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Some Hidden Truths about Cancer

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ABSTRACT

Cancer is a deadly disease because we do not fully understand its mechanism and, like many other deadly diseases before, do not know how to manage it correctly. Inasmuch as this is a blank statement that we all know, it is also a statement acknowledging our desire to know and to conquer this disease, like we did for many other diseases that wiped millions off this planet before. We conquered these deadly diseases because we understood them to a point that we could develop highly effective therapies to control them. For cancer, this proved to be a much harder task than before. We have spent much more resources on cancer than any other diseases we have faced, yet we have hardly changed the deadly nature of it. We thought we have known this disease much better than other diseases but that understanding seems to rest at the level of cancer as a uniform disease, we still seem to be clueless when facing a real-world individual case. Here I would like to discuss cancer as a disease, especially as a deadly disease from few different angles than before. Most my views stem form curiosities accumulated over a dozen years of clinical observations and management of cancer. Many of these curiosities, after persistent pursue, have returned with fruitful answers. This assay present some of these answers with extension to possible truth about cancer as an individual disease.

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Tumors Often May Not Be That Malignant

The definition of cancer is a clinical term for a disease indicating a set of symptoms and death associated with growth of tumors in the host. Whereas cancer is always a systemic disease, tumor may not be. This seemingly obvious difference often is ignored by most clinicians and all patients. To them, a discovery of a tumor means a diagnosis of cancer, and many times a sentence to eventual death. Successes of survival after treatment is always labeled in social media as "miracle". In reality, I have seen many times (as often as 30% cases) of not so deadly tumor cases. The success for survival from a simple surgical removal of tumor is not miracle but a natural consequence of a not so deadly tumor. In other words, not all tumors are highly malignant. In fact, the malignancy of tumors has such a broad distribution ranging from a benign growth (or pre-cancerous growth) to limited local invasive growth to widely metastasized growth. Hardly any two tumors are identical in its malignancy. Strangely enough, most people ignore those non or not so malignant tumors, but assuming that all tumors are deadly dangerous. Like any snake could have lethal bite, when one cannot tell which one snake is not deadly dangerous, he must assume that all of them are all. So, despite that at least 30% tumors labeled as "invasive growth" are not that much malignant to easily cause lives, all tumors are treated equally lethal by clinician and patients. Is there a problem doing so? Yes, there is. Inasmuch as major tumor reductive treatments such as chemotherapy and radiation therapy are agents causing genetic mutations by themselves, the incorrect use of such means on non-malignant tumor cells may cause the generation of a few much more malignant cells among killing many others. The net effect may lead to true recurrence that are much harder to control then the original tumor. For example, about a 25-30% of ovarian cancer cases are caused by inflammation-driven non-autonomous replicating tumor cells that do not have the ability to spread and establish metastasis beyond pelvic cavity despite large tumor size and heavy ascites incubating countless micro-lesions. For these cases, repeated chemotherapy may reduce both ascites and lesion size significantly, and may help to suppress post-surgery recurrence by residual lesions, yet it may also increase the chance of mutation that turns a non-autonomous replicating cells to a variant cell capable of autonomous replication. After all treatments down, visible tumor burdens are gone, these few mutated cells may lead to eventual recurrence much more deadly than the original tumor. Such cases are taking places in daily clinics and I have seen several times of such events and had discussed at least one before [1].

The difficulty is how to measure the malignancy of a tumor, or even more challenging, the malignancy of each component of a mixed tumor as most tumors are probably more mixed than pure. This is caused by the fragmentation in the definition of tumor malignancy in at least three categories. In one category, tumors are labeled by their so-called grade: while grade 1 (G1) means tumors consisting of high differentiation structure similar to normal tissue, for example lung alveoli, grade 4 (G4) indicates a tumor of lowly differentiated structure (or lack of any normal tissue structure). In group-based statistics, G1 tumor is often much less lethal while G4 tumor is highly lethal. In another category (the famous TNM staging), tumors are labeled by their distribution in the host. While early stage (Stage 1and II) tumors growing locally without spreading to other locations are considered less malignant, late stage (Stage III and IV) tumors with nearby or distant metastases are considered more malignant and lethal. It is difficult to say which of these measurements is more accurate because they cover majority cases with statistical predictions but leave many exceptions in individual cases. Current clinical practices adopt the TNM staging system and set detailed clinical

management guidelines based on this staging system [2]. A third unofficial yet widely accepted measurement of tumor malignancy looks at the activeness of tumor replication using markers such as Ki-67 in pathological analysis. Although there is no close link between high expression of Ki-67 in tumor cells and clinical outcome in patients, a general trend of high expression of Ki-67 (both in degree of expression in single cell and proportion of cells with high expression in the entire tumor) towards poor prognosis seem to exist and is often taken seriously by patients reading their pathology reports. These three categories, looking at different aspects of tumor behavior, all have their reasons to be chosen, yet none gives accurate and individualized measurement for a real-world case. A true measurement of tumor malignancy for individual should take all of these aspects into considerations. Inasmuch as most cancer death is caused by systemic spread of tumor, ability to form individual metastasis is the most critical factor influencing tumor malignancy. But current clinical measurement of this property of tumor only depends on TNM imaging and pathology analysis of surgical samples. The problem is the lack of tumor spread on imaging and pathology report may not indicate the lack of such ability by the tumor. Limitation of establishment of tumor metastasis is the hallmark of concomitant antitumor immunity, thus only when this immunity is absent, the lack of tumor metastasis may indicate the lack of ability to form metastasis. In reality, since over half of tumor cases may contain some degree of naturally occurring antitumor immunity, the evaluation of tumor malignancy based on lack of distant metastasis should be cautious. On the other hand, the lack of ability to form distant metastasis by a given tumor seems to be tightly linked to lack of autonomous tumor replication as indicated by Ki-67 expression. In certain locally invasive non-metastatic tumors such as thyroid cancer, the lack of Ki-67 expression is a common observation. On the contrary, in metastatic thyroid cancer cases, the tumor is always found to expression Ki-67. Similar situation has been observed in other tumors that the lack of expression of Ki-67 is always associated with lack of distant metastasis, and when there is a metastasis in such tumor, tumor cells in the metastatic lesion always express Ki-67 [1]. This seemingly tight association between autonomous replication and ability to establish metastases at distant locations makes sense. On the other hand, adequate expression of Ki-67 in a tumor does not guarantee that the tumor has ability to establish distant metastasis. The process of formation of tumor metastasis involves multiple steps ranging from tumor cell spread through blood and lymph paths to seeding at normal tissues and forming a blood supply (angiogenesis). Any defect in any of these steps would prevent the establishment of distant metastasis. In our experience, we have seen many tumors that fail to form metastases, locally and distant despite high expression of Ki-67. In addition, the location or micro-environment of a tumor lesion may have a critical limit on tumor metastasis. While primary tumor is metastasis-promoting, there is no convincing evidence to show that distant metastasis is capable of secondary spreading. The ability to spread to distant site and to establish metastasis by a primary tumor may be the specific micro-environment of the primary location, or may be the characteristics of the primary tumor cells. So far, our close observations seem to point to the micro-environment of the primary tumor that is critical for spreading and formation of distant metastasis. This is rather good news for cases where tumor variants formed at metastatic sites may stay there. Since escape from immune control through genetic mutation is a common feature of tumor evolution under pressure by immunity, this lack of secondary spread by metastasis seems be to a much-needed blessing.

One more aspect of tumor malignancy is the ability and rate for a tumor to generate variants capable of escaping from current control by therapy. Constant genetic mutation is a basic characteristic of a growing tumor. Under selective pressure by therapy, any mutation that generates escape variant would have a chance to become dominant population eventually. Mutations that lead to escape from targeted therapy in lung cancer is the best illustration of this mutation-induced population switch. While intra-molecule mutations may be overcome with new generation of the same inhibitor class, mutations in other driver genes results in complete loss of control by a single class of target drugs. In almost all patients taking targeted drug therapy, such escape eventually develops, only different in timing. A rapidly changing tumor population therefore is much more lethal than a slowly changing population, and this translates to difference in patient survival. This constant variation through mutation is exactly why stable and long survival with tumor burden is such a luxurious hope for most cancer patients. On the other hand, mutation is only generated during tumor replication. Thus, any means to reduce the total number of replication events shall limit tumor variation. Two obvious ways would achieve this goal: to minimize tumor burden thus the number of total replication-capable tumor cells; or to slow down tumor replication rate significantly. Targeted therapy and antitumor immunity could suppress tumor replication and surgical removal of visible tumor burden could reduce total number of tumor cells. The combination of these two controls should create a situation to avoid tumor variation, thus achieve long term survival benefit [3].

Finally, the ability for a tumor cell to generate local inflammation is a critical yet totally ignored aspect of tumor malignancy. In essence, cancer is called cancer not just because it is a tumor but also it presents with deadly symptoms that are almost always the consequences of inflammation, local or systemic (cachexia). Almost no clinicians know how a tumor induces local inflammation and the significance of this event. Through the study of the mode of tumor replication, we have identified two modes of tumor replication based on growth factor requirement: the autonomous and non-autonomous replication [3, 4]. The autonomous replication relies on intrinsic mutational change that sends growth signal continuously to the replication pathway. In comparison, non-autonomous replication relies on growth factors coming from outside of the tumor cells. Local inflammation contains some of these growth factors that can drive tumor cell replication. Local inflammation is induced by chemotactic factors released by autonomously replicating tumor cells [5]. Thus, a tumor capable of driving high level inflammation can produce severe symptoms and drive the replication of non-autonomous replicating tumor cells. In some extreme cases, a small number of autonomously replicating tumor cells, often less than 3-5% of total number of tumor cells, can drive the growth of the rest more than 95% of non-autonomously replicating tumor cells. They also produce severe symptoms when the actual tumor burden is not so large. Because it is the symptom that cause tumor death, and symptoms are directly related to inflammation, the ability to induce inflammation is directly proportional to tumor malignancy.

Thus, tumor malignancy is composed of four aspects: the ability to replicate actively and autonomously; that ability to spread to distant sites; the ability to generate escape variants; and the ability to induce inflammation. Each of these aspects independently and coordinately contribute to the overall malignancy of a given tumor. Among these aspects, the ability to spread to distant sites seems to be decisive for the fate of life or death. A locally growing tumor,

regardless how fast it replicates, how severe symptoms it induces and how fast it mutates, as long as it lacks to ability to metastasize, its much lethal than a tumor that is not so fast-growing, with less symptoms but forms distant metastases. This is the reason why the TNM staging seems to be well accepted system for gauging tumor malignancy. Of course, there are many exceptions. For example, in all cases of brain glioma, the ability to induce severe local inflammation is the primary cause of rapid death. One needs to look all of these aspects when facing an individual cancer case. The accurate assessment of tumor malignancy in an individual case is critical for the accurate choice of management. As mentioned above, bombardment of non-malignant, non-autologously replicating tumor cells with chemotherapy or radiation causes mutation and tumor variation in residual tumor, that leads to recurrence driven by more malignant variants. On the contrary, when the malignancy of a non-malignant tumor is correctly evaluated, proper management avoiding these mutagens can be arranged. For example, for those seemingly serious ovarian cancer cases, surgical removal and local inflammation control after surgery may achieve much more satisfactory outcome than putting patients under multiple rounds of post-surgery chemotherapy [3]. It is difficult to convince any clinicians not to do post-surgery chemotherapy unless we know that doing so is harming rather than helping patients. That is why assessment of tumor malignancy is necessary and critical for cancer management. Even for most deadly cancers such as pancreatic tumor where patient survival is short, there may be cases where tumors are not highly malignant. Wrong and aggressive treatment is often the cause of accelerated death. Through the decade-long period of our observation, we have seen many cases where tumors are not that malignant and deadly across almost all types of solid tumors. One needs to assess carefully but definitely the malignant potential when facing a case of cancer, not assuming it must be deadly.

The Significant Role of Concomitant Antitumor Immunity

Antitumor immunity as a natural force against cancer is well-accepted by the medical society, especially with the development of checkpoint blocking therapy in recent years. But its role as a natural existence in cancer patients is continually ignored by the medical society. On the one hand, we seem to highly appreciate the use of activated antitumor immunity to treat cancer patients, so much so that many times the use of checkpoint inhibitor therapy has reached abuse level around us [6]. On the other hand, no one seems to know how much the naturally occurring antitumor immunity without using any therapy helps majority of cancer patient to battle this deadly disease. Without this naturally existing antitumor immunity, most patients with malignant tumors would die much sooner. One good reference is the case of hyper-progression taking place during some checkpoint inhibitor therapy-treated patients, a situation that is caused by over depletion of antitumor immunity [6]. The horrifying nature of this event is exactly what would happen if that patient had no naturally occurring concomitant antitumor immunity to begin with. Rapid progression of certain lesions in a patient with relatively stable course of disease often is also the result of mutation and escape from naturally established antitumor immunity. Such event marks the beginning of the terminal stage for the patient. By definition, concomitant antitumor immunity is an antitumor immunity co-existing with a tumor regardless whether the tumor continues to progress. Although this antitumor immunity is not strong enough to eliminate the target tumor, its presence has two major effects on tumor progression. First, it suppresses tumor replication thus limiting the progression of existing lesions. Secondly, it has the ability to eliminate newly established metastasis due to its ability to kill small tumor burdens. Due to this limitation on the establishment of new metastasis, concomitant antitumor immunity is the most significant factor contributing to disease control and patient survival as we all know that primary tumors rarely kill hosts and most patients die of cancer metastasis [7]. The effective limitation on cancer metastasis is the reason for many patients under prolonged survival with tumor burden.

Another key role played by the concomitant antitumor immunity is the key contributor of efficacy for almost all tumor reductive therapies [8]. These therapies range from the traditional ones such as surgery, chemo and radiation therapies to the more advanced therapies such as targeted therapies and more recent checkpoint inhibitors therapy. It is the activation of a pre-existing antitumor immunity that contributes to the real long-term efficacy of tumor reductive therapies. What keeps tumor from post-surgery recurrence is not the lack of tumor metastasis before surgery, but the monitoring and guarding by residual antitumor immunity existing before surgery [9]. Delayed recurrence is the consequence of a natural decay of this immunity. Any means to enhance this pre-surgery concomitant antitumor immunity would directly translate to enhancement of the residual antitumor immunity after surgery including to enhance the persistence of this immunity. In this aspect, neoadjuvant chemotherapy that activates concomitant antitumor immunity would contribute to enhanced protection against recurrence following surgical removal of tumor burdens [10]. Chemotherapy without the support of concomitant antitumor immunity may only result in short term tumor suppression through direct killing of tumor cells, and is often followed by accelerated tumor rebound. But when antitumor immunity is present and activated by chemotherapy-released tumor antigen and other mechanisms, the result could be a persistent suppression of tumor replication and elimination of certain small tumor metastases [11]. Even when activated antitumor immunity induce target tumor to express checkpoint molecules that resist to immunity suppression of replication, the activated immunity is still capable of eliminating tumor metastasis [6]. Thus, the efficacy of chemotherapy with or without involvement of antitumor immunity is totally different. Similarly, radiation therapy may activate antitumor immunity through the so-called abscopal effect that exhibits tumor suppressive effect on distant tumor that is not radiated. Yet, radiation therapy may also lead to suppression of antitumor effect that results in explosive growth of distant tumors. This is a true revelation of the metastasis-preventive function of a concomitant antitumor immunity when it is quietly working. Only when it is lost that its importance becomes obvious. Other local tumor reductive therapies such as Radio frequency ablation (RFA) and Transcatheter Arterial Chemoembolization (TCAE) used in liver tumors also rely on the activation of a pre-existing antitumor immunity to clear the residual tumors after the therapy-mediated killing [8]. Without the working of an activated concomitant immunity, these therapies often lead to incomplete tumor elimination and many times with satellite lesion development. The only tumor reductive therapy that seems not relying on the help of antitumor immunity to exhibit efficacy is tyrosine kinase-targeted therapy with small inhibitors. These inhibitors suppress growth signal transduction through binding to receptor kinase, quenching continued replication-driven signal due to mutation in these kinases. For example, several growth factor receptor mutations in lung cancer have been identified and small inhibitor drugs have been developed. These drugs have demonstrated significant clinical benefit in the past 20 years. Although the direct efficacy of these drugs seems not related to antitumor immunity, but antitumor immunity is a very critical part preventing development of drug resistance associated with targeted therapy. The cause for most drug resistance in targeted

therapy comes from the progression of non-target tumor cells that is always present. Their replication is not suppressed by target drug, but often controlled by concomitant antitumor immunity. Massive tumor cell death associated with early use of targeted drugs often activate this antitumor immunity, yet subsequent persistent use of targeted drug often leads to inhibition of this antitumor immunity (our unpublished observation) and subsequent loss of control of replication and growth of non-target cells. This is the main reason for eventual development of drug resistance in most cases. Based on this understanding, we have developed intermittent use of target drugs to avoid inhibition of concomitant antitumor immunity when it is present in a case. Such manipulation not only prevents inhibition of antitumor immunity, it actually activates this immunity through a yet unknown mechanism. The success has been impressive in multiple tumor types and with various target drugs (manuscript in preparation).

Antitumor immunity is also critical for suppression of tumor-induced inflammation that is the major cause of various symptoms and cancer death. This is achieved through two mechanisms. One is the reduction of chemokines for inflammation secreted by actively replicating tumor cells. These chemotactic factors are produced by autonomously replicating tumor cells to drive the replication of non-autonomous tumor cells, a coordinated growth pattern in many tumors, mostly adenocarcinomas. The suppression on active replication by antitumor immunity directly leads to reduced or cancel of production of inflammation-inducing factors and stoppage and death of non-autonomous replicating cells (the mechanism of tumor volume reduction by targeted drugs that only inhibit autonomous replication without actually killing target cells). Since local and systemic inflammation is the cause of cancer symptoms, suppression of the origin of inflammation leads to control of symptom and prevention of death. The second mechanism is the natural regulation between innate and adaptive immunity. Revolution of the immune system in human has created the two-step mechanism to deal with natural threat of infection: The innate immunity in the form of inflammation reacts to danger signals with massive local responses, while the subsequent adaptive immunity takes over and eliminate invaders thorough accurate antigen-dependent responses. The coordination between these two steps leads to the quenching of innate inflammation by adaptive immunity to reduce the pain and suffering of the host. The same mechanism is also working in cancer patients where innate immunity is incited not by infection but tumor. Almost all tumor-associated symptoms are results of this innate immunity. Similarly, this innate immunity may be regulated by antitumor adaptive immunity. It is therefore not surprise to see the loss of the adaptive immunity in terminal stage of cancer due to various reasons. Any measures that can maintain this antitumor immunity may therefore translate to direct survival benefits.

Immune recognition of individual tumor is a highly unpredictable event due to the fact that tumor antigens are totally different in different tumors. The HLA-defined 8-10 peptide antigen is individualized due to genetic variation, and the T cells that recognize these peptide antigens are also defined by individual genetic layout. The result is a highly variable mix of antigens and immune recognitions in various patients. Depending on the source of antigen peptides, immune recognition of a tumor population may range from almost all cells to only a minority portion. When a critical protein for cell survival is the source of antigen peptide, and when any mutation in this peptide is incompatible for survival, escape due to mutation becomes impossible and the immune recognition becomes "root" recognition, meaning that all tumor cells are recognized. Tumors with such immune recognition are tightly controlled by concomitant antitumor immunity, difficult to establish any new metastasis once immune recognition is established, and hardly can generate immune escape variants. Patients with such concomitant immunity bear good prognosis and survive much longer that for the majority average. In contrast, when immune recognition comes from newly mutated peptides that are not critical for cell survival, the concomitant antitumor immunity based on these antigens (neo-antigens as they are called), would only control the progression of tumor cells bearing such antigens. This immunity therefore will not control other tumor cells that do not express this mutation. A good example is the emerging of autonomous replication associated with distant metastasis in certain cancer cases where primary tumor replicates only by non-autonomous replication locally. Interestingly, such situation is often accompanied by emerging of immune recognition, too [3]. In cases with more than one autonomous replication driver, each population may have their independent immune recognition. This is often visible by the changes of representative tumor markers during therapy courses (our unpublished observation). It is obvious that the "width" of immune recognition is a critical factor in a given case of cancer. Unfortunately, since tumor antigens are often hard to identify, there is no established way to measure how broad an immune recognition in a given cancer case is. However, certain clinical experiences may help to evaluate. For example, a strong presence of large number of T cells infiltrating a tumor evenly often indicate there is no obvious variant tumor population that is not recognized by the concomitant antitumor immunity. On the other hand, in a tumor presented with more than one structure and grade, T cell distribution may show obvious bias in that certain population of tumor may have little or no T cells infiltrating while others have plenty. This is a clear sign of partial recognition of tumor population. Due to the lack of immune recognition in one portion of a mixed tumor, one would expect to see the progression of this portion and distant metastasis formed by this variant. In such complicated case, we are actually dealing with not one, but two or even more tumors with independent growth patterns and concomitant antitumor immunity. The patient's survival, of course, would be determined by the worst balance of tumor malignancy and concomitant antitumor immunity among all sub-populations.

Thus, one can see that antitumor immunity is involved in almost every aspect of cancer. Unfortunately, it has been continuously ignored by clinicians when managing patients. For example, no clinician knows how to choose the right timing for surgery based on the status of the antitumor immunity in a patient. As such, he does not know whether tumor will recur after surgical removal of the primary tumor in that patient. Oncologists do not choose chemotherapy to activate patient's antitumor immunity (or else he would not bombard his patient with continued highly toxic chemotherapy drugs). They do it to kill tumor cells by the direct toxicity of the drugs [12]. When efficacy disappear, they claim that a drug resistance is acquired and move to next line of chemotherapy (often fails, too). Radiation oncologists apply radiation to local tumor for the killing of tumor cells without concern on simultaneous killing of antitumor T cells and its consequences. Even with the so-called immunotherapy using immune checkpoint inhibitors (ICI), clinician's choices often are not based on the status of antitumor immunity. They choose checkpoint inhibitor therapy purely based on hope (for miracle). Many abusive uses that either results in waste of patient's money (because these ICI antibodies are often not covered by insurances) or leads to accelerated tumor progression have been observed (estimated over majority of cases) [6, 13]. In all of these situations,

if clinician could incorporate the status of antitumor immunity when choosing the correct therapy form, a much better antitumor efficacy would be achieved. As a natural consequence, patient survival should be significantly increase. In our decade-long practice of such strategy, we have shown this is the case [2, 13].

Cancer is an Individual Disease

As discussed above, the malignancy of a given tumor is measured by four aspects: (1) the replication rate of the tumor; (2) the ability to induce inflammation to drive non-autonomous replication and cause symptoms; (3) the ability to spread and establish independent distant metastasis; (4) the ability and rate to generate escape variants. On the other hand, the naturally occurring antitumor immunity in majority of cancer cases is also highly variable, but absolutely critical for every stage of the disease. The true course of cancer in every case is therefore influenced by the balance between a malignant tumor and a naturally developed antitumor immunity. Since each of the pro-and con forces have multiple numerous factors, no two cases of cancer are identical. They may initiate by identical mutations (driver oncogenes), but they have different immune recognitions and thus concomitant antitumor immunity levels. The reason that many early stage and later stage cancer cases have similar good or bad prognoses is because that regardless how malignant a tumor may be, a strong concomitant antitumor immunity often account for the good prognoses. The so-called early or late-stage cancer by the TNM staging system often reflect the underlying control of concomitant immunity in each case, thus early-stage cases often have strong concomitant antitumor immunity while late-stage cases have weak or none. This general pattern of prognosis is only meaningful in statistics, but not in individual cases. There are too many "exceptions" that one cannot predict an accurate prognosis for a given case based on statistics. Without knowing what would be the consequence of a selected therapy, put hundreds and thousands of patients with seemingly identical TNM stages into the same treatment plan not only seems foolish, but also dangerous. For this reason, clinical management based on TNM staging system is a wrong approach in violation of the individual nature of cancer as a disease. Despite blamed by many clinicians to be over simplified and inaccurate, the guideline-depicted group management based on TNM staging system has been fully adapted by the mainstream medicine for decades and there is no sign that it will be abandoned anytime soon. As a result, millions of cancer patients will continue to suffer the damages brought about by this approach in cancer management. On the other hand, approaches based on newer information on individual cancer case have been emerging. The most obvious is the introduction of genetic analysis to identify the driver genes for tumor replication Development of small molecule inhibitors for certain cancer driver kinases have achieved significant impact on patient survival in several solid tumors such as lung, liver, breast and ovarian cancers. These achievements, although limited due to only small number of cancer patients are suitable for the individual management, nevertheless represent a trend to identify individuals in a TNM-defined group patients who would fit for individual management. If these efforts are acceptable to mainstream medicine, individualized management for all cancer patients should also be acceptable. The only barrier is that we do not know how to apply individual management for all cancer patients.

Our research and clinical approaches in the past decade seem to indicate that a deep understanding on tumor malignancy and concomitant antitumor immunity in each cancer case seems to make such effort possible. The key is an accurate assessment of tumor malignancy and concomitant antitumor immunity in each case. Simple classification of patients according to the TNM staging system is not enough. Rather than focusing on TNM staging, we look into each of the above discussed factors influencing disease prognosis and try to obtain an overall assessment of survival for a given patient. For example, a TNM-designated stage IV case may not be that desperate at all if there is a concomitant antitumor immunity in place at the time of diagnosis. The presence of distant metastasis should be an event taking place before the establishment of antitumor immunity, thus not all metastases are eliminated after establishment of this immune recognition. As long as immunity recognizes all lesions in the patient and no new metastasis can establish, the case may have a similar prognosis as a stage II case in that so long as all visible lesions are eliminated, the residual antitumor immunity could protect against recurrence and the patient may have a long-time recurrence-free survival or even clinical cure. Similarly, a stage I or II case may not be cured if there is a lack of immune recognition at the time of surgery and latent metastases exist already. In many cases, a much more accurate assessment of prognosis is obtained simply by incorporating the status of concomitant antitumor immunity into the analysis. We have carried out such analysis in every case and some of these analyses have been described in previous reports [7].

Rushed Tumor Reduction and Aggressive Treatments Are Often Not the Best Choices

Current cancer management has a unwritten rule that killing tumor lesions as soon as possible is always the right thing to do. The rationale behind this rushed intervention is common sense in that there is no reason to let tumor lesion continue to grow if one could start the tumor reduction therapy now. If such timely intervention is still not enough to control the tumor, how can it be more beneficial to start the treatment at a later time? This idea is deeply rooted in the minds of patients as well as clinicians. They don't see any other way but to kill at the first sight. When it comes to selected treatments, clinicians want them more frequent and more aggressive to maximize the killing of tumor cells. If possible, they always prescribe to continued cycled treatments that bombard the tumor with toxic drugs or radiation or other forms of physical or chemical killing. This is all based on the assumption that the more tumor cells killed by each cycle of therapy, the more efficacy would be achieved and the longer the patient would survive. The reality is that this line of thinking has no scientific basis and lack clinical observations to support. All efforts to increase chemotherapy dug dosing to the maximal limit have failed in history. But they refuse to stop a continuing therapy until there is clearly lack of response or the patient is too weak to be treated anymore. Clinicians believe that the problem is not at the steps of therapy selection and the timing of the selected therapy, but the ability to tolerant these therapies by their patients.

Yet, according to the important roles played by concomitant antitumor immunity as discussed above, rushed therapy directed to reduce tumor burden may not always benefit the patient. Take the example of the above discussed Stage I and II cases rushed to surgical removal of primary tumor before immune recognition is established, the correct way to deal with such case should be to make sure the presence of a strong concomitant antitumor immunity is in place before removing primary tumor. If immune recognition is absent, one should not rush to the removal of primary tumor because by then distant metastasis may have already taken place. Removing the largest tumor burden in the host only eliminate the future chance to establish immune recognition. Without immunity to protect against establishment of metastasis,

recurrence would take place and the patient is doomed for death. Although this situation is not common, it does happen due to early or accidental discovery of the primary tumor. In such cases, if the tumor is not discovered, an immune recognition may take place eventually and depending on the balance between tumor malignancy and antitumor immunity, the case may have a good or bad prognosis. As long as latent tumor metastasis is formed, early discovery and removal of the primary tumor without concomitant immunity in place is not a blessing but a curse.

Timing in chemotherapy is also a critical factor influencing long-term efficacy. To most people, the purpose of chemotherapy on visible tumor burden is tumor reduction through direct killing of tumor cells. But this is wrong in that the true efficacy of chemotherapy in this situation is the activation of concomitant antitumor immunity [11, 12, 14]. The activated antitumor immunity increase suppression on tumor replication, and direct killing of tumor cells through immune mechanisms [15, 16]. Compared to direct killing of tumor cells by drug toxicity, such antitumor mechanisms are much more efficient in that they often last longer without further help from therapy [13]. Besides on the established tumor burden, activated antitumor immunity is more effective eliminating newly established metastasis in a prolonged period. Since most cancer death comes from metastasis, reducing establishment and growth rate of metastasis translates to increased survival. An example of this translated survival benefit for chemotherapy-activated antitumor immunity is the neo-adjuvant chemotherapy given before removal of primary tumor in some solid tumor cases, most commonly in breast cancer patients. Our observation indicates that as long as a patient has decent levels of concomitant antitumor immunity, neo-adjuvant chemotherapy always activates such immunity before surgery to remove primary tumor. In these cases, an enhanced immune protection is established by the neo-adjuvant chemotherapy, even when the therapy failed to demonstrate significant tumor burden reduction by imaging standard. On the contrary, if a patient lacks concomitant antitumor immunity, neo-adjuvant chemotherapy often fails to demonstrate the activation of antitumor immunity regardless weather a short-term tumor reductive effect was achieved. In such cases, post-surgery recurrence is a highly possible consequence [10]. Thus, the real purpose of chemotherapy on visible tumor burden is not primarily tumor reduction, but activation of antitumor immunity [12]. Tumor reduction may be and often is a natural consequence of activated antitumor immunity but should not be the focus of chemotherapy selection. In this aspect, timing of chemotherapy becomes critical in that chemotherapeutic drugs are often suppressive to immune cells, the frequent use may lead immune suppressive. Based on the long working period of an activated antitumor immunity (which can be monitored by the changes of tumor markers), cycled chemotherapy should be applied much less frequently than the current practice (often 21-days). For example, in every case we manage, chemotherapy is suggested based on the profile of antitumor immunity reflected by tumor markers that reflect the activity of tumor replication. Once the underlying concomitant antitumor immunity is activated by once cycle of chemotherapy, the next cycle of treatment may be applied as far apart as 5-10 weeks later. No loss of control by immune recognized tumor has been observed by such practice and patient benefits ranging from symptom control to drug toxicity have been preserved (our unpublished observation).

Timing in radiation therapy is another good example of why rushed treatments ate not best choices. Radiation is lethal to tumor cells as well as to immune cells. Due to the killing of tumor cells and release of tumor antigen by the dead tumor cell, concomitant antitumor immunity could be activated and is responsible for the so-called abscopal effect (suppression of distant lesions following local radiation on one lesion) [17, 18]. On the other hand, radiation often causes explosive establishment of distant metastasis as well. This is most likely due to the suppression of concomitant antitumor immunity which is the constant force against metastasis. If an explosive establishment of distant metastasis following radiation therapy takes place, one can be sure that the antitumor immunity responsible for the lack of new metastasis somehow disappeared. The most likely reason would be that immunity inside the treated lesion is also eliminated by radiation. Our observation indicates that in real-world cases, radiation-caused progression is more often than abscopal effect. Since early animal study has shown that activated antitumor immunity is likely resistant to radiation-mediated immune suppression, we have been paying attention on the relationship between activated immunity and immune suppression [19]. Our observation thus far seems to support the finding in animal study. Interestingly, this is the opposite to the sensitivity profile of tumor cells to radiation. It is well known that actively replicating tumor cells are more sensitive to chemotherapy and radiation-mediated killing due to the fact that damage of these agents takes place during active DNA replication. Why is activated immunity is more resistant to radiation is currently not clear. In clinical practice, radiation oncologists have developed two types of radiation plans. The “low-dose, high fragmentation” plan uses 1.5-3Gy doses for each daily treatment and a total course of 50-60Gy for the entire course. The “high dose, low fragmentation” plan is the opposite that applies 5-8Gy each daily treatment and a total of 40Gy for most cases. The organ location of the target lesion often influences the selection of these two plans, but our experiences seem to indicate that the high dose, low fragmentation plan is more likely to preserve concomitant antitumor immunity while the low dose, high fragmentation plan seems more lethal for the target tumor. The timing for radiation treatment is critical because that if we wang to preserve concomitant antitumor immunity already present in the target lesion, we need to activate this immunity before applying radiation to the lesion. Rushed treatment does not consider this issue and therefore may bring deleterious consequences.

Our previous reports have repeatedly shown that the recently popular immune checkpoint inhibitor (PD1/PDL1 blocking) antibody therapy is based on partial T cell depletion and the depletion of T cell should not be too much to cause the loss of antitumor immunity [6, 13]. Aggressive treatment plan such as doing of anti-PD1 antibody every 3 weeks does not increase the response ratio but often lowers it. This mistake is the main reason why this therapy has a more glorious reputation than its real-world performance [20-22]. In our hands, early experiences had indicated very high portion of hyper-progressive disease due to depletion of antitumor immunity in patients with confirmed presence of such immunity [6]. Once we have identified the true mechanism and have adapted a much less aggressive plan for antibody doing, we have avoided the happening of hyper-progressive disease in all ICI therapy-treated patients. The response ratio has not achieved 100% not because we have not used more antibodies, but because in some patients the recognition of the Fc binding site by macrophage is not matched, therefore no depletion of antibody-bond T cells could take place [13]. In such case, aggressive dosing is a waste of money and should still be avoided. Unfortunately, we are still witnessing abusive use of the ICI therapy that causes many damages than benefits in patient turned to us after being wrongly treated by their doctors. Concurrent chemotherapy in the

most recent practice by many clinicians only pushes the problem of immunity depletion to a later time to cover the appearance of hyper-progressive disease, it does not resolve the problem [7].

Even during the tumor kinase-targeted therapy with small molecule inhibitors that does not require antitumor immunity, antitumor immunity is still involved to prevent outgrowth of non-target fraction of the treated tumor. Most targeted therapy-treated cases contain minor fractions of other non-target tumor cells that is the cause of eventual drug resistance when under selective pressure of target drugs that suppress the replication of the target cells. In many cases, these non-target cells are controlled by concomitant antitumor immunity. But with continued use of the inhibitors on target cells, suppression of concomitant antitumor immunity is often observed and this immune suppression leads to outgrowth of the non-target cells. The often-observed accelerated progression following drug resistance in target therapy is caused by this immune suppression mechanism. Based on this understanding, a more reasonable approach in the case of mixed components with concomitant antitumor immunity is to use the target drug intermittently to avoid suppression on antitumor immunity. Our experiences in most such cases have indicated a surprisingly good effect in that not only is the suppression of antitumor immunity avoided, but also the antitumor immunity is often activated by such intermittent use of target drugs, leading to satisfactory control and reduction of overall tumor burdens (manuscript in preparation). In a strikingly comparison to cases treated by the mainstream adapted target therapy which always develop drug resistance, our cases treated by intermittent target therapy rarely develop resistance, and some achieve complete responses. It is not the target drugs that caused the reduction of tumor burden, but the activated antitumor immunity that is ultimately responsible for such efficacy.

The War on Cancer Needs More Tumor -Killing Drugs but Even More New Medical Thinking on How to Use These Drugs More Effectively

Medical society at large has always believed that the breakthrough to win the war on cancer will come from the development of new tumor-killing drugs and other means of killing tumor cells. With the development of so-called immunotherapy in the past decade, this hope has not shifted, but strengthened, despite the fact that immune checkpoint inhibitor drugs do not kill tumor cells directly. The activation of antitumor immunity as a form of powerful antitumor therapy has been well accepted, yet the presence of a concomitant antitumor immunity and its critical roles as discussed above has continuously been ignored. Inasmuch as we do not know how to use a drug or tumor-reductive therapy correctly (so far, we don't), more new drugs will not solve the problem of cancer. Take the example, of recently popular Immune Checkpoint Inhibitor therapy (ICI) with antibodies to PD1/PDL1, varieties of antibodies have been approved on the market, one has made the number 1 cancer drug sale on the market, ye these antibody drugs have nor made significant improvement on cancer cure rate or survival, despite the fact that many isolated "miracles" have been observed by the clinicians prescribing these drugs. The overall impact of ICI therapy on cancer survival has not surpassed that of targeted therapy with small molecule kinase inhibitors. Why is a miracle drug has not brought miracle to cancer field? We have presented our interpretation of this odd phenomenon in previous publication [6, 13]. In essence, these ICI antibodies work by a mechanism not fully recognized by the mainstream society. Instead of the main stream-adapted "Blocking Model" in which interaction between the checkpoint pathway ligand and receptor (for example, PD1/PDL1) is blocked by administered antibodies specific for these molecules, thus preventing there interaction leading to down regulation of antitumor immunity, we have proposed an alternative "Depletion Model" in which these antibodies activate antitumor immunity by depleting T cell temporarily causing imbalance of homeostasis and subsequent homeostatic recovery to activate antitumor T cells that are not depleted by these antibodies. This model has thus far explained all clinical puzzles associated with the use of ICI antibodies, including the trigger effect (single drug administration brings months of sustained response), hyper-progression (accelerated tumor progression following drug administration), and autoimmunity that is often lethal. The disappointing performance of the ICI drugs in real-world clinical setting vs what was reported in many clinical trials is caused by a large portion of non-beneficial cases or even clinical harms. In many clinical trials, such cases have been removed from analysis under various excuses, mostly sudden symptom deterioration before first efficacy evaluation. The deterioration of symptoms is often the result of loss of antitumor immunity that controls tumor-induced local inflammation that leads to symptoms. The removal of such cases during clinical trial analysis exaggerate efficacy and hide damages. Maybe this manipulation is only from ignorance but not deliberate and malicious, but the data from these clinical trials is highly twisted and misleading, that it has prompted many wrong applications of ICI therapy in the real-world clinical setting that caused many accelerated deaths [7]. This is the truth behind the huge discrepancy between clinical trial data and real-world experiences, not just for the case of ICI therapy, but many other drug trials (ADC drugs, antibody drugs and CART cell therapies).

By recognition of the true working mechanism, we have been able to distinguish the patients that are most likely to benefit from ICI therapy and those that may suffer hyper-progressive disease by using these antibodies. ICI therapy based on the depletion model has thus far produced much more satisfactory results. About 70% more patients undergoing ICI therapy by our practice show positive and durable responses to the therapy while the rest showed no benefit or damage due to the lack of antibody Fc receptor recognition by patient's macrophage, a critical requirement according to the depletion model. Even in such cases, response to the therapy may be achieved by switching to a different ICI antibody with modified Fc receptor-binding sequence. This example shows that lack of cancer-fighting drugs is not the most serious challenge facing today's medical society, it is the understanding of how to us available therapies more effectively that is the main challenge. This claim is true for the classic therapies (surgery, chemo and radiation therapies); it is also true for newly developed "fancy" therapies. And it will be true for the future drugs coming into the field. To fully understand the mechanisms of current therapies, one needs to look into the obvious clinical puzzles these therapies have brought to the real-world setting, not to avoid them as we have discussed before [2]. Take an obvious example from the small targeted drug therapy field. An excellent responder may only contain a minority of their tumor cells expressing the mutated target molecule. This is not explained by the adapted mechanism of targeted therapy because if most of the tumor cells do not even have the mutated target gene, how can a single drug working only on mutated gene product control the who tumor? There is clearly something logically wrong, but the medical society has chosen to ignore this scientific paradox all together for decades [4]. If this pattern of ignorance represents how the medical society treats clinical puzzles (it does seem so), we are far from knowing how to use the available therapies correctly. Until then, we are still facing what Dr. Dunphy had described "grope in comparative darkness"

70 years ago [23, 24].

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