

All that glitters is not gold.

(National idiom)

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The sentiments that were stirred around the evidence-based methods in the cancer therapy and their efficiency motivated me to write this article. The most active persons, who expressed their opinions, were either anonymous bloggers or specialists from other walks of life who have never treated cancer patients. Interestingly, though, how lay people can sometimes put themselves in a capacity to know better than physicians, once they want to add such critical remarks. But ***where exactly the oncologists sin against the truth?***

At first ***by not informing a patient about his or her true prospects.*** Every cancer patient silently hopes to be treated fully or to have a complete recovery, but in fact only small portion of them can achieve it. One must also take into account that former cancer patients have an increased risk not only to recurrence or metastases but also to more frequent development of tumours in other locations, if compared to healthy individuals. A person might think — the more modern or aggressive the therapy the larger are chances to recover fully. It is not easy for a physician to convince a patient to consent to certain toxic therapy, which can also entail persisting consequences to health in general; perhaps therefore a hope is involved — maybe you will benefit from it (the patient hears — maybe I can be healed). It will help to some part of them — it will prolong life, reduce suffering, but will not heal. The patient in the latest stages of the illness wants to hear and actually hears what he wants the most — to get rid of cancer. We can often hear in mass media reprimands about false hope given to cancer patients that is actually a lack of understanding about the real practice or unwillingness to face the truth. **There is no panacea in oncology! Neither in the cheapest nor the most expensive segment.** If one manipulates with the term “lifesaving medicine” one actually lights up a misleading beacon at a rocky coast. Just like a drowning man trying to catch a straw, also a cancer patient is ready to do whatever it takes to get that expensive medication that a state cannot provide. We hear loud donation campaigns to get modern, innovative cancer treatment remedies, but after some time it all calms down and those who waited in hope are just buried in Latvian graveyards leaving wounds behind in the hearts and wallets of their relatives. By honestly informing a patient about the true situation, spread of disease and helping methods we at least give an opportunity for a patient to make his or her decision at least in the later stages of the illness. On the moment when the patient's life becomes a line segment, it would be only normal to take into account how the patient wants to spend that remaining time. To spend more time among the dear ones or to suffer with severe side effects of toxic medicines, to be constantly connected to systems or to stay in hospital on a regular basis. I can draw a parallel between the situation and the fairy-tale about a brother who stands in the crossroad — if he rides to the left, he will meet a dragon; perhaps he manages to cut off some of his heads but new ones will grow instead. This is by no means an easy conversation but if we are to lay the cards on the table, the patients quite often choose symptomatic therapy to avoid additional suffering. Many countries even recommend putting the patient in palliative and symptomatic care as soon as possible. Not only this therapy will be easier to handle but it will also allow the patient to decide individually about the quality of his or her remaining life under the shadow of the cancer, not to speak of expenses. It is true that opinions of patients and relatives may differ and often the relatives are those who choose on the patient's behalf.

Secondly, ***by claiming falsely that today we can cure cancer***. In some portion of cases — yes, but in the majority of cases — no (taking into consideration the proportion of latest stages of the illness in Latvia), if we understand that healing means complete removal of the disease for the rest of the life. **There are only three scenarios in the oncology – recovery** (majority of patients in stages I and II), **extending a qualitative life** (majority of patients in stages III and IV) **and releasing from suffering** (today — theoretically for everyone who needs it). Frequently referred five-year survival rate is a surrogate indicator, very convenient to compare the short-term impact of different therapies on the survival rate and to provide a general overview of prognosis for a person with certain tumour stage. Five-year survival rate means that the patient stays alive five years after setting the diagnosis and starting of therapy. It is measured in per cents, describing the patient group in general. There is no percentage for a patient and only binary division exists — whether the patient is alive or not. For example, five-year survival rate for 68%, although it sounds good, it nevertheless says that only 68% of the analysed patient selection was alive on the date of report. But it does not say that they are completely healed and healthy. Perhaps a patient dies a week after reaching the formally calculated five-year survival rate threshold. But the published statistics does not say a word about it.

Unfortunately, one can hear occasionally that if a cancer patient is alive five years since the illness he or she is cured. The disease, however, may come back or develop metastases also 10, 15 and even 30 years later. The medical literature and conference screens are full of illustrations showing hope-inducing curves depicting how the innovative medications extend life. But in the end these patients die of their cancer or its metastases. The non-relapse period (time from setting a diagnosis and starting a therapy until the first recurrence of the illness), the time until next metastases are instruments used when organising extensive clinical trials. But what is the benefit for a certain person? The majority of cancer patients want to live a long and happy life instead of 5 years or even some weeks or months more. But the non-progressive survival rate, unfortunately, does not correlate to real, clinically relevant extension of qualitative life. Often also the very patients and relatives think that the worse the tolerability of a medication and more side effects the better the impact on the cancer cells and the deadliest for them. However, the side effects are also a scream of tissues and cells about harm done. Unfortunately there is not a correlation between severe side effects and favourable responsiveness of the cancer on the therapy.

Thirdly, ***by naming the recent medications as innovations without any substantiation and discrediting the former ones***, one distorts the real picture in the society's understanding that an additional funding for purchasing the medicine and their import will solve the problem of cancer. In Christmas of 1971, the U. S. President Richard Nixon signed a multimillion targeted investment in creating new medicines, because the existing chemotherapy (which, by the way, is still used) did not fulfil the expectations of scientists, physicians and patients regarding the recovery from cancer. An intense work started and new paths were searched for in what we today know as targeted therapy and innovative remedies. 46 years have elapsed, but people still suffer and die from the cancer. I was truly surprised at the fact that my colleagues were terrified at the large mortality indicators pertaining to the intestinal cancer in Latvia, explaining it with lack of new medicines, at the same time pretending not to see the indices of delayed diagnosis. In 2016, according to the updated data of SPKC of 12.06.2017, 867 patients out of 1,048 had morphologically set diagnosis (82.7%) of colorectal tumours (C18-C21) while only 366 patients or merely 35% were diagnosed in early stages (I+II).

Primarily delayed intestinal cancer is a serious challenge; the more cases will be there, the more we will fall behind from the countries with larger proportion of early diagnosed cancers in terms of mortality rate. The major problem therefore is not the lack of modern medications but a timely discovery of the

illness. Those who think (or are informed) that the more recent the medication the more efficient and better tolerable may also come to a disappointment. It is so in some cases, but not always. The main criteria in medicine in case of any drugs are their efficiency, safety and tolerability, regardless of the manufacturing or registration date. The medicine cannot afford an opposition — outdated vs modern. One can speak so only regarding the cars, ties or handbags. But the minds of people (both patients and their relatives) can be twisted to an extent unimaginable.

We know the conventional side effects of the chemotherapy and we also can handle them (more or less). Undesirable side effects of many innovative medicines, such as autoimmune reactions, are a riddle for both physicians and scientists. There was separate sittings devoted to it in the last ESMO congress in Madrid — how to discover them timely, how to evaluate and treat. In that congress I also did not read or hear any sensational report that someone would have been completely treated by means of these innovative remedies. It would require many years therefore it is more convenient to refer to the indicators I already mentioned to allow daydreaming to those who desire to recover.

Fourthly, ***by putting too much of weight on the drug therapy or even reducing it to chemotherapy and therapy with innovative remedies***. It does not pertain to oncohematological diseases that are treated basically with drugs. Treatment of solid tumours is based on three pillars — surgery, radiotherapy and systemic drug therapy. The surgery is the oldest method, mentioned in the oldest written evidence, but we can speak of serious cancer surgery starting with the middle of the XIX century, after anaesthesia was introduced. The surgery is a local therapy method that removes the cancer focus and it is not affected by either the speed of cell division or possible sensitivity or resistance to rays or drugs. If a surgeon agrees and offers a surgery, one should not decline it. In early discovered stages the surgery is the basic treatment method and it may be the case that no additional methods are required. Nowadays surgery can significantly extend survival rate also in patients with very far progressed process, by surgically removing separate metastases. What has been removed will probably make no problems. No matter how invasive this method is locally, it affects the state of the healthy tissues elsewhere considerably less. It is true that oncosurgery has become less invasive during the last ten years. Surgeries during which organs are preserved are almost a daily practice in case of some tumours. Why? Because the remaining cells will be destroyed by means of radiation or systemic therapy.

The radiotherapy began in the turn of XIX and XX centuries. It is also a local therapy method that can be applied alone or in combination with others. Different tumours have different reactivity to radiotherapy therefore this method is not always applicable. Method's possibilities are restricted by different health conditions of patients, which sometimes require refusing from the radiotherapy in the very beginning, and sometimes it must be stopped or doses of radiation and regimen must be changed. It is, however, still a method of choice in case of many tumours, especially metastases and various complications. The stereotactic radiosurgery that is available in Latvia is a step towards a more selective destruction of a tumour in especially hard-to-reach locations, which besides is a short one (1-5 procedures), very well tolerable by patients and having a minimum impact on the healthy tissues.

The systemic drug therapy in the oncology began along with the World War II, when drugs were created not only to heal oncohematological but also solid or mass tumours. Not only is it the most recent method, but also one that develops and spreads most rapidly. Yet, it would not be correct to reduce the systematic drug therapy to chemotherapy and innovative remedies. Today we have more extensive range — hormonal therapy, biotherapy, targeted therapy, immunotherapy, including cancer vaccines, dendritic cell therapy, oncolytic virotherapy, check-point inhibitors, therapy with different cytokines.

Significant paradigm shift can be observed during the last years (a strong evidence was also the ESMO 2017 congress), where the **immunotherapy** celebrated its walk of fame. To be more specific, not remedies to affect body's immunity and complex means to boost natural protection, but extremely narrowed approach which employs blocking or activating of certain receptor or protein on cancer cell's surface. But we all know that cancer is able to change very quickly. Nevertheless this not so harmless method is combined with other therapies and adapted to patients with tumours of different localisation. Let's hope that the panacea has been found, although the published, randomised, double-blind and other seemingly perfect studies do not evidence that.

I would also like to speak about the frequent reference to guidelines, which are still merely a recommendation. The prescription medications are prescribed by a physician. Interestingly that both American (NCCN) and European (ESMO) guidelines do not provide only one true course of a therapy. The scope of methods offered is rather wide and a physician can choose also from the range of "old medicines." Besides one can also find in the guidelines such offer as the best supportive care which does not necessarily mean "writing off" the patient, but instead respecting of the wholeness of his body functions. It is common in Latvia to blame that a registered and compensated medication is included in the national guidelines, such statement being absurd in itself. One can also hear or read reproach that the new and efficient remedies should be included in the compensation lists. The list of compensated oncological medications in Latvia basically corresponds to the recommendations of the World Health Organisation. Besides, each year approximately 5,000 patients die from the cancer in Latvia, and the major part of them received drug therapy in some stage of the illness and one part have received them during the last months of their lives. Basically these have been evidence-based medications that have been tested in smart clinical trials. Why did they die then?

Fifthly, *by claiming unsubstantiatedly that only evidence-based therapy can be efficient*. The idea of the evidence-based therapy belongs to the insurance companies and healthcare funders (for example, British National Health Service) in order to regulate the drug use according to some substantiation that is based on evidence. Today we hear that unless a drug is tested in randomised double-blind clinical trials it is not only efficient, but also safe for a patient. Actually a good conception that bases on evidence has turned into medical totalitarianism.

In order to register a medication one must have objective data about its efficiency and safety. What do we see in the global experience? I will mention just some examples. In March 2011 FDA (Federal Drug Administration) registered a medication ipilimumab to treat inoperable or metastatic melanoma, on the basis of a double-blind randomized clinical trial involving 676 subjects (MDX010-20) and referring to the total survival, no-progression survival and frequency of the best total response as the general goal. The best response to the therapy was observed in 10.9% of patients out of all who received drug monotherapy. Due to severe side effects 10% of patients suffering from them stopped using the medication. A correct trial with clear goals. Some years later we can see another summary publication¹ about the same drug. It is an assessment of several trials (prospective, retrospective, double-blind, randomised), including 1,861 subjects with inoperable or metastatic melanoma. High level summarising study showed that the average survival was 11.4 months with following plateau stage 3 years later. Is it much or little — the question is relative. Meanwhile in the Chemoprotocols Manual 2017 (www.chemoprotocols.eu) we can read, for example, about use of pazopanib in treating metastatic sarcoma in soft tissue (not only fatty tissue) after an unsuccessful chemotherapy. The goal — no relapse survival in comparison to placebo group. This third phase study was carried out in 72 healthcare establishments in 13 countries. Besides, it was also a masked trial where neither patient nor physician nor data processor knew who received the active substance and who didn't (placebo

group). Referring to this particular study² the authors conclude that the average no-progression interval for 369 recruited subjects was 4.6 months in comparison to 1.6 months in placebo group and the average survival was respectively 12.5 against 10.7 months in the placebo group. Nevertheless side effects were frequent in drug group: fatigue (65%), diarrhoea (58%), turning of stomach (54%), weight loss (48%) and hypertension (41%). The theses do not reveal what was the proportion of patients who actually reacted to this therapy, yet the final conclusion says that this drug is a new therapy opportunity for these patients. A correct conclusion that is based on trials and therefore also in the evidence. These were only two randomized examples. **In the oncology there is not a single medication what would guarantee 100% effect, especially in case of spread or metastatic illness** (even a short-term), not to mention full recovery. Therefore if, in case of a randomized double-blind study it is established that the drug under the study is efficient for X% of patients, then it was not efficient for the remaining part (100% - X%) and by transferring the data of a carefully planned and perfectly recruited study to the real life, the numbers may appear even worse. Nevertheless these 100%-X% patients will be offered an evidence-based but possibly an inefficient therapy for them, not to mention the tolerability.

There is another randomised example about side effects³ observed in correct high-level studies. 945 untreated patients with inoperable or metastatic melanoma (stages III and IV) in a double-blind, III phase randomised trial were divided into groups 1:1:1, in order to ordinate either nivolumab in monotherapy, nivolumab in combination with ipilimumab or ipilimumab. The goals of the study were to compare no-relapse survival and total survival. The average no-progression survival in the combined group (Nivolumab + Ipilimumab) was 11.7 months, but the total survival was not indicated in that publication due to small time span of the observation. Therapy related side effects in nivolumab group were observed in 82.1% patients, in the combined group 95.5% while in ipilimumab monotherapy group in 86.2% patients. The most frequent were diarrhoea, fatigue and itch. Meanwhile grade three and four side effects were observed in 16.3%, 55.0% and 27.3% of patients respectively. Due to variable severity of side effects the therapy was discontinued by 7.7% of patients in nivolumab group, 36.4% in the combined group and 14.8% in ipilimumab group. Yet it is stressed in the conclusions that nivolumab alone or in combination with ipilimumab provided a credibly longer no-progression survival than ipilimumab alone. If you wish to live longer, count on possible side effects. Therefore a physician would have to honestly inform a patient both about the design and efficiency of the published trial as well as the expected survival and toxicity. In Latvia we can usually see paternal relationships between a physician and a patient, and the latter is usually not asked for his or her opinion. But we can change it if we want to.

In the concluding part I would like to point at a Biblical similarity, namely, the Sabbath was made to meet the needs of people, and not people to meet the requirements of the Sabbath. Also medical technologies (including various drugs) have been created to help people (instead of creating additional suffer and disproportionate expenses) instead of patients serving the market outlet for drugs that are not always equally efficient and safe, no matter what fancy trials it took to examine them.

1 Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, Patt D, Chen TT, Berman DM, Wolchok JD. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma// J Clin Oncol. 2015 Jun 10;33(17):1889-94.

2 van der Graaf WT, Blay JY, Chawla SP, Kim DW et al.; EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial// Lancet. 2012 May 19;379(9829):1879-86.

3 J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma// N Engl J Med 2015;373:23-34.