

There are introduced some pro inflammatory methods already in use in cancer therapy. This summary is made to clarify that FD is not the only pro inflammatory method.

#### Embolisation

Arterial embolisation is the most similar method to devitalisation. Embolisation is conducted by metal coils, particulate agents as polyvinyl alcohol, soluble sponge, lipiodol with chemotherapy. The same effect is made by vessel ligation. (Goode J., 2004, Cancer imaging) Stopped blood supply results in coagulation necrosis the same necrosis type as seen in devitalisation but the necrotic process is much slower and less intense. (Fortyn K., 1987, Morphology) There is no mentioned induction of autoimmune complications connected to this procedure in review literature. The only possible immunology based complication mentioned is pyrexia 48-72 hours in the cases of HCC. Participation of chemotherapy in pyrexia must be taken into consideration since in most cases embolisation of HCC is conducted concurrently with chemotherapy. (Goode J., 2004, Embolisation)

#### Coagulation necrotic tissue in human body:

There is an interesting case study describing fate of necrotic tumor tissue in human body. 35 years old woman was treated for acute intra-abdominal hemorrhage originating in hepatic tumor perimeter of 7 cm. The bleeding was stopped after selective arterial embolisation. Patient underwent elective segmentectomy of affected segment according to department's protocol 6 months after embolisation. The patient was asymptomatic at this time. The resected tumor consisted only of necrotic material. The necrosis was so advanced that there was no possibility to determine histologic diagnosis. Diagnosis was assessed anamnesticly on the history of prolonged use of COC, age of the patient and the fact that the tumor was vascularized only arterially as a hepatadenoma. (Huurman AL, 2006, Necrosis)

#### Embolisation devitalization comparison

Both methods cause the same type of necrosis. Devitalization creates two departments. The departments are decidedly separated by overlapping mattress sutures. One department contains tumor tissue which undergoes necrosis and for some time inert processes which increase the concentration of proinflammatory substances. The other is separated by sutures from the first department and is unaffected by hypoxia. Communication between these departments is enabled only by small area among the sutures.

Embolisation also creates two departments one with tumor tissue undergoes necrosis the other is unaffected. The difference is that there is saved communication between these departments by lymph vessels and in some cases there is also saved vein supply. Saved communication leads to dilution of pro inflammatory substances in the necrotic tissue which results in slowing removal of necrotic tissue and decreases the peak and affective time of proinflammatory gradient activity in the vicinity of tumor. Affective time in this case is the time when proinflammatory gradient is above the level of immunosuppressive gradient in the nearby immune tissue which is sufficient enough to cause shift to Th1 polarity.

#### RFA:

RFA causes coagulation necrosis by application of high frequency alternating current resulting in the increase of temperature in targeted tissue to 60 up to 100 degrees C. (Haen P, 2011, More) The more over protein denaturation occurs when the temperature is above 45-50 degrees of C, thermal coagulation at 70 degrees of C, tissue desiccation at 100 degree of C. Tumors of diameter up to 1 cm are electrocoagulated by placing the probe in the center of the tumor. 30 seconds after the procedure reached 60 degree of C. Larger tumors are electrocoagulated by placing the probe repeatedly at the deep margin of the tumor. Targeted temperature don't have to be reached due to heat sink especially near major vascularized structures in such cases the temperature can reach about 45 degree of C. (Bilchik J., 2001, Radiofrequency)

It causes modest and transient up to several days changes in cytokines levels. There has been

reported increase or no change of IL1 beta, IL-6, TNF and postinterventionally IL-10 in peripheral blood. No serious inflammatory response was documented. Elevated levels of HSP-70 was found in margin of ablation zone in animal model lasting for up to 24 hours. The same finding – elevated level of HSP-70 was detected one day after procedure in cancer patient correlating to applied energy. RFA also leads to activating of cellular immune response the extend of this activation varying on tumor type individuals and timepoints. Infiltration of transitional zone by macrophages, plasma cells, DC, CD3+ and CD4+ has been reported in animal models as well as infiltration of neutrophils and lymphocytes in distant untreated metastases. (Haen P, 2011, More)

RFA deviatization comparison:

RFA creates spheres of different tissue injury from tissue desiccation to protein denaturation. It reasonable to suppose that in the vicinity of ablated tissue the temperature decreases to normal levels in some distance. Different stage of tissue damage creates proinflammatory conditions as being shown above. The proinflammatory area of the ablated region is much larger than in the case of devitalisation but it leaks the regulatory mechanism which would ensure remaining of sufficient proinflammatory gradient for sufficient time. Benefit of deviatization is in existence of this mechanism ensured by small area of communication between proinflammatory depo and it vicinity.

Cryoablation:

Cryoablation applies the temperature of – 160 degree of C to affect tumor. It destroys tumor by formation of ice crystals in cell and by causing ischemia by vascular and endothelial tissue. 1 to 6% of patients suffers with SIR called cryoshock phenomenon. This method according to danger model should have immunosuppressive as well as proinflammatory affects. Immunosuppression is thought to be caused by apoptotic cells proinflammatory affects by necrotic ones. This duality is supposed to clarify later proinflammatory response which is preceded by previous stage of immunosuppression. There has been found significant elevation of INF gamma, TNF, IL-6, IL-12 but not IL-10 several hours after procedure. Elevation of TNF and INF can remain elevated for up to 4 weeks. Results of inducing specific antibodies is inconclusive. There was found Th1/Th2 ratio increase in treated patients with liver metastases. (Haen P., 2011, More)

Cryoablation to devascularisation:

It seems that all amount of cryoablated tissue in some way influences immune system which is the same as in deviatization. There is possibility that the unregulated speed of releasing proinflammatory substances can be responsible for cryoshock phenomenon.

Spontaneous regression of thoracic metastases

Spontaneous regression is a regression or disappearance of metastatic tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease. (Everson TC., 1959, Spontaneous) Regression of thoracic metastases is reported in literature to accure in 0,8-7%. (Pramod Rao, 2011, Spontaneous) Among the most cited cases of thoracic metastases disappearance of RCC in literature from 1951 to December 2007 are decrease in tumor burden, from a partial or total nephrectomy, irradiation of primary tumor, activation of immune system, changes in diet, intake of nutritional supplements, drugs or herbal medication, hormones, steroid. Biological causes include infection, fevers, septicemia. (Toshita Kumar MD, Nick Patel DO, Arunabh Talwar MD, Spontaneous regression of thoracic metastases)

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