ISSN: 2573-9565

Review Article

Journal of Clinical Review & Case Reports

Seventy Years of Dunphy's Puzzle Revisited

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Submitted:22 July 2020; **Accepted**: 28 July 2020; **Published**: 05 Aug 2020

Abstract

In 1950 Dr. J Englebert Dunphy published an essay titled "Some observations on the natural behavior of cancer in man" in the New England Journal of Medicine in which he challenged the main stream concept of cancer as a "steady and irrevocable growth" by describing four cancer cases with unpredictable outcome ranging from spontaneous regression to explosive metastases after resection of primary tumor. His main point is to raise the awareness that there is a "local tissue resistance" that causing cancer to go through periodic arrest or even regression amid general trend of progression. The question to be answered "is not what makes the cells suddenly grow, but what has held them in abeyance for long". With this question answered, he hoped in the future, "it may be possible to determine the growth curves of a given tumor so as to plan extirpation at periods of quiescence rather than during periods of very active growth". 70 years have passed since Dunphy's original writing and we know that what he called "natural tissue resistance" in his essay is what we call antitumor immunity today. Yet even with this knowledge, today's cancer surgeons still do not base their surgical decisions on the actual interaction between tumor and host antitumor immunity. They still do not plan the surgical timing based on tumor growth profile. This essay is a revisit of Dunphy's view by analysing the cases in Dunphy's original essay with today's knowledge and by presenting a few more cases in which we followed his hypothesis and obtained desired outcomes.

Introduction

In 1950 Dr. J Englebert Dunphy, then a young attending surgeon at the Department of Surgery, Harvard Medical School, published a working hypothesis titled "Some observations on the natural behavior of cancer in man" in the New England Journal of Medicine [1]. In that essay, Dr. Dunphy described four cancer cases the outcomes of which seemed unpredictable at the time. Although could not explain what had influenced each of those cases to be what they were, he intended to use them to make an argument that cancer is not always what we think it is: a steadily and irrevocably progressing disease, but has some period of growth rest or even regression amid progress. These rest and regression seem to be caused by the host, not part of the tumor's own biology. He used the term "local tissue resistance" for that host influence. Today, we call it antitumor immunity and we know a lot more of it than 70 years ago. Yet this revisiting essay is not about how much more we know this "local tissue resistance", but about how much we have done with this knowledge in terms of making more effective treatments to achieve significantly better clinical outcomes. In that regard, we did very little for the past 70 years. Dr. Dunphy's intention was clear when he described those cases and raised the issue of unpredictability of cancer behavior naturally or towards clinical interventions. He wanted us to try to understand the mechanisms causing these behaviours behind and to plan battle plans accordingly. That desire to change the situation was again strongly expressed in another essay titled "Changing Concepts in the Surgery of Cancer" in 1953, in which he described the situation that a surgeon dealing with cancer surgery "is seriously handicapped in setting the extent of a procedure by an almost total ignorance of the biological propensities of the lesion he is attempting to treat [2]". He further demonstrated his argument by pointing out that "The most radical operation on a seemingly early lesion may be followed by widespread and rapidly progressive metastases and, contrariwise, a palliative resection undertaken with no hope of permanent cure may result in an extraordinarily long period of wellbeing for the patient. Until an accurate appraisal of the growth potentialities of any given tumor can be made, the surgeon must continue to grope in comparative darkness." 70 years have passed and we are still in darkness when it comes to the outcome of cancer surgery or, in a matter of facts, many other cancer therapies. The cancer surgeons today still cannot accurately predict the outcome of almost any cancer surgery with certainty. Despite how much we know about antitumor immunity, the cancer surgeons today still do not consider this factor in his plan of surgery. It is not that today we do not know what can rest tumor and hold them in abeyance for long; it is that we have not used this knowledge to improve outcomes of cancer surgery in specific and cancer therapy in general. Is this knowledge useless for clinical adaption or have we not tried? That is the focus of this essay. In the following sections, we will go through the four cancer cases Dr. Dunphy cited in his original essay and the "biological propensities" as we see behind these cases. Furthermore, we will present four cases in which we try to show that understanding the "biological propensities" behind each cancer case does seem to change the outlook of the battle against cancer. Our emphasis is at elevating our current view of cancer beyond the traditional two-dimensional TNM staging into a three and four-dimensional world where each cancer case is viewed with more precision and dealt by

individualized strategy with maximal survival benefits.

Revisit of Dunphy's puzzle 1: Spontaneous Cancer Regression

The first case Dr. Dunphy described in his essay was a case of spontaneous cancer regression in a 56 years old woman. At the diagnosis, the primary pelvic cancer was large and inoperable and the patient was on a course to die after two years when a spontaneous regression took place and she recovered with tumor regressed completely. She enjoyed subsequent 7 more years cancer-free until a recurrence was discovered and removed by surgery. She remained cancer-free thereafter. Spontaneous cancer regression is rare but has been amply documented throughout modern medical history (see for a collection of reports) [3]. The mechanisms behind this phenomenon are complicated and varied from case to case, but shall belong to two categories in general. One is for not-so-malignant cancer, regressing under host-dependent change of local growth environment; the other is for truly malignant cancer eradicated by activation of antitumor immunity like in this case. The puzzle here is not whether it is due to antitumor immunity for the regression, because the subsequent recurrence after 7 years (immunity decay) and the observation on the well capsulated recurred tumor (immune-mediated antigen encircle) all pointed to the presence of antitumor immunity. The puzzle is about the dramatic timing of such spontaneous tumor regression or why was antitumor immunity activated? Will this spontaneous activation of antitumor immunity take place in other cancer cases? The answers to these questions, based on our studies, observations and reasoning, are simple: 1) Antitumor immunity is likely activated in most cases of cancer; 2) The timing of its activation influences the prognosis of a case critically. The explanation of these answers, however, may not be simple, but they are scattered throughout the subsequent sections in this essay. In our observations, immune recognition of a growing tumor is a highly variable process among individual cancer patients, influenced by the nature of varying tumor antigens, local environment for antigen release and pickup, and composition of T cell repertoire for antigen recognition. In this woman's case, the presence of the primary tumor, although large and widely scattered in the pelvic, was not symptomatic (the cancer was discovered by hospital visit due to ventral hernia), indicating one of the two extremes: either slowly growing and without immune attack, or under the tight control of a strong concomitant antitumor immunity. Judging from the fact that spontaneous tumor regression took place after onset of terminal symptoms two years following diagnosis, it is most likely the former. The onset of antitumor immunity that caused the total regression of the widely spread pelvic tumor should be a result of tumor necrosis under large tumor burden and the activation of innate immunity. In a number of cancer cases where we saw lack of immune recognition upon diagnosis, the initial lack of symptoms and the sudden onset of severe symptoms subsequently following tumor progression seem to be common features hand-in-hand (our unpublished observation). In occasional cases, we could detect the connection between onset of symptom and spontaneous tumor regression as indicated by dropping of sensitive tumor markers. Unfortunately, the late onset of antitumor immunity, especially under large tumor burdens is always lethal to the host, not because of the tumor, but because of the immune responses. Such immune-based pathogenic effects are common in viral infection [4]. It seems that the differentials in levels between tumor burden and an immune response to control this burden determines the violence of the immune response in that an early onset of concomitant immunity is always mild in symptoms while a late onset is mostly lethal to the host. We could fathom that in rare cases where the late onset of antitumor immunity was able to reach maximal effects and reduce tumor burden before killing the host, and that is the case of "spontaneous cancer regression" [3]. In other words, the onset of antitumor immunity is always "spontaneous", whether it can lead to tumor regression before killing the host is variable among cases. In many early onset cases such as most accidental discovered (during physical check-up, for example) stage I lung cancer, it is likely, based on our observation of antitumor immunity in the resected tissue, that the lesion will regress completely if left alone (our unpublished observations) [5]. If so, spontaneous tumor regression is not rare at all. Dr. Dunphy, in summarizing the first case in his essay, also stated, "Although this is not the usual course of neoplastic disease, it is probably more common than has been realized." Once we understand the influential forces behind immune recognition and attack of a given cancer, the prediction could be made with decent accuracy. Only in this respect, the case described by Dunphy seems "miraculous" since by the general rule, late onset of immunity is mostly lethal. The point we want to raise here is that by understanding this phenomenon, we should always be prepared for the late onset of immune recognition that is not stoppable (our unpublished observation) in cancer patients lack established concomitant immunity under large tumor burdens. If we could somehow reduce or cope with the accompanying immunopathogenic effects, more "miracles" of spontaneous cancer cure may reveal themselves. One thing hopeful about the late onset of antitumor immunity is the high level of tumor burden inducing an equally high level of immunity enough to wipe off the entire tumor burden, but only if we can keep the patients from immunity-induced death. Is that possible? Dunphy's first described case says yes.

Revisit of Dunphy's puzzle 2: The Latent Cancer Metastases and Their Awakening

Cancer metastasis is the most common feature of cancer cases. With the term "latent metastasis" we describe a group of cancer metastases that have a delayed kinetics of establishment, so that instead of coming up quickly upon disseminated to distant sites, they have the ability to appear after a long delay in time, often over 10 years. The New England Journal of Medicine had reported one extreme case in which an organ donor who had a stage I melanoma resected and stayed cancer-free 17 years ago died of a car accident and donated her kidney to a recipient who subsequently developed melanoma metastasis in the transplanted kidney [6]. This case indicated how long a cancer metastasis could be latent and that disseminated cancer cells may stay in latent state in distant sites for the life span of the host. In the second case cited by Dr. Dunphy in his essay, a 69-year old woman who had breast cancer surgery 14 years ago went to the hospital for cholelithiasis. After cholecystectomy, her tissue samples were analyzed and a discovery of a breast cancer metastasis was identified in the resected appendix. The fact disseminated breast cancer cells may still be able to bring disease was also evident when only two weeks after surgery, the patient experienced chest pain and pleural effusion. The pleural effusion was tapped and breast cancer cells were found in the fluid. This initial cancer recurrence in the pleural effusion then went away in the next two year. The question we would like to raise here is not why latent cancer metastases exist, but what causes them to wake up after long period of latency like in this case. In our view, there are two types of delayed establishment

of metastasis: One is the type that comes up 1-3years post-surgery. This is the most dangerous type that causes majority cancer death in surgery patients. The other type, like in this case, is the type that comes up occasionally after at least 5-year mark for clinical cure. There are fundamental differences in the mechanisms behind these two types.

In the first case, there is no "delay" in that metastases actually establish all along the post-surgery period of time. The reason that one only sees establishment of recurrence/metastasis after a delay of 1-3 years after removing primary tumor is because that all established metastases following surgery are eradicated by a protective antitumor immunity concomitant with primary tumor before surgery. Only when this immunity decays below a protective level that newly established metastases are visible. This model which we call as "post-surgery cancer recurrence window model" (depicted in Figure 1) can explains many cases of cancer recurrences, but is not the explanation for the tumor recurrence in this case cited by Dunphy. The delayed recurrence in this case is most likely due to change of micro environment that facilitates establishment of disseminated cancer cells that have no ability to establish by themselves (section 5 will discuss such a case). The change of tumor microenvironment in this case was triggered by the cholecystectomy. The pleural effusion appeared two weeks after the surgery does not seem to be independent establishment of breast cancer metastasis planted 14 years ago, rather, it was the result of stimulation by the surgery. From the tumor point of view, all disseminated cancer cells that fit to establish independent growth due to ability to replicate in local condition should have done so soon after they settle down at distant sites. The reason they could not do so must be defects embedded in the biology of that disseminated cancer cell. Until there is a change of local environment, for example inflammation or trauma, to compensate for the defects, this cell should remain "dormant" forever. But the presence of many of such disseminated cells all over the body of the host does present opportunity for recurrence forever. In our observations, pleural effusions and ascites are the two most common forms of local change of environment that favors awakening of disseminated (often by surgery-induced implanting) non-self-driven metastases. On the other hand, like in the case cited by Dunphy, presence of cancer cells in the drainage of the fluids from pleural effusion and ascites does not always lead to massive establishment of visible metastases in those locations. In fact, in most time, like described in this case, cancer cells disappear spontaneously after dissipation of fluids (either through active tapping or through spontaneous absorption). Occasionally, these recurrence episodes leave a few permanently established metastases, and these metastases always contribute to eventual death of the hosts. In preparation for such event, caution should always be given when one is dealing with dramatic change of local environment in individuals who had cancer. At least in our hands, because of this awareness, active draining of pleural effusion and ascites has been practiced and this precautious measurement does seem to have avoided establishment of permanent metastases in the chest and the pelvic cavities (our unpublished observations). In the case where permanent metastases are established following the awakening of dormant non-self-driven cancer cells, we always find that these metastases are driven by autonomous replicating cells that obtained this capacity during the growth of the non-autonomously replicating cells. For these metastases, the newly generated mutation that drives autonomous tumor replication is often not recognized by previously established antitumor immunity (or else they would not be able to establish to begin with). The correct strategy in dealing with these situations would be to aggressively removing or distinguishing these metastases before they grow out of control. The challenge is at how to evaluate the situation and take proper move. By combining disease history, especially the history of antitumor immunity and current test results, one can indeed make proper choices. In the later sections, examples will be presented to demonstrate this argument.

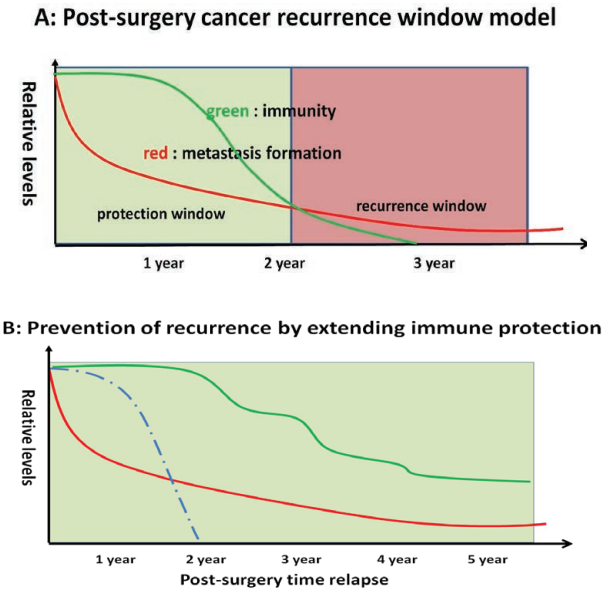


Figure 1. The post-surgery cancer recurrence window model. (A) This model assumes that all disseminated cancer cells that have the ability to form independent metastasis will do so permitted by environment. Since removal of primary tumor terminates the continued supply of cancer cell dissemination, the residual disseminated cancer cells will continue to form metastases at a decaying rate depicted by the red line in the graph with time lapsing. Similarly, the post-surgery antitumor immunity will decay gradually following the shape of the green line in the graph due to the lack of antigen stimulation. The actual decay rates for each process and for each cancer case will vary, but the rule remains the same: metastasis is established only when 1) there is still independent formation of metastasis taking place; and 2) immune protection levels drop below certain threshold (depicted as the cross between the two colored lines in the graph). The time window before this threshold is the period that metastases cannot establish due to immune protection and the time window after is the period that recurrence may establish provided there is still independent formation of metastasis by disseminated tumor cells. (B) Based on the process depicted in (A), assuming no changes could be made for the process of metastasis formation by disseminated tumor cells, slowing the decay rate of antitumor immunity post-surgery from the dotted blue line in the graph to the solid green line would significantly extend the protection window beyond the time point at which all disseminated tumor cells that have the ability to form independent metastasis have done so. After that point, even antitumor immunity may continue to decay; a clinical cure is achieved due to exhaustion of metastasis forming ability of disseminated cancer cells.

Revisit of Dunphy's puzzle 3: The Myth about Incomplete Cancer Surgery

In the third case cited by Dr. Dunphy in his essay, he described a case of a 55-year old women with colon cancer discovered due to abdominal pain. Laparotomy found that other than the primary tumor at the splenic flexure, few liver metastases were visible. Resection was made to the primary tumor leaving the liver metastases untouched. Eighteen months later the patient returned with a large 12-cm tumor in the ovary causing pain, irregular bowel movement and virginal bleeding. The tumor was removed and found to be an adenocarcinoma, probably metastasis of the previous colon cancer. At the time of the second surgery, the liver appeared nodular with more metastases but only slightly enlarged in sizes. Few months following the second surgery, the liver disease progressed and patient ran a downhill course with cancer cachexia. Dr. Dunphy used this case to emphasize the differential growth in the same patient between different metastases, in this case between liver and ovarian metastases. While it is also a common observation by us, this is not the best case to make this point. First of all, the evidence provided in this case cannot rule out the possibility of a primary ovarian cancer instead of a colon metastasis. Also, the liver metastases progressed significantly during the post-surgery period. Possible explanations for the differential growth of different metastases in the same host can be multiple, ranging from entirely different tumor replication potential driven by very different mutations to very different sets of local environment. What we see in this case that deserves discussion is a case of incomplete surgery and its immunological consequences. Today, cases like this (colon cancer with multiple liver metastases not resectable) are most likely rejected by surgeons based on guideline recommendation. The post-surgery course in this case has proven they are probably right. But the reasons behind the guideline are obscure because guidelines are formed not by reasoning, but clinical evidence, so it is an evidence-based medicine. Alternatively, we seek for a logic explanation in all cases that we handle. In this and many other cases where guideline rejects surgical management due to distant metastases or based on TNM staging, we agree with the recommendation but care about the reason behind. Viewed from an immunological point of view, cancer surgery impacts the balance between tumor and host antitumor immunity in multiple ways. While complete removal of visible antigens (tumor burden) under a concomitant immunity leaves this immunity standing alone and favors formation of immunological memory, the incomplete removal of antigen has few uncertainties that one of which is reduced immunity for reduced antigen [7-13]. This is most likely the reason a surgeon rather has a complete surgery or none at all, because the reduced antitumor immunity leads to uncontrolled establishment of distant metastases that were under control by the concomitant immunity before surgery. But this explanation is only for cases where a pre-surgery concomitant antitumor immunity is protective against metastases [13]. In cases where there is no such concomitant antitumor immunity before surgery, there would be no post-surgery protection and whether explosive metastases take place may be determined by other factors (like the next case cited by Dr. Dunphy). Under some situations, incomplete surgery could be beneficial as Dr. Dunphy stated. In such cases, based on our observations, the antitumor immunity is either preserved (not down regulated) or actually gains upper hand and clears the residual tumor (we will present one such cases in later sections) [14-16]. The difference seems to be caused by the activation status of the immunity at the time of surgery. Activated immunity seems to be able to ignore the down regulation by reduced antigen loads whereas a resting one is not [17]. The obvious solution to avoid this problem then will be to activate antitumor immunity before surgery [16]. In that case, the time of surgery will be largely determined by the status of antitumor immunity not tumor burden. This is most likely the success behind neo-adjuvant chemotherapy in many cases as we have shown that chemotherapy under presence of concomitant antitumor immunity may activate the underlying immunity [18, 19]. Interestingly, neo-adjuvant chemotherapy capable of reducing tumor burden has always been used by surgeons to choose the timing of surgery. While tumor response to chemotherapy often goes hand-in-hand with activation of immunity, they do not always go together as our own animal studies (our unpublished results and Figure 2) and clinical experiences have indicated. For example, many cases of neo-adjuvant chemotherapy in breast cancer often demonstrated an initial response and a subsequent stalemate due to immune activation and inhibition of tumor replication that makes tumor cells insensitive to continued chemotherapy killing. In these cases, timing of surgery should be picked based on the status of antitumor immunity, often 1-2 rounds of chemotherapy instead of 6 rounds recommended by the guideline. Cases following this selection criterion for surgery have demonstrated heightened presence of antitumor immunity in surgical samples and fared good post-surgery prognosis (our unpublished observation).

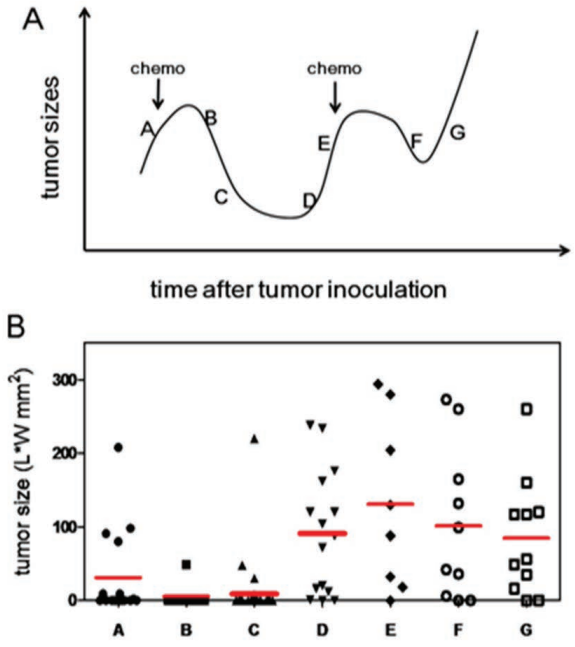


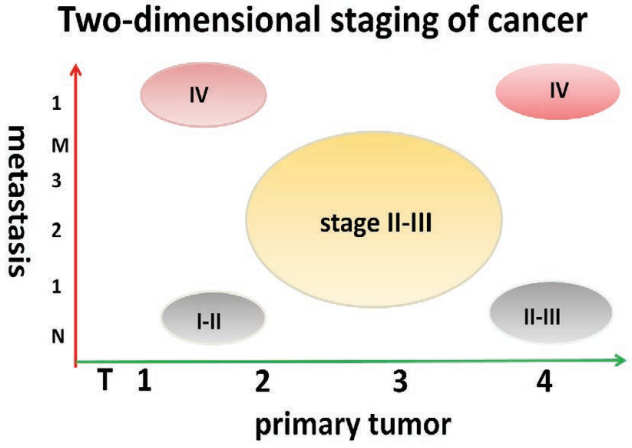
Figure 2. The best timing of surgery following neo-adjuvant chemotherapy. This test answers the question of what is the best timing for surgery after neo-adjuvant chemotherapy to reduce tumor burden. Panel A shows the experimental design and the time points at which surgery to remove the primary tumor was performed. Mice were inoculated with the MCA207 sarcoma cells. Tumor growth was depicted by the curve. When tumors grew to 10-13mm in diameter, 15 of the tumor-bearing mice

were taken for surgery to remove the primary tumor (point A). The rest tumor-bearing mice were allowed to continue progression till they reached 12-15mm in diameter when they were treated with a single dose of cyclophosphamide (point chemo). 5-7 days after the treatment when some tumor-bearing mice began to show time regression (point B), another 10 tumor-bearing mice were taken for surgery to remove primary tumors. After 14-17 days following chemotherapy, when tumors regressed to the point C in the graph, another group of 10 mice were taken for surgery. Thereafter attention was given to mice with tumors stopped regressing and started to relapse (point D), 14 such cases were collected and subjected to surgery. Another group of 8 mice were taken for surgery when their tumors relapsed to the original size (point E). The remaining tumor-bearing mice were then treated again with cyclophosphamide (chemo) and 10 responders were taken again for surgery (point F). The second response is always shallow and tumor rebound sooner after response. Finally, 10 respond-relapsed mice were collected for surgery at point G. After two weeks of waiting, all of the tumor-free mice from A-G groups were challenged on the opposite flanks with $5x10^5$ tumor cells, a challenge dose that always yield 100% of tumor take in naïve mice. The tumor take and individual tumor sizes at 18 days after tumor challenge were shown in panel B. The results indicate that neo-adjuvant chemotherapy increased post-surgery protection against tumor establishment. The optimal surgery time after chemotherapy is during the response period (point B, C), not necessary the lowest tumor burden (point D). Since our previous studies indicate that tumor responses after chemotherapy correlate with activation of antitumor immunity [18,19], this test demonstrates that selection of surgery timing following neo-adjuvant chemotherapy should be based on the status of antitumor immunity.

Revisit of Dunphy's puzzle 4: The Unpredictable Consequences of Cancer Therapy

Dr. Dunpy used the last case in his essay to demonstrate how unpredictable outcome a cancer surgery can get. In this case, a 59-year old man was diagnosed with colon cancer in the descending colon. The observations made at the time of surgery to resect this tumor showed multiple metastases in adjacent lymph nodes but not in the liver. After surgery, however, a quick and explosive growth of metastases took place in the liver and the patient died in 10 weeks post-surgery due to liver failure. Frustrating cases like this are happening every day in cancer management. A surgeon cannot tell cancer patient that he will be cured before surgery; he cannot even make the call after. A medical oncologist cannot tell a cancer patient what will likely be the effect of a prescribed chemotherapy or checkpoint immune therapy beforehand, either. An effective local ablation therapy that destroys the target tumor may lead to the spring up of multiple distant metastases in the next few months that quickly lead to death. All of these tell us that the unpredictable consequence of cancer therapies is probably the only predictable thing in cancer management. Then what is the reason for that unpredictability? Do cancers behave radical and not by the laws of nature? Or we just don't know the laws behind cancer? Just like no one can accurately assess the weight of a cylinder by looking at the projected circle in a two-dimensional plan; no one can solve a linear equation with two unknowns with only one equation given; we can't just manage cancer with only TNM staging in a two-dimensional world. We need to elevate to a three and four-dimensional world and look at this disease in that scope. When we do, we find that things are quite predictable and operate logically.

In our observations, at least one additional dimension we can add to the existing TNM staging system for better assessment of each individual cancer is the degree of antitumor immunity (Figure 3). In a three dimensional world, an "early" stage by the TNM staging may not be truly early stage if it has no concomitant immunity due to "early (time-wise)" in establishing time, while a "late" stage by the TNM staging may not be that bad if it has established a strong concomitant immunity (the false stage IV cases). In fact, in most cases of malignant cancer (because there are less malignant and not malignant cancers out there), the degree (quantity and quality) of antitumor immunity is always a more decisive factor influencing prognosis than the TNM staging of the case. In most cases, the TNM staging is hand-in-hand with the degree of antitumor immunity because lack of antitumor immunity is often the reason a cancer has more aggressive local invasion (T), local (N) and distant metastasis (M). That is the reason why this staging system has survived the statistics analyses. But it is never accurate enough to be individualized, to accurately predict the response of a given cancer to a given treatment. If assessment of individual antitumor immunity is incorporated into the current TNM staging system, we then have the three-dimension staging system (Figure 3) that is highly accurate in making individual prediction. After all, cancer is an individualized disease due to varying antigen and immunity in each case that deserves individualized treatment. In addition to antitumor immunity, we have also looked into the growth potentials of each cancer and identified autonomous and non-autonomous replicating cells and their possible interaction by induction of inflammation (see the next section and [20]). This can operate independently from antitumor immunity but at the same time, can be strongly influenced by antitumor immunity, and therefore may serve as another dimension in our assessment of each individual case. Putting all of these together, we now have a much clear view of each individual cancer, their natural behavior and their possible responses to various treatments. With such system in hand, we can often accurately predict a theoretical surviving limitation of a case as early as the time of diagnosis, or at any time thereafter. The advantage of this accurate assessment is obvious when it comes to planning, not just for surgery, but a management plan to obtain the maximal surviving benefit. After all, what Dr. Dunphy wanted 70 years ago was to remove the uncertainty and bring clarity in cancer management. In the next part of this essay, we will present a few cases where we apply this principle in cancer management.



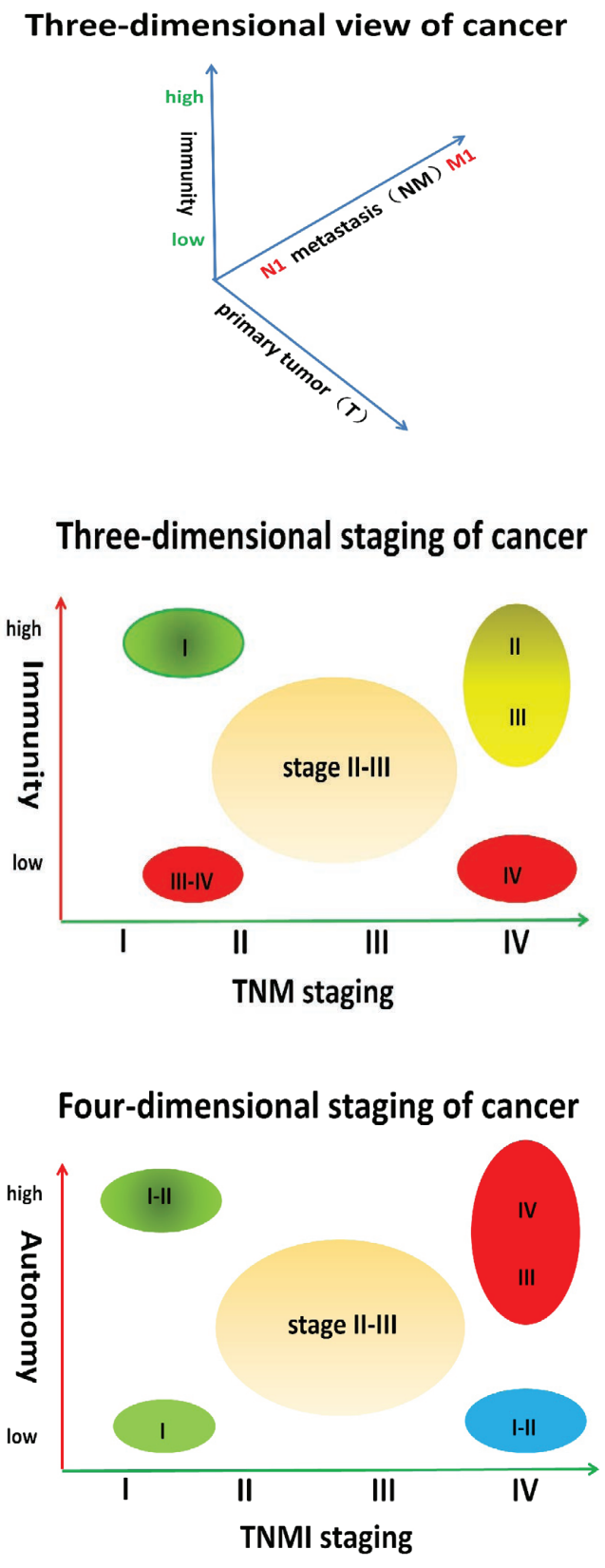


Figure 3. Evaluation of cancer staging. The classic TNM staging is illustrated in panel A. We can consider this as a two-dimensional view of cancer as compared to only gauging cancer by the size (one dimensional view). This is clearly more accurate as it introduced the dominant factor of metastasis on top of tumor burden. The TNM staging has been supported by clinical observations in statistical meaning, but not accurate enough to make individual prediction. The addition of the levels of antitumor immunity, another dominant factor over metastasis, introduces a three-dimensional view of cancer (panel B). This is more accurate than the TNM staging as some of the extreme cases can be identified (panel C). Finally, another factor, cancer autonomy (autonomous or self-driven replication), is discovered and added to the previous three-dimensional cancer staging to form the four-dimensional cancer staging with even more accuracy in extreme cases (panel D). The three and four-dimensional staging have been used in our prospect and retrospect evaluation of each cancer case to obtain an accurate picture of each cancer and its interaction with the host.

Revisit of Dunphy's puzzle 5: Know the enemy: the growth potentiality of the tumor

Cancer is notorious for unchecked growth, but not all cancer cells grow the same. The best example is the total control of a cancer by TKI targeted therapy in which often the target mutation that drives the autonomous tumor replication is only present in a minority portion of entire tumor cells (the so-called mutation frequency in genetic testing report). First of all, why does only a portion of the entire tumor cell population contain the mutation that drives tumor replication? Secondly, why are the other tumor cells not containing the TKI targeted mutation controlled by TKI therapy? These are not anecdotal observations but common feature of TKI therapy, yet there has been no adequate explanation offered, not even questions raised. Our recent report has offered reasonable explanations for these questions [20]. In our views, many tumors contain two populations of cells different in the mode of replication. One is able to sustain a self-driven replication through mutations in growth-related signal transduction cascades such as EGFR. Tumor cells with this self-driven ability disseminated to distant sites are capable of forming independent blood supply and establish metastases. The other cannot sustain autonomous replication, but is driven to replicate by host factors. The most common host factors to drive the replication of these non-autonomous cells are associated with inflammation. There is often a connection/coordination between these two populations of tumor cells in a given cancer. The autonomously replicating cells produce chemotaxis factors for inflammation during their active growth and the inflammation in turn drives the replication of the non-autonomous cells to grow [21-23]. TKI therapy achieves near complete control of the entire tumor through controlling the replication and metabolic activities of autonomous population and the subsequent cut off of chemotaxis factors for inflammation leads to shut down of the replication of the non-autonomous population We have explained this interaction using a lung cancer case in a recent report [20].

Here we present another case of ovarian cancer in which tracking tumor replication profiles provided explanations for subsequent two recurrences and a disease-free survival thereafter. A 46-year old woman went to hospital for persistent stomach discomfort. CT imaging revealed a lump of 6.6x7.2CM in the left ovary. The tumor was then resected. Pathological report showed a large (11cm) clear cell cancer. Despite the large tumor, adjacent lymph

nodes did not show tumor metastases. Post-surgery adjuvant chemotherapy was arranged. Various small tumor nodules were detected in the peritoneal and pelvic cavities during chemotherapy. A PET-CT examination 10 months after surgery showed active metabolic signal (SUV>8) in one small tumor nodule (1.3x0.8 cm) between liver and spleen among several other small and less active metastases throughout the peritoneal and pelvic cavities. The patient then resisted further chemotherapy and these previous metastases dissipated gradually without any more treatments. By 30 months after surgery, CT imaging showed the nodule between liver and spleen increased in size (32.x1.7 cm). This recurrent tumor was resected by a second surgery. Two more rounds of chemotherapy were arranged post-surgery. Six months following second surgery, a recurrence of a nodule of 2.9x2.5 cm at the surgery site was confirmed by CT imaging. It was considered a recurrence due to incomplete surgery. A third and more extended surgery was again performed. Sensitive tumor markers (CA125 and CA199) returned to normal ranges after surgery and remained low thereafter. Imaging tests have since returned unremarkable findings. The patient remained disease-fee until now (18 months after third surgery).

This case came to ask our advice soon after the third surgery. We looked the previous three surgery samples for clue. Our evaluations focus on the two additional dimensions: status of concomitant antitumor immunity and status of tumor autonomous and non-autonomous replication. For the primary tumor, concomitant antitumor immunity (CD3) was not present, but was present in patches in the samples from the second surgery and third surgery. Detailed examination indicated that T cells from recurrent tumor are mainly CD8 type and they seem to have the ability to destroy tumor structures (Figure 4). In the contrary, autonomous tumor replication (as represented by Ki-67 staining) is absent in the primary tumor. The growth of this tumor was likely the result of highly active non-autonomous replication as detected by PCNA staining (Figure 4). Autonomous replication became abundant in the recurrent metastasis from second and third surgical samples while non-autonomous replication remained active. Putting these observations together, we could deduce a disease course for this case and predict an excellent prognosis, despite this is a case with repeated recurrences. The patient had long history of ovarian cysts with oophorocisitis. It is likely this condition caused the transformation of ovarian epithelial clear cells into in situ carcinoma. The growth of this primary tumor, despite highly active, was entirely dependent on local inflammation provided by ovarian cysts. Although tumor cells disseminate, they could not form independent metastasis without a mutation to turn replication autonomous. This explains the situation of large primary without metastases at diagnosis and first surgery. The post-surgery chemotherapy stimulated temporary growth of disseminated non-autonomously replicating tumor cells thought induction of inflammation. This is evidenced by the establishment of various small tumor nodules in the peritoneal and pelvic cavities during chemotherapy. Furthermore, the carcinogenic nature of chemotherapy drugs may have created the mutations that turned tumor replication into autonomous, thus the final establishment of the recurrent metastasis after chemotherapy. Although most temporary metastases during chemotherapy dissipated gradually following treatment cessation, one self-driven metastasis remained and progressed to the true recurrent nodule resected by the second surgery. This explains the presence of abundant Ki-67 signals in this tumor. The consequent self-driven tumor cells were recognized by host immune system and an antitumor response was activated at the time of second surgery. The activated status of the immunity was preserved on the recurrent tumor following second surgery that was known not complete due to close proximity and entanglement with spleen. With the more complete surgery, this antitumor immunity was left and should have turned into a protective memory against further recurrence that is driven by the same mutation. Based on the above analysis, the prognosis of this case should be excellent for two reasons: 1) the primary tumor does not contain autonomous replication, thus all of the disseminated tumor cells from this large primary tumor, although large in numbers and widely distributed throughout the body, do not have the ability to form independent metastasis. 2) The only metastasis that contained autonomously replicating tumor cells was completely resected and an immune memory should be formed after final surgery. If any disseminated tumor cells from this metastasis remained, they cannot form new metastasis due to immune protection. Thus, this case shall remain recurrence-free for a long time. The patient was advised about this prediction and no adjuvant therapy was prescribed.

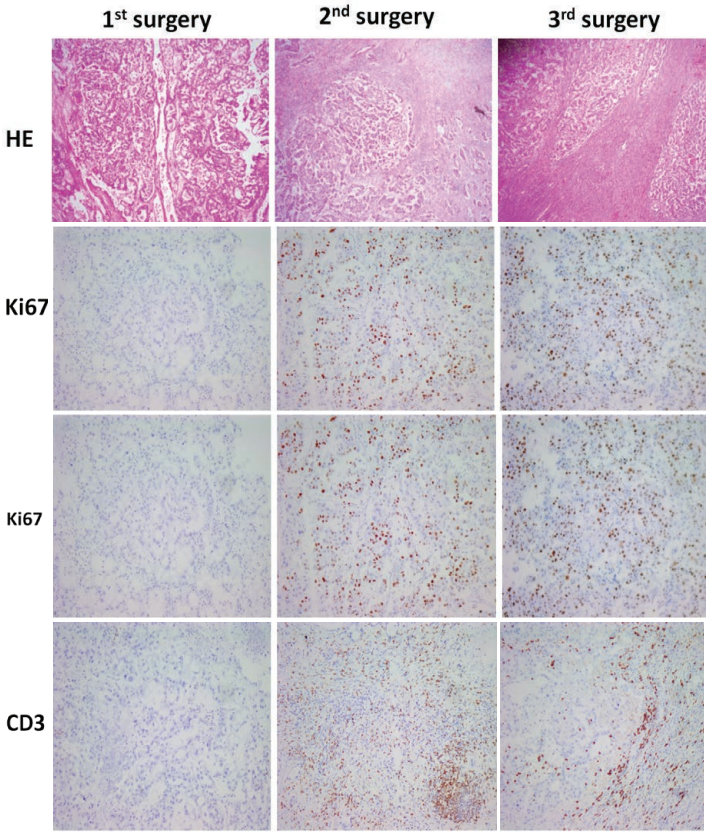


Figure 4. Evaluation of antitumor immunity and tumor autonomous replication in a case of recurrent ovarian cancer presented in section 5 of the text. Three consecutive surgical samples from this case were analyzed for the presence of T cells and tumor autonomous and non-autonomous replication by IHC with antibodies to CD3, Ki-67 and PCNA. The images from stained slides of the of each tumor was selected and presented. Micrographs of 40x magnification for HE and 100x for other staining are shown for each area.

Revisit of Dunphy's puzzle 6: Know Your Troops: The Decisive Role of Antitumor Immunity

One of the practical needs in cancer management is to predict the likelihood of post-surgery recurrence in each cancer case and

design coping measures based on this assessment. That is partly what Dr. Dunphy wanted to achieve for the patient. Here we present one case to show how knowing the status of antitumor immunity in a given cancer can lead to proper post-surgery management for recurrence. A 70-years old woman of good health went for a physical check-up and significantly, elevated γ-glutamyl transpeptidase (550) was found. Subsequent CT imaging found a lump in the left liver near the hailer area and slightly dilated biliary and hepatic ducts. The tumor markers CEA and CA199 were both highly elevated, thus a hailer cholangiocarcinoma was suspected. The tumor was resected and measured 6x4x2cm in size. Post-surgery pathological analysis confirmed the diagnosis of a cholangiocarcinoma. Based on the poor prognosis of hailer cholangiocarconoma in general and the large tumor size and continually elevated tumor markers post-surgery of this case in specific, a grim prognosis was made and the patient was urged to continue with adjuvant chemotherapy. However, the patient was intolerable to the prescribed chemotherapy after one round of gemcitabine-based treatment and refused further treatments. A suspected liver metastasis was identified at this time. The case then came to us for advice. An evaluation of the surgical sample for the status of antitumor immunity revealed an active carcinoma but with massive concomitant antitumor immunity. Large numbers of CD8 T cells with activated status were found infiltrating the entire tumor, intersecting, surrounding and destroying tumor structure throughout the entire tumor (Figure 5). Based on this evaluation, we predicted an excellent post-surgery prognosis despite the presence of post-surgery liver metastasis, because even if surgery were incomplete, the observed activated antitumor immunity would be able to eradicate any residual tumor burden before forming a strong and lasting memory. We advised the patient to accept additional chemotherapy to eradicate the single liver metastasis (or any new ones that may be coming), but the advice was refused by the patient due to fear of intolerance to chemotherapy. A radio frequency ablation (RFA) was arranged instead but was not carried out, because the metastasis regressed completely at the time of RFA. The patient remained recurrence-free until now (25 months after surgery).

The post-surgery tumor recurrence window model (Figure 1) has been applied many times in our studies to predict (proactively) or explain (retrospectively) tumor recurrence following cancer surgery. The main operating principle of this model is to assume that disseminated autonomously replicating tumor cells will form metastases at the earliest possible moment permitted by local environment. At the same time, whether they could form metastases depends also, on whether there is a host antitumor immunity present at the given time. The balance of these two processes determines whether there will be a metastasis established. With time elapsing, both processes decay, and there will be a time point after which all actively replicating disseminated tumors are depleted and that is when a clinical cure is achieved. From clinical observations, the depletion of active formation of metastases by disseminated cancer cells in most cases is before 5 years, but how early is difficult to gauge at the present. On the other hand, the decay of naturally established antitumor immunity is always faster than 5 years, often in the window of 1-3 years, leaving the patient exposed to delayed recurrence. Any efforts to change the biological behavior of the cancer and its disseminated deposits are unlikely at the current time, but enhancing antitumor immunity is within the goals of reasonable efforts. This example of cholangiocarcinama demonstrated that regardless of the common statistics against good prognosis for this cancer in general, presence of elevated antitumor immunity is more influential on the post-surgery prognosis than the statistics and clinical staging. Thus in our opinion, this individualized evaluation of tumor and host immunity should be the most useful information for each cancer case.

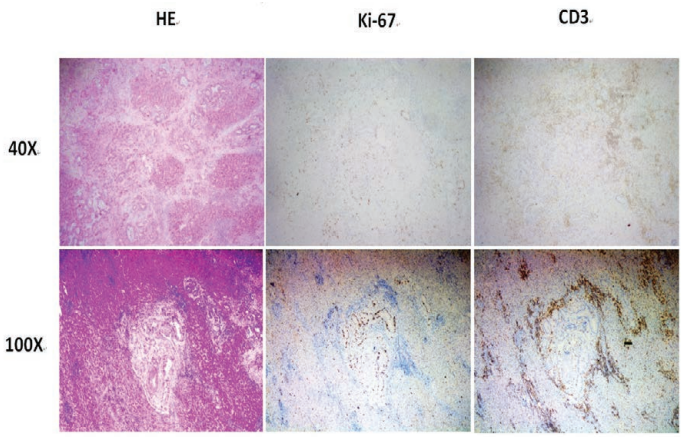


Figure 5. Example of a cholangiocarcinoma with strong concomitant antitumor immunity and excellent post-surgery prognosis. The surgical samples from the case presented in the section 6 of the text were stained for HE, Ki-67 and CD3. Micrographs (40x) of the same area from each staining are presented here. An enlarged area (100x) showing intense surrounding and destruction of tumor structure by massive T cells is also presented.

Revisit of Dunphy's puzzle 7: The predictable consequences of the battle

The wish Dr. Dunphy had 70 years ago is to have the surgeon "know" the consequence of each cancer surgery just like that in most other general surgeries. That wish has not been fulfilled due to the lack of knowledge on what causes cancer recurrence. Multiple factors contribute to cancer recurrence, but among them, the status of antitumor immunity seems to be the most critical one. With a strong antitumor immunity at the time of surgery, even when incomplete like the previous case, the residual immunity is able to clear the residual tumor and leave a protective immunity. In this respect, focusing on raising a strong antitumor immunity before surgery is likely to yield good post-surgery prognosis, thus fulfilling the 70-year wish by Dr. Dunphy. The following case is one example for such approach.

A 66-year old man experienced persistent coughing and chest tightness went to hospital. CT imaging showed a nodule of 8.3x4.9 cm in the mid-lower lobe of the right lung with enlarged mediastinal lymph nodes. Bronchoscopic biopsy confirmed presence of lowly differentiated tumor, possible mixture of adenocarcinoma and squamous cell carcinoma of the lung. No distant metastasis was identified. Due to location and size, the local doctors rejected surgical approach and prescribed 4 rounds of standard chemotherapy with pemetrexed and platinum concordant

with radiation treatment of 60Gy of the primary tumor and adjacent lymph node metastases. These treatments brought primary tumor shrank to 2.5x1.9 cm with symptom relief. But few months later, the primary tumor relapsed to 5.4x3.3 cm. The patient experienced sour shoulder that turned out to be a metastasis confirmed by biopsy. Subsequent brain MRI showed three less than 1-cm metastases. An adrenal metastasis was also identified by CT. The case was deemed hopeless and only brain radiation was offered by local hospital. It was at this time, the case came to us seeking immune-based therapy approaches. The first thing we did was to evaluate the underlining concomitant antitumor immunity using the only available biopsy sample from the shoulder metastasis. The results of a comparison between tumor proliferation (Ki-67) and T cell presence (CD3) against the HE background (Figure 6) indicated that the metastasis is composed of mainly lowly differentiated tumors mixed with squamous cell carcinoma. Tumor proliferation is active within the squamous tumor area with Ki-67 index reaching >70%. On the other hand, there is clearly a presence of evenly distributed T cell infiltration into the tumor. Most T cells are CD4 subtype (not shown), and the state of these T cell are benign (inactivated). There was no clear sign of antitumor activity associated with these T cells (inhibition of tumor replication or destruction of tumor structure and cells). The possibility of the expression of checkpoint molecule PD-L1 by those actively replicating tumor cells was confirmed by a third party analysis (not shown). Overall, this initial analysis by us pointed to a case of active tumor replication and adequate presence of infiltrating T cells with function blocked by checkpoint pathway [24]. Because that this case had good levels of concomitant antitumor immunity, theoretically it could be cured if all visible tumor burden could be removed/eradicated and the antitumor immunity could be activated and turned into a strong protective memory. The failure of previous therapy with combined chemo and radiation treatments was most likely due to the inhibition of concomitant antitumor immunity, which in turn led to the rebound of treated primary tumor and loss of control on distant metastases. The presence of concomitant immunity in the shoulder biopsy indicated that the inhibited immunity recovered after 2-3 months following radiation. Based on this rationale, we designed a step-wise path to eradicate visible tumor burdens with intension to elevate antitumor immunity along the way. The brain metastases were treated by gamma-knife radiation. The quick drop of tumor markers (Figure 7) supports that these brain metastases were true. Shoulder metastasis was treated by intervention chemotherapy that seemed effective by continued dropping of tumor marker. The response was persistent, indicating activation of antitumor immunity. After the response stopped, therapy with systemic chemotherapy combined with periodic interleukin-12 (IL-12) was initiated and led to response to continue (Figure 7). Finally, the residual adrenal metastasis was eradicated with radiation frequency ablation (RFA). After all these, we decided to assess the possibility of final surgery to eradicate the residual primary tumor and the mediastinal lymph node metastases. Pre-surgery PET-CT analysis confirmed there were only two metabolic active nodules in the patient: the mediastinal lymph node and the shoulder soft tissue metastasis (Figure 8). Considering that a strong and persistent response had been observed with the treatments, this tracer uptake may not be all tumor-associated, but the sign of immune response (our previous unpublished observations). Surgery was performed and post-surgery recovery was unremarkable. The post-surgery pathologic analyses indicated a primary tumor of mixed squamous cell carcinoma and lowly differentiated adenocarninoma with large area of fibrosis intertwined with patches of viable tumor cells (Figure 9A). Tumor proliferation was active with Ki-67 labeling index varying largely. Like the previous biopsy sample of shoulder metastasis, the most active patches of tumor proliferation were associated with the squamous cell type and showed >50% of strong Ki-67+ cells. On the other hand, analysis of the resected mediastinal metastasis showed a uniform structure of lowly differentiated tumor (Figure 9B) without intense fibrosis. Tumor proliferation was inactive with average Ki-67 labeling index around 10-20%. The presence of T cell was intense. Most T cells are of the CD8 subtype (not shown), and majority of T cells were activated. In both the residual primary tumor and mediastinal tumor, presence of PD-L1 expression was also assessed. There was low portions (<5%) of PD-L1-expressing tumor cells in both tumors. Together, these observations point to a case of active residual tumor after treatments and elevated antitumor immunity increased in both number and activation status. Based on this result from post-surgery analysis, we judged that this level of antitumor immunity would be strong enough to clear any residual tumor and translated into a protective memory thereafter. The patient was put on two rounds of chemotherapy (pemetrexed and platinum) to facilitate clearance of residual tumor. The shoulder metastasis that was not resected was treated with 40Gy radiation thereafter and all suspected abnormalities dissipated over time. He remained recurrence-free until now (39 months after surgery).

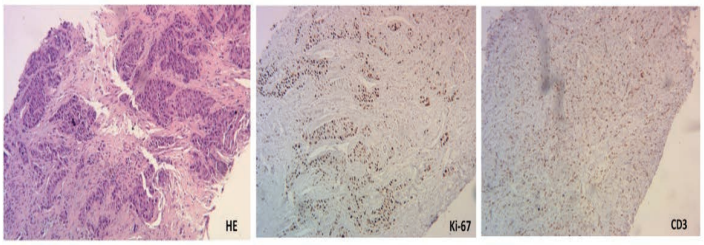


Figure 6. Evaluation of concomitant antitumor immunity in the lung cancer case presented in section 7 of the text. Shoulder biopsy sample was stained by antibodies to tumor replication (Ki-67) and T cells (CD3). Micrographs (40X) of the same area from each staining and the HE staining are presented.

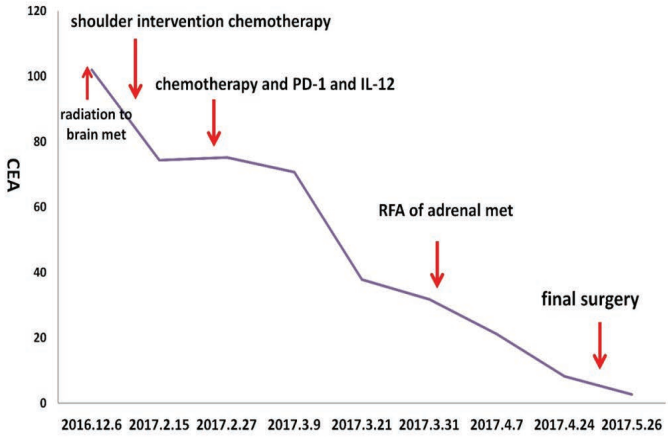


Figure 7. Responses to various treatments by sensitive tumor

marker (CEA) in the lung cancer case presented in section 7 of the text. The values of CEA is plotted against the testing date in the graph. Various treatments are marked by arrows.

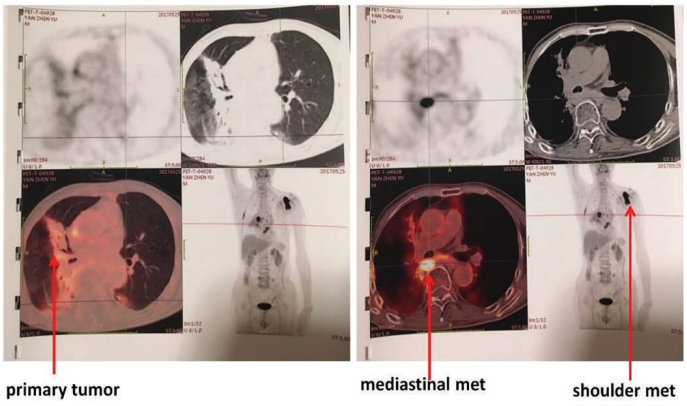


Figure 8. The pre-surgery PET-CT showing metabolically active sites in the lung cancer case presented in section 7 of the text**.** The location and metabolic signals of three tumors (the primary tumor, the mediastinal lymph node metastasis and the shoulder metastasis) are marked by arrows in the graph. The SUVmax for these tumors are: primary tumor (2.3); mediastinal metastasis (7.5) and shoulder metastasis (7.9).

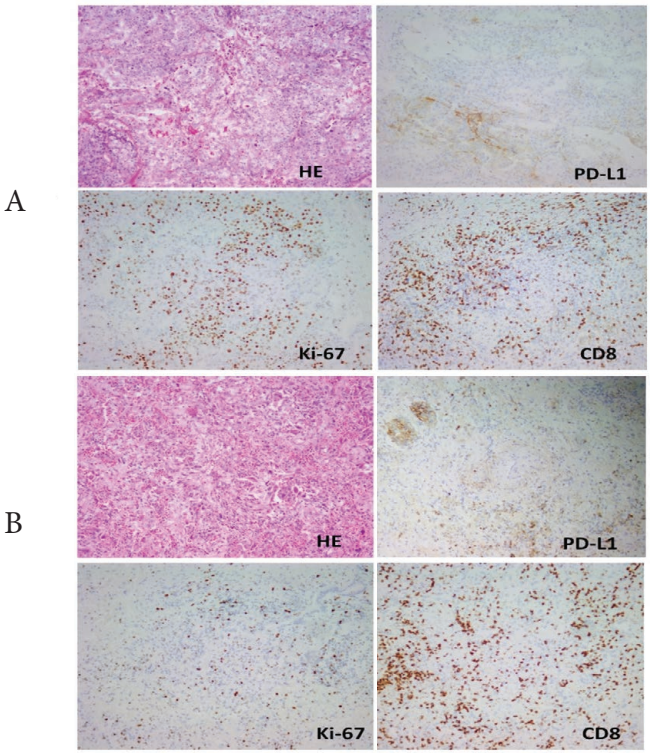


Figure 9. Tumor replication and presence of concomitant immunity in primary tumor and mediastinal metastasis from the lung cancer case presented in section 7 of the text. The surgical samples from primary tumor (A) and mediastinal (B) were stained with antibodies to tumor replication (Ki-67) and T cells (CD3 and CD8). Third party was used for stain of PD-L1 expression in tumor samples. Micrograph images (40X) of the same area in each sample stained by HE, Ki-67, CD8 (representing most of T cells found in the samples) and PD-L1 are shown.

Revisit of Dunphy's puzzle 8: Beyond Dunphy's puzzle

Many cases are not so lucky like the above one for that there is poor or none concomitant antitumor immunity to begin with. The consequences of therapy often is "predictable" that regardless what form of tumor reduction, the tumor always return with even more vigor and a grim prognosis always follow. Common examples include most glioblastoma of the brain, most late stage ovarian carcinoma, most soft tissue sarcoma, most cholangiocarcinoma, most small cell lung cancers, etc, the list is long. In these cases, simply giving tumor reductive treatments would not be able to activate and expand antitumor immunity like the above case. Surgeons know by heart to avoid tumor resection in metastatic disease. The question, therefore, is not uncertainty but certainty for a depressing fate. In most such cases, the lack of a working concomitant antitumor immunity is responsible for the lack of therapy control of the tumor. In order to win a battle, one needs to raise an antitumor immunity. In many cases, the lack of antitumor immunity may not be due to the lack of tumor antigen, but an issue of poor antigen presentation due to many factors including location (immune privileged sites such as brain and liver), tumor vasculature (lack of spontaneous necrosis), timing (newly generated immune escape variant) and available naïve T cell receptor repertoire (influenced by genetic and aging factors). Yet most of these problems can be bypassed when tumor antigen is presented in an optimal environment of subcutaneous vaccination. Until this is tried, we do not have to through the towel. Here we present one such case of Stage IV colon cancer with concurrent and recurring liver metastases that present with a week concomitant antitumor immunity throughout the disease course. A 51-year old man presented with irregular bowel movement and bleeding accompanied with weight loss went to hospital in mid-2014. He was diagnosed with colon cancer with s single liver metastasis. Surgery was performed to remove both the primary tumor and the single liver metastasis. Post-surgery pathological analysis confirmed a medium-differentiated colon adenocarcinoma. Twelve rounds of adjuvant chemotherapy with Oxaliplatin and oral Capecitabine were prescribed and finished uneventfully. The sensitive tumor marker CEA returned to levels under 2. In November 2016, the patient experienced back pain and went for hospital check-up. A liver nodule measuring 6.5 x 5 cm was indentified. This tumor was resected again. Pathological analysis confirmed the sample as a liver metastasis from the colon cancer. It was at this time that the case went to us for help. We first checked the tumor replication and antitumor immunity in the samples from the first and second surgery. The findings indicated that the primary tumor was active with around 60% of tumor cells replicating as revealed by Ki-67 staining. On the other hand, there was only small number of T cells present in the interstitial space in tumor structure, mostly CD4 by subtype and no clear antitumor effect. The simultaneously resected liver metastasis by the first surgery showed more active tumor replication (Ki-67 around 80%) and lack of concomitant antitumor immunity. These observations would predict a lack of adequate post-surgery immune protection following the first surgery and would be consistent with subsequent recurrence. In the liver metastasis from the second surgery, tumor replication was less active than that in the primary tumor (Ki-67 around 40%). The presence of T cell, on the other hand, increased slightly in

number, but they were still mostly found in the interstitial space with no clear antitumor activity towards the tumor. Since the previous gap between first surgery and recurrence went two years without immune protection, we suggested the repeat of 12 cycles of chemotherapy. The patient took the option of chemotherapy and finished all treatments by June, 2017. By the end of 2017, tumor marker CEA which was sensitive previously started to rebound slowly and by May, 2018 a recurrent liver metastasis measuring 4.1x4 cm was seen at the S7 segment of the liver by imaging tests. The recurrent tumor was initially treated with transcatheter arterial chemoembolization. The treatment was effective reducing tumor size significantly. However, the tumor marker started to rebound two months after, indicating incomplete eradication. The residual tumor was then treated by RFA. Again, responses were seen by both tumor marker and imaging tests, yet tumor rebounded after three months. These observations point to a lack of involvement of antitumor immunity. By early 2019, tumor progression had accelerated and the metastasis measure both large (8x8 cm) and active on PET-CT (Figure 10). At the same time, all available conventional treatments had been exhausted for this case and the prognosis was grim. It was under this desperate situation that we recommended the approach of active immunization with tumor vaccine. This design has two important arms: for the first arm, we need to drastically reduce tumor burden to tip the future balance between tumor and antitumor immunity towards the immunity side; for the second arm, we need to increase the level of antitumor immunity through optimal immunization with tumor antigen. For this, the recurrent liver tumor was resected again and the fresh tumor tissue was mechanically disrupted and tumor cells killed by repeated cycles of freeze-and-thaw, the oldest way of whole cell vaccine that has been tried in the past. Upon pathological analyses, we saw a tumor that was highly active with >80% cells stained positive for Ki-67. Again, there was only limited number of T cells present in this tumor, indicating a lack of concomitant antitumor immunity (Figure 11). It is clear from this observation that without effective immune control, this case would have recurrence again. To activate an immune protection, this vaccine material was injected subcutaneously onto the forearm location ten days after post-surgery recovery. To ensure a Th1 response, we used IL-12 as adjuvant during vaccination. After three repeated vaccination 5 days apart, we began to see local redness and swelling response 6-10 hours after vaccination, indicating the presence of an ongoing (as against a delayed) immune response, consistent with presence of residual antigen from surgery. Continued vaccination finally generated strong DTH response, which indicates the clearance of antigen in the patients in the absence of vaccine and deposit of a strong protective memory (Figure 11). Tumor marker CEA returned to under 2 following surgery and vaccination and the patient remained recurrence-free till now (8 months after surgery) without other conventional treatments. Periodic vaccination with strong DTH has been maintained, and the vaccine material generated from the third surgery is enough for lifetime supply. Based on our experience with the success of tumor vaccine, as long as DTH has been reached by vaccine, tumor recurrence is completely controlled (our unpublished results).

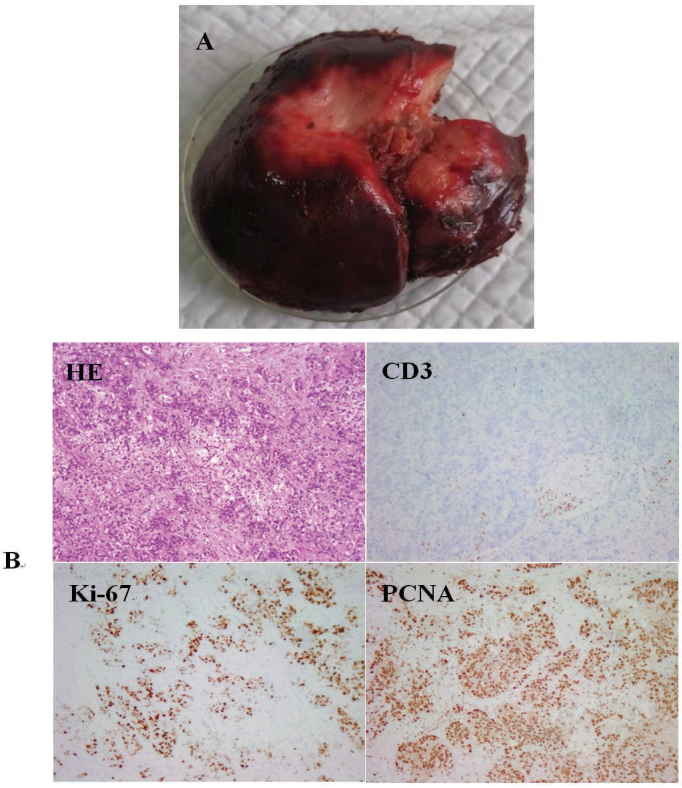


Figure 10. Tumor replication and concomitant immunity in the recurring liver metastasis resected for vaccine use for the colon cancer case presented in section 8 of text. The 8x10 cm liver metastasis (A) was resected and tumor proliferation and concomitant antitumor immunity were evaluated with antibodies to Ki-67, PCNA, CD3 and CD8 (B). Tumor replication was highly active by Ki-67 and PCNA. In contrast, T cells were absent in most part of the tumor with small patches seen at the periphery of the tumor (shown in the high magnification (100x) of micrograph image). It is nor the representative area, but a rare area where few T cells could be seen.

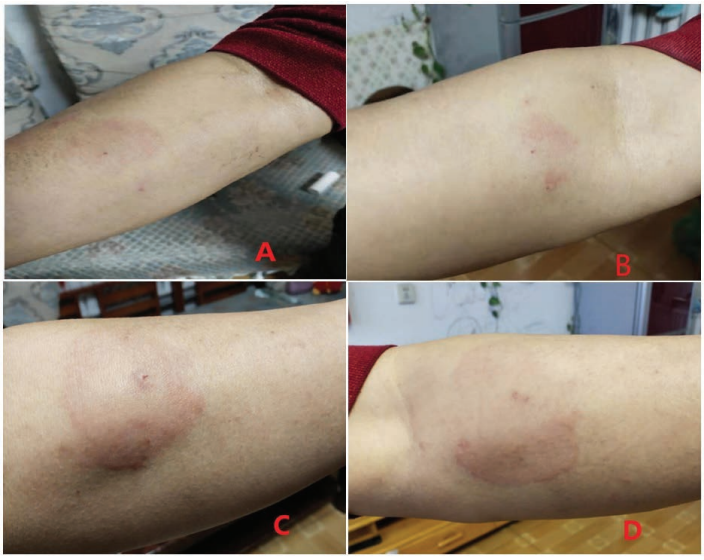


Figure 11. Change of local responses to vaccination with continued vaccination in the case of colon cancer with recurrent

liver metastases presented in section 8 of the text. Local redness and swelling were recorded at indicated time points after tumor vaccine injection. Only the most obvious responses from each round of vaccination are presented to show that multiple vaccination leads to a switch of local responses from immediate (6-8 hour post vaccination) to delayed (>24 hours post-vaccination) type indicating final clearance of tumor antigen and deposit of immune memory in the patient. The pictures of responses are from (A) 2nd vaccination, 8 hous; (B) 4th vaccination, 8 hours; (C), 5th vaccination ,12 hours; and (D) 7th vaccination, 30 hours.

This example best demonstrates the battle principles that we have been advocating and practicing: To create a situation in which maximized force can be used on minimal tumor burden for long-term control. In our mind, the equation of clinical cure for cancer can be divided into two parts: tumor-free + continued tumor-free. They are totally different as all previous efforts by mainstream medicine have been focused on the former and leaving the latter to luck. In contrast, we have focused on the latter. It should be point out that this "force" does not have to be antitumor immunity. The best example is the use of effective TKI drugs to create long-term control under minimal tumor burden [25]. The use of tumor vaccine has been widely tried in the history and mostly failed to show "statistical significance". Part of the reason for the failure is that these efforts, like many others in cancer management, are highly fragmented in that it was singled out and put up alone against tumor burdens that vaccination may not be able to eradicate. In other studies in which minimal tumor burden was reached by surgery, vaccination was often carried out immediately following surgery when in many cases a residual antitumor immunity is functioning even without the help of vaccine (which is just tumor antigen moved to subcutaneous location). The most critical need for vaccine in these cases is when post-surgery antitumor immunity decays gradually to non-function level (Figure 1). This is often 1-3 years later, not immediately after surgery. Had the timing been moved to that window, or had vaccination decision been individualized according to post-surgery evaluation of concomitant antitumor immunity, there may well be clear benefit of delayed vaccination (our unpublished results). Finally, for vaccine to start or activate a weak immunity, the use of IL-12 is critical, as IL-12 has been shown to be very powerful vaccine adjuvant in animal studies [26, 27]. This is well expected, as IL-12 is the central cytokine connecting innate and adaptive cellular immunity. Inasmuch as many cancers out there lack concomitant antitumor immunity and relapse after surgery, this example presented here should serve to raise the question: why not try it in every necessary case after assessing the status of concomitant antitumor immunity in surgical samples. Not only is it correct thing to do, it is also practical to carry out.

The Concluding Remarks

Dr. Dunphy's thought-provoking words of 70 years ago have long been forgotten, and cancer still remains the most challenging problem facing today's mainstream medicine. It is not that we still don't have the means required to win the battle. Since the "war on cancer" declared, we have developed huge weaponry against tumor cells. It is that we don't know how to use these weapons we have. If anything that the four cases we present here demonstrate, it is that cancer is an individual disease requiring individual battle plan. Just like playing a game of chess, one cannot win most games by following a pre-written step-by-step strategy book; we cannot cure cancer by following a pre-written rigid one-size-fits-all guideline. For the cases presented here, they are not the only successful ones that we have handled; neither are they the most dramatic ones. They are selected because they are relatively simple for making our argument clearly. In most of our advised cases, the situation is often complicated involving several factors intertwined together, but the bottom line is always clear: the levels of concomitant antitumor immunity are the most contributory. Because that the underlying interaction between tumor and host antitumor immunity is highly variable, and because this underlying antitumor immunity is critical for almost everything from cancer development to death, one must know this situation at each given moment in order to choose the correct move. It is not that we don't have the way to know it (or else we would not be able to do what we did in these cases), it is whether we want to. Dr. Dunphy pointed out in another follow-up essay in1953 [2]: "In this darkness, however, there are rays of light, the perception of which will be enhanced by a distinct change of traditional concept of nature of cancer. This change of concept is of more than philosophic importance to the surgeon." After all these years and many cancer deaths, are we ready to change the concept?

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