

The Effect of Immunology on Surgical Outcome: an Observational Hypothesis

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Abstract

Surgery is the oldest and still is the most effective way to eradicate solid tumors. Yet the actual mechanisms behind successful or failed surgery in cancer management remain obscure. Two seemingly identical cases subjected to similar surgery procedure may turn out with totally opposite outcomes with one cured and the other ended with explosive recurrence and rapid death. Such are scenarios in the past that prevented surgeons from even attempting to treat tumors of late stage cancers. Are there any hidden explanations or it is just the unpredictable nature of cancer? This article attempts to provide a comprehensive analysis on this issue from immunological point of view. The explanations and the hypothesis behind remain to be tested, but first we need to recognize the need to do so.

Keywords: Surgery; Solid tumors; Chemotherapy; Immunological point

Introduction

Surgery is the oldest and still is the most effective way to eradicate solid tumors. Yet surgeons have been "seriously handicapped in setting the extent of a procedure by an almost total ignorance of the biological propensities of the lesion they are attempting to treat. The most radical operation on a seemingly early lesion may be followed by widespread, rapidly progressive metastases and, contrariwise, a palliative resection undertaken with no hope for permanent cure may result in an extraordinary long period of time of well-being 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 total darkness." These are the words of Dr. Dunphy who in 1953 in a commentary titled "Changing concepts in the surgery of cancer" [1] after he discussed four cancer cases that demonstrated how unpredictable the disease may progress and respond to well established treatments in another commentary he published in 1950 [2]. Unfortunately, 70 years have passed and we have no clear answer to the conundrum that Dunphy illuminated. In this commentary, we attempt to change thinking about cancer surgery by analyzing it from a new immunological point of view. We hypothesize that this analysis will provide satisfactory explanation to common confusions in cancer management including cancer surgery. As such, this commentary is a continuation of the previous view we have published on the immunological aspects of classic cancer chemotherapy [3].

What is the concept of cancer surgery? Since the beginning and continues until today, the primary goal of cancer surgery has been the complete removal of all tumor. But by current knowledge of the systemic nature of the disease, this often cannot be achieved. Primary cancers metastasize early to distant locations often before clinical detection [4-12]. Then how can a local treatment such as surgery on the primary tumor result in eradication of disseminated tumor cells in

distant locations? The fact is that it can but the mechanism cannot be because of complete removal of all tumor cells by surgery. These are the questions we attempt to answer here.

The truly unpredictable nature of cancer progress and response to treatment was well illustrated 70 years ago by Dr. J. Englebert Dunphy [2]. In his classic commentary entitled "Some observations on the natural behavior of cancer in man" he described four cases of cancer that had totally unpredictable outcomes in responses to various treatments (or not). In the first case, Dunphy described a dramatic spontaneous cancer regression occurring in a terminally ill patient.

Spontaneous tumor regression is no longer a mysterious phenomenon as more and more cases have been reported [13-20]; however, a dramatic reversal from near death to complete tumor regression is still rare and commands high attention. What caused this dramatic reversal and spontaneous tumor regression? And why did it occur before death? A systemic enormous anti-tumor effect like this can be explained by immunity, or what Dr. Dunphy called a "natural resistance". Subsequently there is a gradual decay of this immunity following the regression of the original tumor (7 years in this case) that may account for the recurrence. Furthermore, upon tumor recurrence, the decayed immunity was stimulated and returned forming again a concomitant anti-tumor immunity. The description of well encapsulation of the recurring tumor is consistent with this explanation because tumor encapsulation is often the result of immune cell encirclement. Experienced surgeons realize that well encapsulated tumors have a better post-surgery prognosis as this is a sign of immune cell recognition and infiltration [21-23]. In this case, the patient remained disease-free after removal of the recurrent tumor supporting the plausibility of the return of the anti-tumor immunity and its continued surveillance after surgery. This case represents several important aspects of cancer and immunity that are still poorly recognized today. For example, the presence of an anti-tumor immunity has long been acknowledged, yet its exact role in each cancer patient remains unidentified and often totally ignored. In cases of

dramatic spontaneous tumor regression like this, the role of anti-tumor immunity is often accepted, but in other patient where there is no clear sign of its presence it is often ignored. Then does concomitant antitumor immunity exist broadly in cancer patients? Recent clinical success of the immune checkpoint therapy, such as PD-1 blockade, supports the presence of concomitant immunity in seemingly hopeless patients because its mechanism is the removal of inhibited anti-tumor immunity [24], implying that it is present but inhibited. Then, what did the inhibited immunity do before it was inhibited? Or, what happens to such immunity after tumor removal? Like in this case, if the concomitant anti-tumor immunity protected this patient from further recurrence for a long period of time, then it may be the same for stage I-III cancer patients who have had their primary tumor removed by surgery and remain clinically disease free. If so, the strength of the concomitant anti-tumor immunity does not have to cause total regression of tumor, it just needs to be sufficient to protect the host from recurrence of tumor after surgery. After all, from an immunological point of view, a complete clearance of antigen signals the ongoing immunity to form an immunological memory [25,26]. It may not be critical how the antigen is cleared, by surgery, chemotherapy, radiation or immune response, as long as it is cleared in the presence of an effective immunity, a subsequent immunological memory will develop [26,27]. On the other hand, if the antigen is not cleared, the concomitant immunity not only fails to convert to memory, but it may shrink because of a reduced level of tumor antigens [25,28]. This explains the accelerated progression of tumor following incomplete cancer resection (the 4th case cited by Dunphy). The disease reversal just before death in this case is consistent with a late initiation of concomitant immunity. We note that in this case, the cancer was not discovered by symptoms, but rather accidentally during surgery for a ventral hernia. It appears that there was no anti-tumor immunity at the time of diagnosis from two observations: the lack of cancer-related symptoms (inflammatory symptoms are a clinical sign of immune response) and the presence of wide spread of metastases (a finding that suggests lack of immune surveillance). Excision of tumor at this stage would not result in a long period of disease-free survival due to lack of immune protection. Even in some of the "early detection" cases where there was no metastases detected at the time of tumor removal, quick recurrences can occur after surgery (the 4th case cited by Dunphy). A lack of concomitant immunity is likely the real reason why these cases fail. On the other hand, both the development of a terminal stage and then the dramatic reversal may also be explained by heightened immunity. Immune response causes most of the suffering and even the fatality associated with various viral infections raging from flu, hepatitis to more lethal viral diseases such as SARS and Ebola. Why wouldn't immunity to cancer be similar? In this patient, the anti-tumor immunity eventually started and was amplified to attack the large tumor burden. This severe immune attack destroyed the tumor and also brought severe side effects from an inflammatory response. The difference between this patient and many other fatal cases is likely a thin balance between complete tumor eradication and lethal immunopathology. If complete tumor destruction takes place before severe side effects kill the host, it is a dramatic reversal of disease like in this case; otherwise the host dies before the complete destruction of tumor burden. Judging from the fate of most cancer patients, it is the latter one that is always the case. In this regard, it is also puzzling that not all tumor destruction by anti-tumor immunity is associated with severe symptoms. We, and others, have observed that asymptomatic lung cancer diagnosed during routine annual checkups often presents with intense immune response at the site of tumor, indicating that these tumors regress quietly

without ever being noticed. It is not clear why such a strong immune response does not cause symptoms. One observation suggests that these immune responses are always Th1-type that inhibits tumor replication. So the scale and the type of the anti-tumor immune response (Th1, Th2, Th17, etc.) may determine the presence and severity of symptoms in cancer patients.

In the second case cited by Dr. Dunphy, a 69-year old woman underwent cholecystectomy and appendectomy. Small breast cancer metastases were found in the appendix 14 years after apparently curative breast cancer surgery. Two weeks after the current abdominal surgery a pleural effusion developed and breast tumor cells were found in the fluid. A third thoracentesis a year later showed no more tumor cells in the pleural cavity. Again, we see strong evidence for anti-tumor immunity. Breast cancer has a more favorable prognosis among several other major solid tumors such as lung, colon, ovarian, stomach and liver (www.ssr.cancer.gov). It is not coincidental that concomitant anti-tumor immunity is also more prominent in breast cancer [29-32]. Biopsy and surgery tumor samples from breast cancer patients consistently indicated heightened immune responses characterized by presence of large numbers of T cells that coincide with destruction of tumor structure and inhibition of tumor replication (our unpublished observation and [33]). As we have pointed in discussion of the above case, a strong concomitant anti-tumor immunity is likely to translate into better post-surgery protection through conversion into high levels of immune memory. In this second case, it had been 14 years. What is intriguing, or disturbing, is the rapid appearance of cancerous pleural effusion soon after an unrelated surgery to remove the appendix and gall bladder. General anesthesia and surgery can inhibit the immune response. For example, surgery may cause a temporary immune suppression and stimulation of tumor growth through factors that are secreted for wound healing [34-36]. Local inflammation results in many factors that trigger cellular growth and angiogenesis, and may cause cancer recurrences that can occur even 5-10 years later. After a long latency period, only those disseminated individual tumor cells that cannot establish vascular supply by themselves are left, because those that can have done so already. The observation that latent cancer metastases from donor tissues develop in recipient patients following organ transplantation is consistent with this hypothesis [37]. These observations suggest that cancer may continue to be a life-threatening disease even when it is previously eradicated macroscopically [38]. Recurrence and metastases seem to follow two modes of establishment: a self-driven way that establishes a vascularized growth based on the inherent ability of the disseminated tumor cell itself, and an environmental-driven way that accomplishes initial vascularization by the help of a changed local environment then followed by self-sustaining growth. In a predictable and consistent environment after eradication of primary tumor by surgery or other means, one would expect to see the action of the self-driven way, and it should follow an L-shaped curve with less and less possibility of metastases as time passes. This is the behavior we see by statistical analysis in most cancer patients. But in each individual case, whether the vascularized cancer can progress further depends mostly on the presence and strength of anti-tumor immunity. Only when such immunity is absent or decays in strength to minimal levels do establishment of metastases occur. In this respect, the residual strength of anti-tumor immunity following surgery should also be L-shaped, protecting the host more when there is more appearance of metastases (antigens), and less when the metastases dissipate. There will be a time when all self-driven vascularization is exhausted and anti-tumor immunity is also out of effective surveillance. Only after reaching this phase, an

environmental-driven vascularization and progression of recurrent cancer will become relevant. In this second case cited by Dr. Dunphy, the quick appearance of cancerous pleural effusion following gall bladder surgery 14 years after the initial breast cancer surgery should be an example of such an environmental-driven recurrence. What is also intriguing and revealing, is what the decayed immunity did after the recurrence. In this case the disease did not progress further and even regressed macroscopically. Such docile behavior of recurrent cancer is rather exceptional by most clinical observations. In general, most patients die of effects of recurrent and metastatic cancer rather than the primary tumor. It is the general observation that once a cancer recurs after surgery, the disease enters a much more difficult phase of management. But in this case, there was no treatments following cancer recurrence and the patient experienced control and subsequently the tumor regressed. The observation is explained again as an action of anti-tumor immunity. It is known in immunology that a repeat stimulation with a recurrent antigen usually causes a heightened immune response compared to an initial stimulation. This behavior of immunological memory should not have exceptions when it comes to anti-tumor immunity. In this case, the return of the breast cancer due to surgery stimulation caused the return of the antitumor immunity that had been dormant due to a long time absence of tumor antigen. The fact that the cancer recurrence was accompanied by a large chest effusion indicated that the tumor recurrence initiated an inflammatory response by the host anti-tumor immune system that was either innate or antitumor-specific. The subsequent control and regression of the pleural effusion supported the fact that the specific anti-tumor immunity that protected the patient from post-surgery recurrence and metastases had returned and amplified. What this case has demonstrated is that like other adaptive immune responses, antitumor immunity behaves similarly in that it decays without persistent antigen stimulation and it will return upon further detection of antigens. This is important because it suggests that recurrent cancer patients should be managed differently from patients who present with the original cancer. If cancer returns after a long period (over a year) from surgery, it is likely that the primary tumor has maintained a concomitant anti-tumor immunity that has decayed. Similarly, we should expect to see that this decayed anti-tumor immunity will return and accompanied by symptoms due to an anti-tumor immune attack. This may explain some of the heightened symptoms associated with tumor recurrence such as pleural effusion, ascites and hepatitis. When the return of immunity is delayed, the recurrent tumor burden is large, often lethal consequences from immunopathology take place.

The third case discussed by Dr. Dunphy is about different behavior of different sites of metastases in the same patient. The original liver metastases from colon cancer progressed slowly for over two years after colon surgery, while an ovarian metastasis of the same tumor progressed rapidly over 6 months, demonstrating a variable growth rate of the same tumor at different sites in the same patient. The differential growth rate of the same tumor at different locations is common and is explained by a different environment that provides different nutritional and growth factors. But there may be an additional explanation based on differential control by antitumor immunity. Since metastases arise from a single tumor cell disseminated from a primary tumor that is often composed of a complex mixture of various mutated tumor cells with specific antigens, the antigenicity of each disseminated tumor cell may not be the same as the primary tumor. In this regard, it may be that a metastasis is a totally different tumor from an immune point of view. As such, a concomitant antitumor immunity raised and maintained by the primary tumor may

not be able to recognize certain metastases from that tumor and thus may not curtail their progression. This heterogeneity in antigenicity may present a serious challenge to immunological management of cancer recurrence. For example, we have seen cases where a heightened anti-tumor immunity returned after a recurrence and caused severe local inflammation that resulted in ascites. During this process, some of the early recurrences disappeared whereas other new ones developed, making it difficult to explain why a heightened anti-tumor immunity strong enough to eradicate previously established early recurrences could not prevent establishment of others. In instances where these immune resistant tumors were surgically removed and analyzed for T cells by immunohistochemistry, the observations always showed a lack of immune infiltrates in such tumors that contrasted significantly to the heightened immune T cell response profiles in recurrent tumors that were sensitive to growth inhibition by concomitant immunity (our unpublished observations). These observations may explain the two extreme directions of change in tumor burden before death in patients with strong concomitant immunity: either significant tumor reduction accompanying life-threatening symptoms or systemic inflammation and wide-spread and explosive progressing metastases.

Another interesting observation from this case is the rather unusual slow progression of residual liver metastases following incomplete surgery. This forms a clear contrast to the next case cited by Dr. Dunphy that was about a 59-year old patient who also had colon cancer. The primary tumor was large, but resectable. At surgery, extensive lymph node metastases were present and the liver was free of visible disease. Nevertheless, the patient died of explosive progression of liver metastases in just 10 weeks following surgery. It seems clear that the cancer surgery had accelerated the death. The side-by-side comparison of the two cases is confusing. As Dr. Dunphy discussed in this case: "The question is not what makes the cells suddenly grow but what has held them in abeyance for so long". Although there was insufficient information about this case, the two-year long symptom history and the lack of visible liver metastases at the time of surgery suggested that there was sufficient concomitant anti-tumor immunity that inhibited the establishment of liver metastases before surgery. This immunity was affected by subsequent incomplete antigen clearance at the time of surgery. It is likely that the residual abdominal lymph node metastases (the presence of which was confirmed at the time of surgery) presented a greatly reduced antigen load. Unlike the previous case where the residual tumor burden is large, the residual tumor burden in this case was small. This new antigen balance could no longer prevent the establishment of liver metastases. In addition to a weakened anti-tumor immunity, the growth promoting effects of surgery itself further made things worse. If so, this case demonstrates the ever more pressing need to preserve established concomitant anti-tumor immunity following cancer surgery. In order to do this, we can propose three approaches. First, complete surgical resection is critical because it assures the clearance of antigen and formation of memory. Second, to make sure that an immune response is not affected by reduction of antigen. This is common in the responses against acute infections where the immunity is intense until complete antigen eradication is achieved. The most critical difference between immune responses against invading microbes and cancer may not be antigen, but the source of antigen: self vs non-self as immunologists have long argued [39-41]. In one mechanism, the difference is presented to responding T cells in the form of certain immune factors produced after seeing non-self by antigen-presenting cells [42]. Such danger-associated factors will then modify antigen-activated T cells to make

them committed to a strong response resisting down-regulation [43-46]. Our previous studies have indicated that when antitumor immunity can be manipulated towards that of anti-infection by providing such a danger factor, dramatic antitumor effects including complete eradication of large tumor burdens can ensue [47]. Further, when antitumor immunity can be activated through combination of chemotherapy and danger signal at the time of surgery, a strong post-surgery protection is obtained [48]. The third is preservation of immunity made by continued supply of highly visible forms of antigen, this may be achieved through post-surgery cancer vaccine made with tumor materials removed at the time of surgery. In fact, supply of cancer antigen at the time of immunity decay should always be the primary consideration for any vaccine trial. If in a case like this one, the immediate decay of antitumor immunity due to incomplete surgery is the concern, tumor vaccine should be given immediately following surgery to keep the immunity from decreasing. In another situation, if the post-surgery immunity keeps working for 1-2 years before decaying (like many solid tumor cases), tumor vaccine should be delayed till then. In this aspect, treatment is case-based, not protocol-based. All of these measurements can be utilized in cancer management, but currently have not. The reason is not technical, but conceptual. Up to now, the way to avoid the disastrous consequence of incomplete surgery has been to avoid it all together through rigid TNM staging guidelines that emphasize surgery for localized disease and avoidance of surgery for distant metastases. However, many stage IV cases have concomitant anti-tumor immunity that can be used as part of an effective treatment plan. In these cases, the balance between concomitant immunity and primary tumor and metastases effectively make them more manageable like Stage II and not Stage IV cases. If the primary tumor and the metastases can be completely excised (which is often able to be achieved), the host will be left with a protective immunity that is as same as surgery on Stage I and II cases. Similar good results have been previously reported without knowing the explanation. For example, in lung cancers with a single brain metastasis, multiple clinical trials have been done to determine the role of surgery. The results are variable with seemingly identical cases some achieving clinical cure and other suffering explosive recurrence and death [49-51]. If concomitant anti-tumor immunity can be assessed in each of these cases, a surgery decision may be based on the status anti-tumor immunity and not the extent of disease. Thus the argument described here is that in many cases, the proper use of anti-tumor immunity will enhance the outcome for cancer patients.

Thus the role of surgery in cancer management may need to be looked from a immune point of view in addition to its traditional tumor reductive role. From this angle, we see at least the following roles of cancer surgery impacting antitumor immunity: First, complete cancer surgery may promote the formation of immune memory by the residual antitumor immunity. The formation of immune memory requires tumor antigen clearance. During a course of infection, successful clearance of the antigen leads to the establishment of immunological memory for that specific antigen. This is the basis for immunization with vaccines. Low-level antigen persistence prevents memory formation and promotes immune exhaustion or tolerance. When these rules are applied to immunity to tumor antigen, we can explain why complete removal of all visible tumor burden (excluding dormant tumor deposits) is critical. Incomplete tumor resection would create a situation of antigen reduction but not clearance, thus inducing the antitumor immunity to shrink without being able to form a memory. As a result, the antitumor immunity wanes and becomes ineffective in preventing future metastases. This explains why

incomplete cancer surgery is often more deleterious than beneficial and underlines the need for complete tumor resection as indicated by cancer surgery guidelines. Secondly, surgery may change the balance between tumor burden and strength of antitumor immunity. This is especially helpful in cases where the tumor burden is overwhelming and exhausts antitumor immunity. In such cases, a significant reduction of tumor burden helps to tilt the balance favoring control of residual tumor by activating residual antitumor immunity. Thirdly, surgery provides the opportunity to reshape the course of antitumor immunity by obtaining tumor materials that can be used as an anti-tumor vaccine to initiate, activate or maintain antitumor immunity. For example, many ovarian cancer women experience tumor recurrence following resection of their primary tumors. Upon examination of their tumor tissue, concomitant antitumor immunity is often absent or weak (our unpublished results). In such cases, the role of surgery in relation to antitumor immunity is not direct. Recurrence is high due to lack of immune protection and always leads to death without effective management options. If tumor tissues from surgery can be used to initiate an antitumor immune response from vaccination, a protective or concomitant antitumor immunity will become available and will likely change the course of disease fundamentally. In our early clinical exploration, we have seen this to be the case. Fourthly, surgery may provide an opportunity to release tumor antigen in situ through heat inactivation (electrocauterization). In many cases, surgeons find out rise-sized metastases upon surgery. Electrocauterization of these micro-metastases in addition to complete removal of primary tumor in the presence of concomitant antitumor immunity often leads to heightened activation of the immunity due to massive release of tumor antigens upon destruction of these micro-metastases during surgery, leading to favorable post-surgery outcome (our unpublished observations). Finally, surgery has a well-known role of promoting metastases. This, under certain circumstances, may actually favor post-surgery prognosis. For example, the more drastic D2 resection of stomach cancer developed in Japan 60 years ago [52-54] has significantly improved the post-surgery survival and is the standard option for today's gastric cancer patients undergoing surgery. Yet the reason behind this improvement has remained mysterious. It cannot be explained with simple removal of lymph nodes hidden with disseminated metastases because if better survival by D2 resection is due to removal of metastases in lymph nodes, this difference should appear soon after surgery within a year. But in reality, the actual beneficial difference in recurrence between drastic (D2) and less drastic surgery (D1) only becomes obvious after a year or even longer of time relapse. On the other hand, this much delayed effect on disease-free and total survival by more aggressive surgery may be explained by the combined effects of surgery-promoted early establishment of hidden metastases and the elimination of these new metastases by residual antitumor immunity following surgery. Thus, effectively reducing the possibility of future metastases when the immunity wanes after 2-3 years. In order for this scheme to work, a concomitant antitumor immunity must be present and functional. In the absence of this immunity, drastic surgery should promote faster but not delayed recurrence. Indeed, in some studies with Western gastric cancer patients, the drastic D2 surgery did show earlier immediate recurrence in some patients [55]. The true difference, therefore, should be the presence or absence of concomitant antitumor immunity. Yet, there is still no accurate way to assess the anti-tumor immunity of a given patient for his or her cancer. This is partly due to great variables in tumor growth and immune anti-tumor immunity in each different cancer patient; partly also due to our total ignorance of its variability and significance. Cancer is not one similar disease, but an individual

disease that will ultimately need an individualized treatment that solves the problem for an individual patient. One key to the problem solution is the host anti-tumor immune response. Individual assessment of the underlying host anti-tumor immunity at any given time in any given patient will be critical to understand and aid such an effort. Currently we do not have a technical method to accurately measure anti-tumor immunity. But this may not be because of our technical incapability, but rather our conceptual acceptance. At least in our hands, applying the concepts and approaches discussed here, we have started to obtain favorable clinical results in a number of difficult cancer cases. Dunphy's observations raised important clues to the value of the host immune response to cancer. We hope that this writing will stimulate others to look into its prevalence and value as it appears to be the key to his conundrum.

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