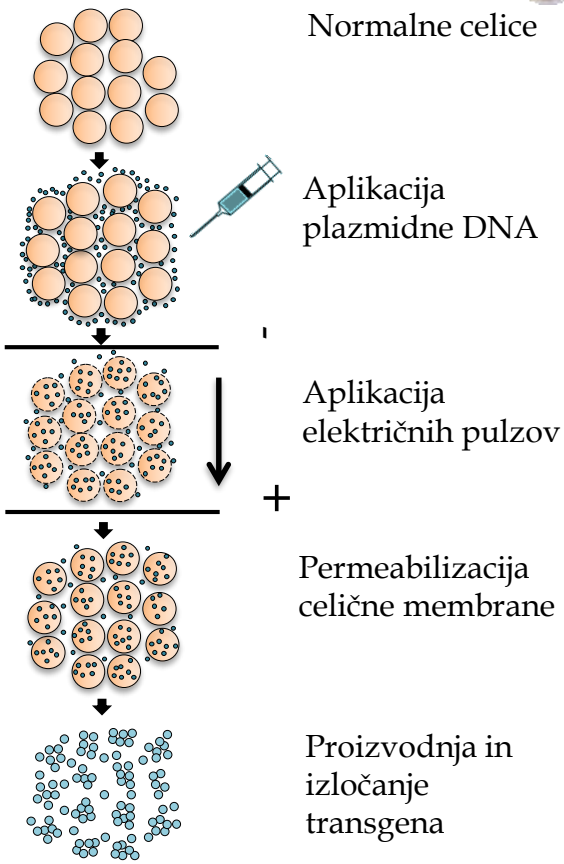
Zdravljenje tumorjev pri psih z ECT in genskim elektroprenosom (EGT)



Elektrokemoterapija



Genski elektroprenos



ECGT z IL-12 pri psih

18 posv z 18 MCTs, različne pasme, 5-15 let

12/18 klinični stadij I, 4/18 klinični stadij II, 2/18 klinični stadij III

ECT

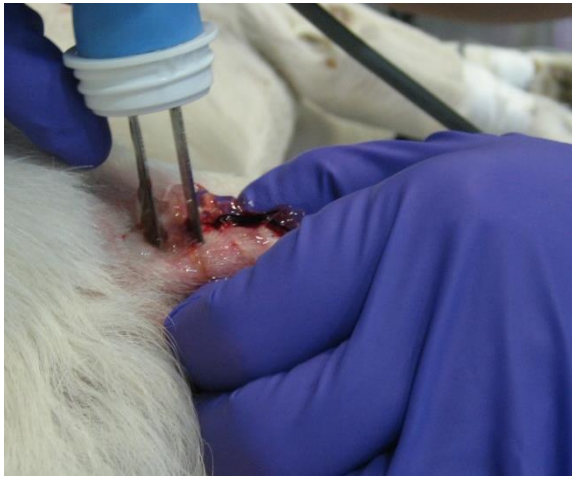
- i/tumoralna aplikacija cisplatina (Cisplatyl; Aventis); ~1 mg/cm^3
- po 1-2 min EP (8 x 100 µs, 1300 V/cm, 1 Hz), ploščate elektrode s 6 mm razmikom

EGT

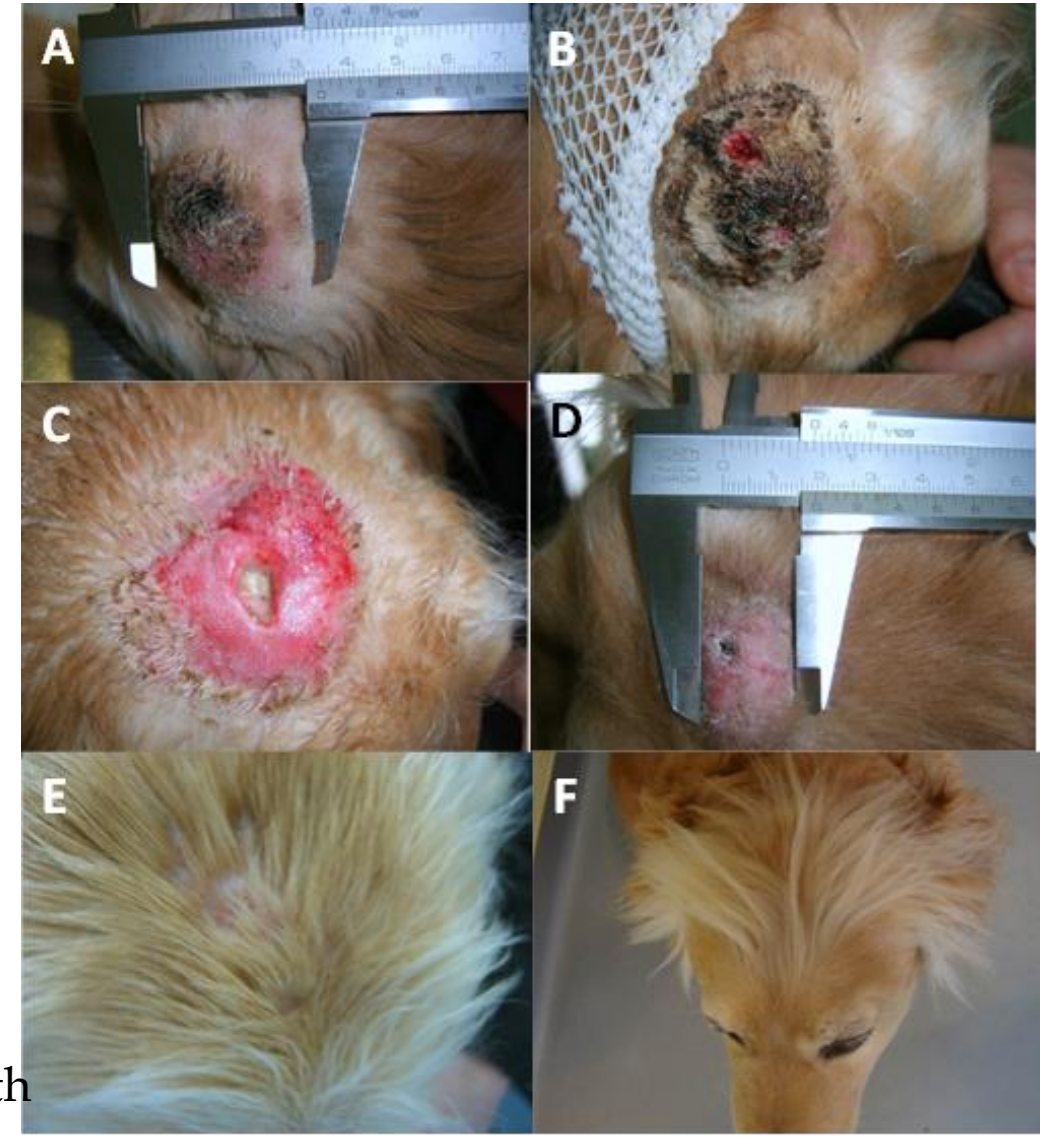
- i/ dermalana aplikacija plazmida v bližini tumorja (pORF-hIL-12, 1-2 mg/terapijo)
- EP: 1 x HV (1200 V/cm,100 µs), ki mu takoj sledi 1 x LV (140 V/cm, 400 µs)

Spremljanje odgovora

- spremljanje : 2, 7, 14 in 28 dni, nato mesečno in od 6 meseca, polletno
- lokalni odgovor (velikost tumorja)
- sistemski odgovor (sproščanje hIL-12, cIFN-ϒ)
- Spremljanje neželenih stranskih učinkov (VCOG lestvica toksičnosti)



Pred th



1 teden po th

2 tedna po th

4 tedne po th

3 mesece po th

3,5 let po th

MCT na glavi 3x3x2,7 – TH: ECT CDDP i.t. + EGT 1 mg plazmida

Rezultati – lokalna kontrola MCTs pri psih

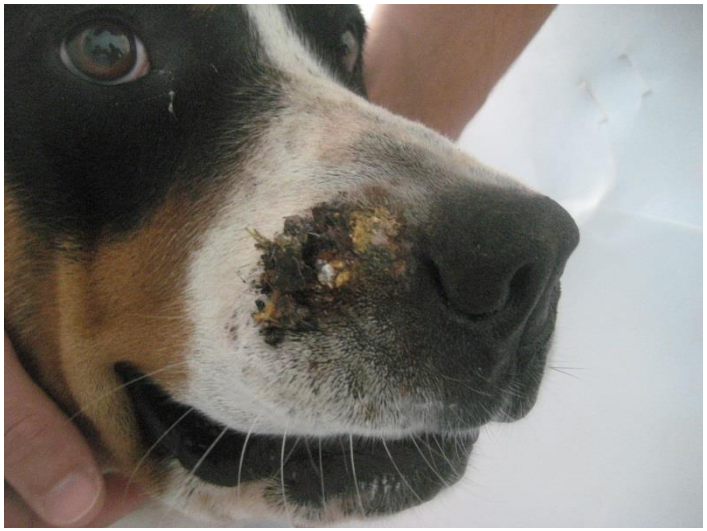
	ECT (Kodre et al)	EGT (Pavlin et al)	ECGT
Število psov Število tumorjev	9 psov 12 MCTs	8 psov 11 MCTs	18 psov 18 MCTs
Protokol zdravljenja	Cisplatin i.tu.	pORF-hIL-12 i.tu.	Cisplatin i.tu. pORF-hIL-12 i.der.
Volumen zdravljenih tumorjev	0.02 to 30.23 cm^3 median 2.9 cm^3	0.03 to 25.4 median 0.6 cm^3	0.19 to 47.1 cm^3 median 2.12 cm^3
CR	62.5%	36%	72.3%
Ponovitve bolezni	1/9 zdravljenih	0/4 zdravljenih	0/13 zdravljenih
Čas spremljanja	2 – 43 m median 26 m	12 m	4 - 52 m median 40 m

Odgovor v korelaciji z:

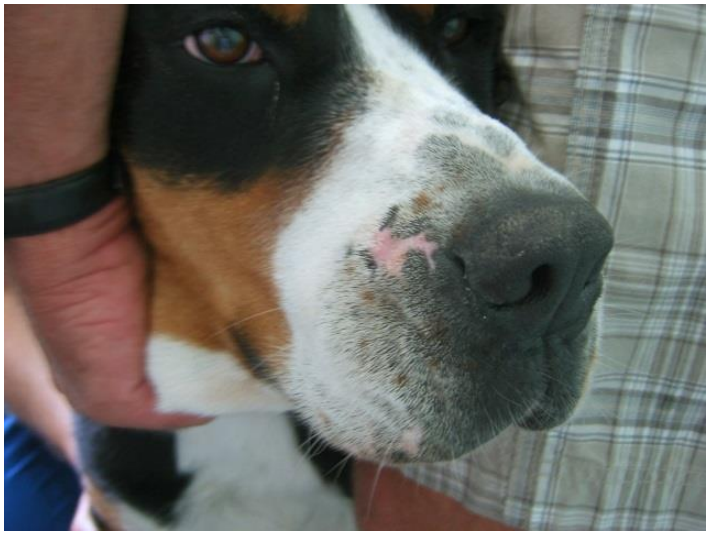
- Velikostjo tumorja: 100% CR pri < 2 cm^3
- Kliničnim stadijem bolezni : 3/18 PD - kl. stadij II/III
- Stopnja malignosti ni vplivala na odgovor

Spremljanje stranskih učinkov

- Nima klinično ali laboratorijsko zaznavnih neželenih stranskih učinkov
- Nima neželenih stranskih učinkov, povezanih s sproščanjem histamina iz granul v tumorskih celicah MCT, ki so posledica mehanične manipulacije



Površinska hrasta na mestu odmrlih tumorskih celic



Manjša brazgotina po prib. 4 tednih – odličen kozmetični učinek

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RADIOLOGY AND ONCOLOGY

research article

Effects of electrochemotherapy with cisplatin and peritumoral IL-12 gene electrotransfer on canine mast cell tumors: a histopathologic and immunohistochemical study

Claudia Salvadori[1], Tanja Svara[2], Guido Rocchigiani[1], Francesca Millanta[1], Darja Pavlin[3], Maja Cemazar[4], Ursa Lampreht Tratar[4], Gregor Sersa[4], Natasa Tozon[3], Alessandro Poli[1]

Results. Histopathological examination of samples at T_0 confirmed the diagnosis and the presence of scanty infiltrates consisted mainly of T-lymphocytes and macrophages. At T_1 and T_2 neoplastic cells were drastically reduced in 7/11 cases, small clusters of neoplastic cells were detected in 3/11 cases and 1/11 cases neoplastic cells were still evident. Proliferation activity of neoplastic cells was significantly reduced at T_1 and T_2 and expression of anti-apoptotic protein at T_1. Microvessel density was drastically reduced in all samples after treatment. The number of T-lymphocytes increased at T_1, although not significant, while Treg were significant higher at T_1 and macrophages at T_2.

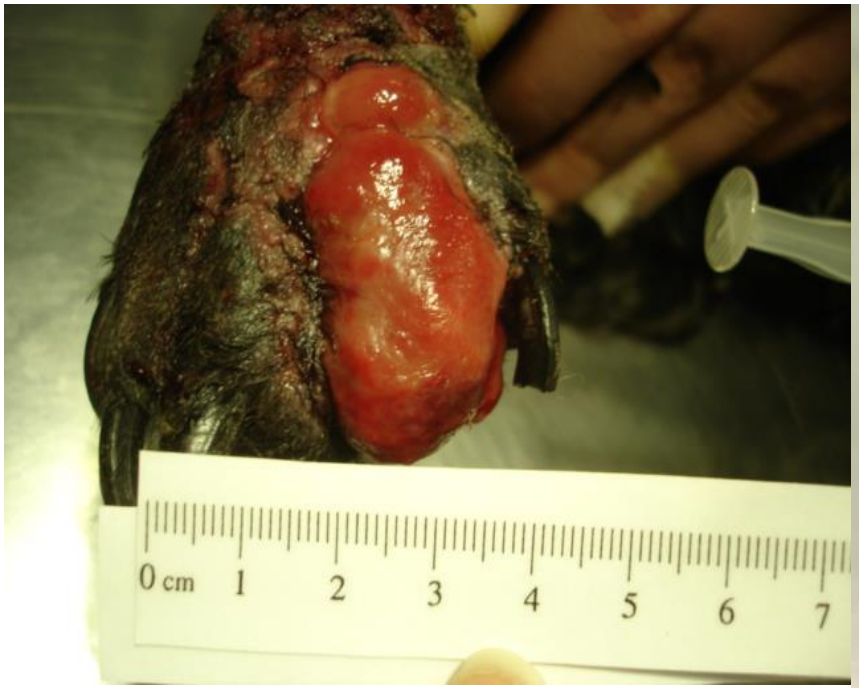
Conclusions. The combined electrochemotherapy and IL-12 gene electrotransfer effectively induced a cellular response against neoplastic cells characterized mainly by the recruitment of T-lymphocytes and macrophages and a fibrotic proliferation with reduction of microvessels.

Radiol Oncol 2017; 51(3): 286-294

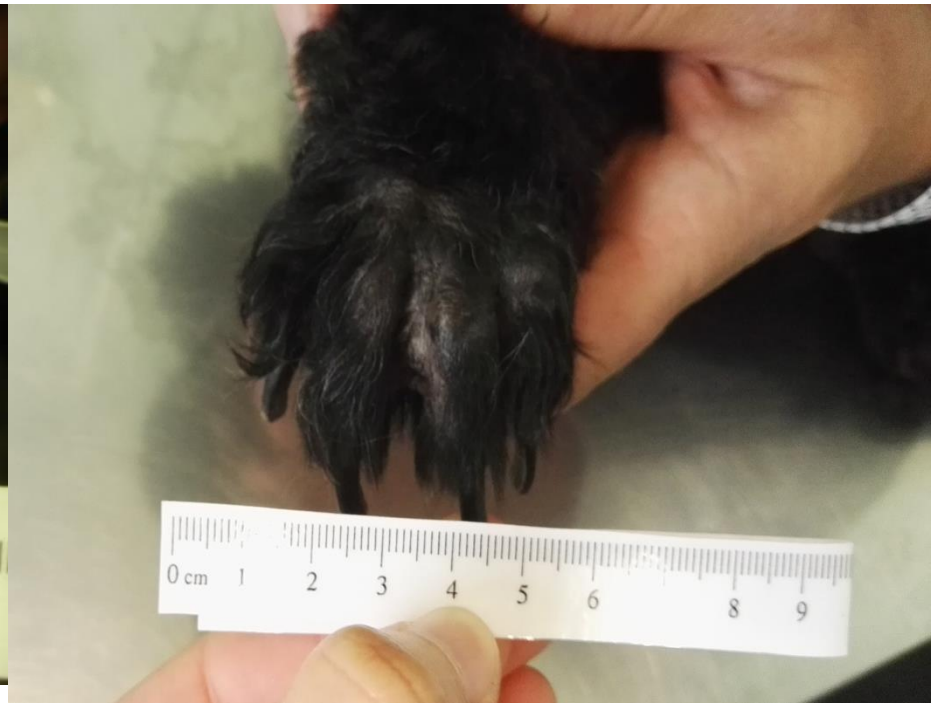
ECGT lahko uporabimo:

- kot samostojno terapijo za zdravljenje manjših MCTs
- kot neoadjuvantno = citoreduktivno terapijo pred kirurškim posegom, predvsem na mestih, kjer ni mogoče doseči čistih kirurških robov in ustrezne lokalne kontrole
- kot adjuvantno v kombinaciji z drugimi metodami (predvsem krg)
- kadar ni možnosti uporabe nekaterih metod zdravljenja (npr. radioterapije)

ECGT – ekstranodalni plazmocitom



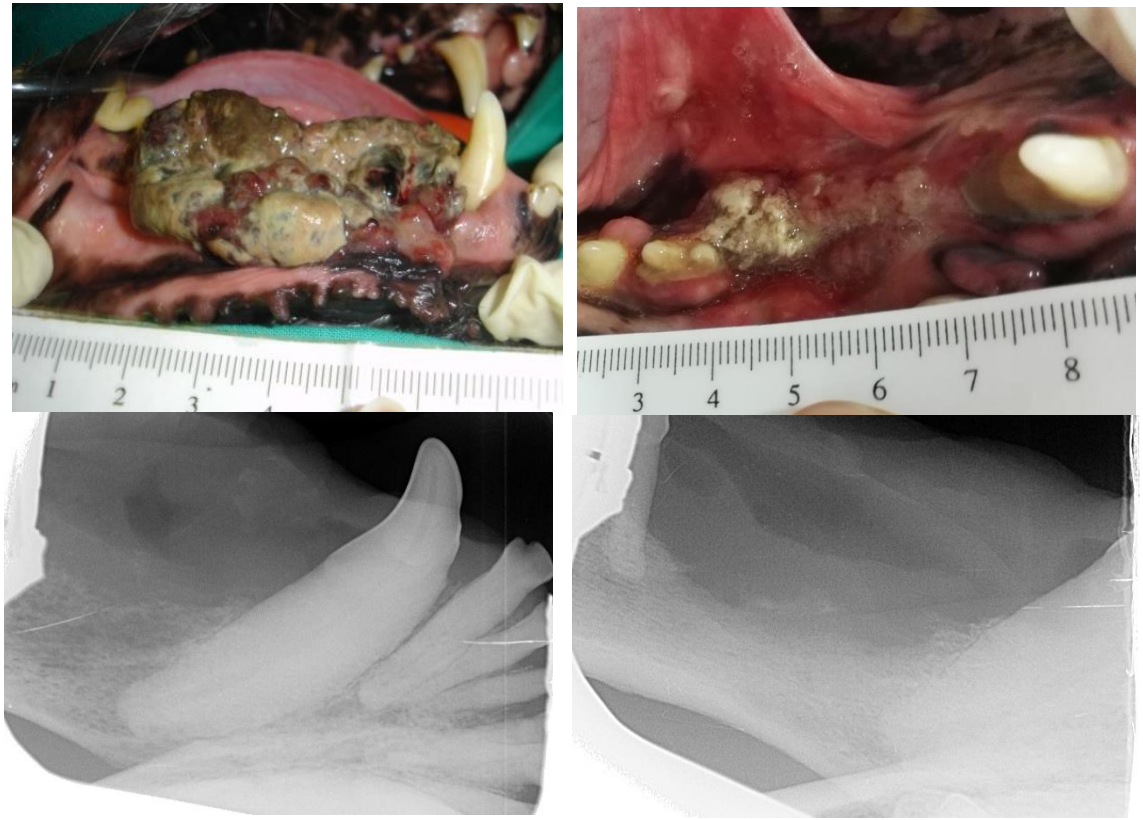
pred ECT+EGT



10 m po th - CR

ECGT v kombinaciji s kirurgijo – tumorji ustne votline psov

- Intracapsularna odstranitev tumorske mase + 4 ECT (bleomicin i.v. + canine IL-12 EGT peri-tumoralno):
  - 2 CR, 1 SD, 1 PD



Tozon et al. neobljavljeni podatki

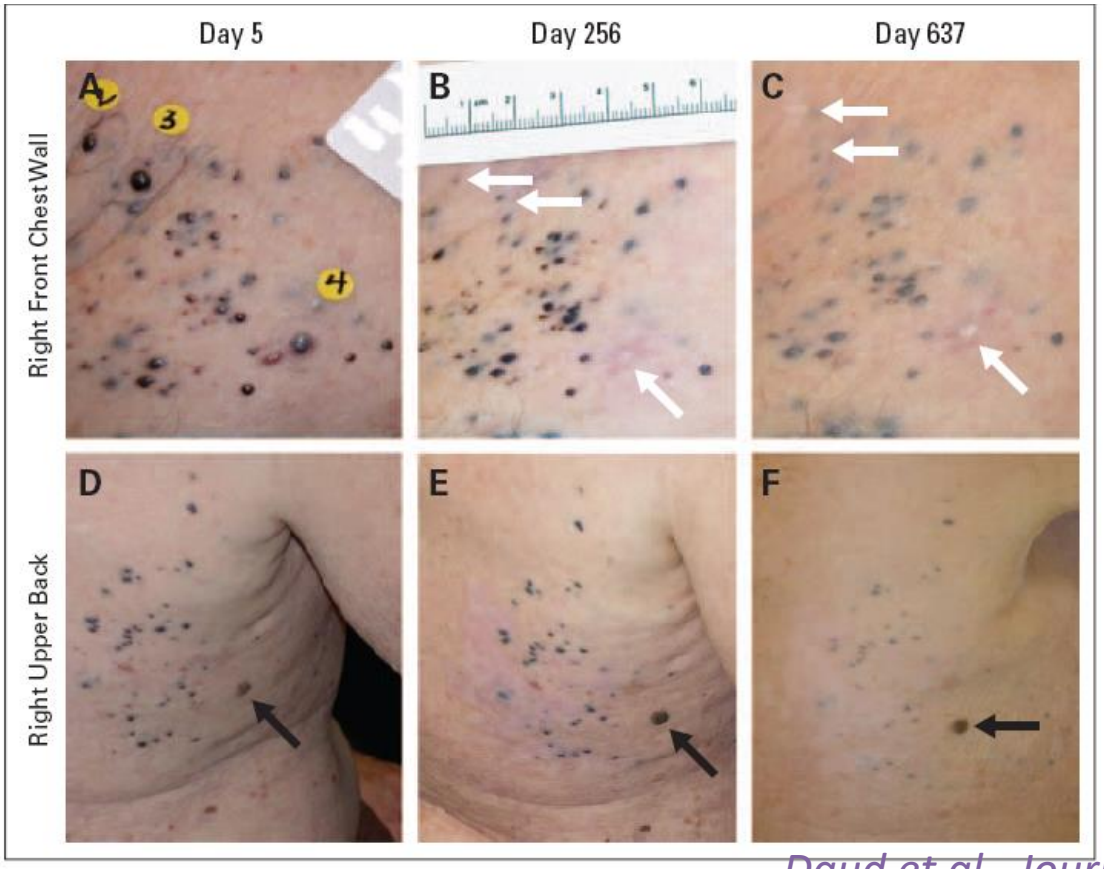


Fig 3. Cutaneous lesions in (A-F) patient 9 from cohort 3 and (G-J) patient 14 from cohort 5. (A-C) Right front chest wall. (D-F) Right upper back. A and D were photographed on day 1 (pretreatment), B and E on day 256, and C and F on day 637. Note that the electroporated lesions (2, 3, 4 in panel A) were resected and the sites are shown by white arrows. The nonelectroporated lesions gradually flatten and fade away. (D-F) The seborrheic keratosis (shown by the black arrows) persists whereas the metastatic melanoma lesions flatten and fade with time.

Daud et al., Journal of Clinical Oncology, 2008

OncoSec Granted Orphan Drug Designation from the U.S. FDA for the Treatment of Unresectable Metastatic Melanoma

JUNE 08, 2017

DOWNLOAD AS PDF

SAN DIEGO, June 8, 2017 /PRNewswire/ -- OncoSec Medical Incorporated ("OncoSec") (NASDAQ: ONCS), a company developing DNA-based intratumoral cancer immunotherapies, today announced that the U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation for pIL-12, otherwise known as tavokinogene telsaplasmid, for the treatment of unresectable metastatic melanoma. Tavokinogene telsaplasmid is the active biologic agent in OncoSec's lead product candidate, ImmunoPulse® IL-12. The Orphan Drug status will provide OncoSec with eligibility for certain development incentives, including tax credits for clinical testing, exemption from a prescription drug user fee, and seven years of market exclusivity.

zahvala

- VF UL:
  - Darja Pavlin, Ana Nemec
  - Veronika Kodre Ručigaj (MF UL, Janssen)
- OI Ljubljana:
  - Maja Čemažar in Gregor Serša
  - Mira Lavrič, Tanja Jesenko,Urška Lampreht Tratar
- BTF UL: Jerneja Ambrožič Avguštin
- FVZ UP: Nataša Tešić
- Veterinarska fakulteta, Univerza v Pizi, Italija: Alessandro Poli
- ARRS (P3-0003, J3-7044, P4-0053, P4-0092)