Summary

Dr. Karel Fortyn's devitalisation (FD) is a novel approach to cancer therapy. It is a surgical method based on the discovery that leaking debris from completely ligated tumour tissue that has been left in situ has the potential to induce specific anti-cancer immunity (**16**). FD seems to achieve the best results in the cases of ligating primary tumors in patients who have not undergone previous chemo/radiotherapy.

At least 11 cases of successfully cured patients by FD (5, 6, **11**, **13**) have been described. Most of these patients were treated in the state of generalized or advanced tumour disease. Only one of them is reported to have received a single dose of chemotherapy prior to FD (6). FD was performed in combination with immunotherapy by interferon alfa in some cases (6). Reports of cured tumours include melanoma (6), colorectal cancer (5, 6), adenocarcinoma of stomach (**11**), adenocarcinoma of kidney (**13**), scirhuss of the rectosigmoideum (6). A new case of a successfully treated patient with generalized colorectal cancer is presented for the first time in this study as an illustration of the potential of FD.

Some basic questions need to be answered in relation to FD. The first issue is the safety of FD, the second is the anticipated mechanism of action and lastly whether there are similar methods in use in contemporary medicine.

The safety of any medical intervention is, undoubtedly, of paramount importance. Extensive literature search has been done to find out whether it is possible to leave ischemia injured tissue in human or animal body without causing serious adverse effects. The research involved reviewing FD oriented research as well as other studies dealing with other issues in which there was ischemia injured tissue left in the body.

It was revealed that non tumorous (**18**; **19**; **20**; **21**; **22**; **23**; **24)** and tumorous **(26, 27,28,29)** tissue with impaired blood supply can be left in animal body without causing serious adverse effects in many circumstances in non FD oriented studies. The same finding has been confirmed in non FD oriented human studies which included non tumorous **(30,31,32,33,34,35,36,37,38,39,40,41,42,43, 44,45,46,47)** and tumorous tissue **(48,49,50,51,52,53,54,55,56,57,58,59).**

Described changes in ischemia injured tissue follow the same pattern in both the FD oriented research (**11** ; **12**; **13**; **14**; 5, **13**; **16**; **13**) and non FD oriented research (**18**; **19**; **20**; **21**; **22**; **23**; **24**) and tumorous (**17**) and non tumorous tissue (**13**; **19**). Arterial and venous occlusion occurs on the macroscopical level, followed at first by a swelling of ischemic tissue, than by shrinking and eventually, by fibrous replacement of the tissue. Fibrous replacement has been confirmed at the microscopical level as well (**17**; **13**; **21**). This process seems to be species independent, at least in mammals (**13**; **19**) and birds (**24**).

Partial tissue fibrousis can also be caused by selective occlussion of lymph vessels as has been demonstrated by Zhang in rat kidneys (**25**). Fibrous replacement can be impaired by the presence of collateral circulation as proposed by Troell in the case of dog´s spleen (**20**). Preservation of testicular tissue in dogs has been reported in some cases by Griffiths (**22**) and ovary in bitches reported by Awasum (**23**).

It can be supposed that reproductive tissue is more resistant to ischemia injury and fibrous degeneration so there is especially needed complete occlussion of lymph and blood circulation which can be guaranteed by ligating the whole tissue as proposed by Morgan who performed ligation of cock testes (**24**). Probably the most interesting finding is the possibility of leaving ligated colon in situ even in the presence of bacteria in the lumen as has been reported in pigs (**12**).

Papac investigated bacterial and endotoxine migration from ischemic colon. The ischemia of colon was induced by ligating of all marginals vessels. The experiment lasted for 6 hours. He could not prove bacterial migration through ischemic wall of colon during this period of time, nevertheless he was able to prove the presence of endotoxine in peritoneal washings and in portal and systemic blood samples as early as 30 minutes after finishing the operations (**88**). A proper examination of stoll can, therefore, be recommended prior to any attempts of colon ligation.

The non FD oriented animal research with induced tumor ischemia inditacate that such an

approache can effect tumor at the site of tumor ischemia injury **(28,29)** and even it´s distinct metastases **(26,27).**

FD oriented research in animal tumor model found difference in effectiveness of FD between the pig (**17**) and rat model (**16**). Insufficient rise in HSPs levels in rat model is thought to be explanation for this difference **(16)**. According to the immunological model of FD presented in this study some other factors can be involved as well. These factors include differences in immune systems of the species, different intrinsic tumour immonogenity of the tumors studied, operational stress, biobehavioral influences.

Observations similar to those of animal models have been made in humans. It has been found that malignant (**52**; **53**; 5, **11**, **13**; 6, 7) and non malignant tumours (**49**; **55**; **56**; **57**; **50, 51**) and non tumour tissue (**30,31,32,33,35**) with impaired circulation can be left in the body in many different situations. There is a wide range of indications for such methods ranging from foetal reduction (**39**) to the therapy of symptomatic fibroids of uterus (**49**) hemangiomas (**57**) or placental tumors in utero (59) in contemporary medicine. Therapy of plancetal tumors in utero (59) and foetal reduction (37,39,40,41) seems to be the most striking evidence of the safety of such methods.

One of the most unexpected finding during the literature search was the commonness of concomitant vein and arterial ligation or arterial ligation only in the therapy of hyperthyreodism in the early 20th century (**52**; **31**; **32**). This method has been declared by Mayo as safe and simple. He advocated its usage prior to thyreodectomy in some cases (**31**). There was also found that ligation of broad ligament containing all structures including blood vessels in the therapy of fibroids of uterus was used in the past (**48**) and rediscovered in contemporary medicine (**49**).

There was found a study indicating partial activation of specific immune system with impact on distinct metastases. There was induced induced ischemia of renal carcinoma of kidney followed by nefrectomy (**53**).

The other task was to identify possible adverse effects in connection to FD as a therapy in which there is left ischemic tissue in the body.

There was found a report about cross reaction among melanoma cells and melanocytes in the presence of high levels of HSP70 by Perez in mice model(**80**), vitiligo in MeLiM pigs during animal testing of FD (**17**) and vitiligo in cases of spontaneous melanoma regression (**89**). These reports support the importance of a HSP pathway in FD but also indicate the possibility of antigen cross activation in the same cell lines. On the other hand, there is a possibility that a reaction involving histologically normal melanocytes, especially in MeLiM pigs can be directed against an unknown mutation in these cells.

A case of peritonitis requiring surgery revision was reported in one out of 25 patients during the first phase of clinical trials as the most serious adverse effect in patients with generalized colorectal cancer. No serious adverse effects were reported in 26 patients with generalized melanoma during the trial (7).

Identification of similar procedures in contemporaly oncology was the third task to be solved since the idea of leaving tissue which is about to undergo necrosis inside human body may seem to be rather odd.

Tumour arterial embolisation is the most similar method to devitalisation. Embolisation is conducted by metal coins, particulate agents as polyvinyl alcohol, soluble sponge, lipiodol with or without in combination with chemotherapy. The same effect is produced by vessel ligature (**95**). A stopped blood supply results in coagulation necrosis which is of the same type as necrosis seen in Fortyn's devitalisation, albeit the necrotic process is much slower and less intense (**13**). There is no mention of induction of autoimmune complications in connection with embolisation in review literature. The only likely immunology based complication mentioned is pyrexia 48-72 hours after the procedure in the cases of treating HCC. Participation of chemotherapy in pyrexia must be taken into consideration since in most cases embolisation of HCC is conducted concurrently with embolisation (**95**).

Cryoablation is another method that induces necrosis of tumor tissue and in which necrotic tissue is left in body. Cryoablation applies the temperature of – 160 degree Celsius to effect tumors. It

destroys tumours by formation of ice crystals in cells and by causing ischemia by injury of vascular and endothelial tissue. 1 to 6% of patients suffer from SIR which condition is called cryoshock phenomenon. This method according to danger model should have immunosuppressive as well as proinflammatory effects. Immunossuppression is thought to be caused by apoptotic cells proinflammatory by necrotic ones. A significant elevation of INF gamma, TNF, IL-6, IL-12 but not IL-10 several hours after procedure has been found. Elevation of TNF and INF can remain elevated for up to 4 weeks. (**96**).

It seems reasonable to assume that combination of FD with reduction of tumour mass, especially of tumour metastases by RFA, embolisation or cryoablation as well as in combination of these procedures with continual or bolus administration of HSPs inside the ligated tumour could decrease the immunosuppressive effect of the tumour and boost the antitumour immune response.

The first immunological model of FD is presented in this study. It was made in an attempt to link results acquired in animal models with observations made in out of clinical trial treated patients. The most important limitation of this model is that it is not based on FD oriented research done in humans but on animal models and laboratory findings.

It is based on the idea that cancer can be viewed as a disease of transformed cells or failure of immune surveillance. The latter approach led to the discovery that cancer is an immunity modifying disease. It has been found that cancer development through time and space is followed by spreading of tumour induced immunosuppression which protects tumour development. These findings were reflected in immunoediting hypothesis (61).

Disturbing or even reversing this process would bring on restoration of immune surveillance and induction of antitumor immunity response. Creating pro-inflammatory insult is a way which could produce such an effect. An ideal pro-inflammatory insult should be able to activate the immune system, however, not cause serious adverse effects such as SIR.

Fortyn´s devitalisation is a method that employs this approach. Pro-inflammatory insult is created by ligation of tumour tissue. In addition, ligation of the tumour severs humoral communication between tumour and the rest of the body. The outcome is the decrease in immunosuppressive activity corresponding to the amount of ligated tumour tissue.

According to this model ligated tumour tissue undergoes changes which increase its immunogenicity and exposure of TAAs.

Tumorous and non tumorous DAMPs leak out of the ligated tumour and stimulate specific and non specific immune response. Activation of pro-inflammatory immune response creates Th1 polarity gradient which reverses tumour protective Th2 polarity of the immune system. The intensity of stimulation of the immune system is regulated by the presence of small areas among overlapping matraces sutures. These small areas create a permeable interface which regulates the intensity of stimulation of the immune system by determining the amount of leaking DAMPs. The size of the area among sutures regulates the time period for which the insult will last since there is only a limited capacity for cells and debris transportation through this tiny space. Pressure among sutures is thought to prevent neovascularisation by not enabling the creation of free space among endothelial cells. At the same time it should enable migration of cells of the immune system inside hypoxic department.

It has been suggested that activation of immune system by HSPs-antigen complexies is the most important mechanism involved in inducing specific anti-cancer immunity response. Another important mechanism proposed is the activation of immune system by TLRs.

There was found that patients with the same histological type of tumour and the same stage of disease can differ in clinical effects and clinical response to FD. Patients with ligated primar tumour seem to be much more responsive to FD than patients in whom there were ligated metastase only.

The observation of different responsiveness to FD in histologicaly same type of tumor can be related to the fact that histologically the same tumour type can substantially differ in its immunogenicity as being shown in LR and LS lymphoma inoculated mice (86). Unfortunately, there is not available a tumour classification based on tumour immunogenicity at present. Despite this fact some indicators can perhaps be of benefit in estimating tumour immunogenicity such as the

level and type of leukocyte infiltration in epithelial and marginal zone of the tumour, which has been shown to be an independent prognostic factor in disease free survival in colorectal cancer (**90**).
There seem to be some ways which could potentially overcome the effect of lower intrinsic immunogenicity such as immunotherapy by interferon alfa which has already been used in combination with FD with benefits (6) or cross activation among TAAs and bacterial antigens. The use of bacterial antigen as an adjuvant in vaccines is already known as „immunologist's dirty secret"(**86**). Moreover, bacterial and tumor antigens seem to activate the same immunological pathways (**91**) and presence of bacteria on the surface of colorectal tumours can be suspected of boosting anti-cancer immunity, if FD is performed in colorectal tumours.
There was regulary observed recurrence of cancer development about a year after ligation of melanoma metastes only. There has been found that each tumour contains a unique accumulation of mutant sequences with novel antigen epitopes that create specific „antigenic fingerprint"of each individual tumour (**80**). The „antigenic fingerprint" and gene expression do not change themselves only among individual tumours but also among primary tumours and their metastasis. The more over immunohistochemical phenotype of metastases differ according to metastatic site (**83**; **84**). So there is possible that primar tumor includes immunogenic antigens which are incommen for itself and all of the metastases. On the other hand metastases can lack these incommen immunogenic antigens.
Another obstacle that would be needed to overcome in order to achieve maximum effectiveness of FD is the evaluation of less immunosuppressive operation management such as the use of laparoscopy prior to laparatomy (**92**) or using spinal block in the management of operative pain (**93**). No less important in humans seems to be proper control of biobehavioral influences (**94**).
Impacts of other factors on the efficiency of FD such as minimal duration of inflammatory insult, status of metabolism, status of hemopoiesis are questions to be solved as well.
The biggest advantage of devitalization, according to Fortyn, is that this method is simple, cheap and can be effective under specific circumstances. The more over patients do not lose precious time if this method is used and found uneffective since neoadjuvant surgery is usually applied in oncology therapy.

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