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Case Report

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Understanding and Management of Cancer Recurrence

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Abstract

Cancer recurrence is defined as the re-establishment of tumor burden following previous eradication of primary cancer by various treatments. Once this event takes place, the prognosis of the patient often becomes grim, signaling the end of life. Compared to the management of initially diagnosed cases, clinical dealing of recurred cancer has been in a state of chaos without consensus and guidelines. The reason for this lack of consensus in dealing with recurred cancer comes from highly variable outcomes to the same treatment in individual case, thus no defined treatments can be planned in advance. Why is recurred cancer more deadly than primary cancer? Why do some cancer cases recur while others don't? Why is it more difficult to deal with recurred cancer than primary cancer? These are challenging clinically relevant questions, the answer to which may help us to understand the mechanism behind tumor recurrence and provide strategy to deal with this deadly event more efficiently. Here, using a few cases, we present our analyses on this issue with focus on the status of antitumor immunity, the most critical factor influencing the outcome of each recurrence. Our analyses and experiences with cancer recurrence indicate that although appearing complicated than initially diagnosed cancer, recurred cancer could be reasonably managed like initially diagnosed cancer as long as its reason for recurrence is clearly identified.

Keywords: Cancer, Recurrent Cancer, Anti-tumor Immunity

Why Tumor Recur After Initial Eradication?

Tumor recurrence is the biological consequence of cancer spread and metastasis. Tumor cell dissemination from an established nodule is a constant process regardless whether these disseminated cells have the ability to form distant metastasis. When they do, metastasis will form. This process is common among all malignant tumors, the only difference is the time and location for the establishment of metastasis among individual cancer cases. Since tumor dissemination begins early during tumor formation, even before imaging detection [1], metastasis should be inevitable in all cases of malignant tumor with ability to form independent metastasis. Yet in reality, not all cancer present with metastasis, many early-stage cancer cases do not show metastasis at diagnosis and many not show recurrence after eradication of primary tumors. There is no convincing explanation for such variation. Cases without recurrence are not because of the lack of tumor dissemination and ability to form metastasis. Many cases present at the time of diagnosis with only primary tumor will form distant metastasis after a time period of 1-3 years following surgical removal of primary tumors. Many other cases actually present with metastasis in surrounding lymph nodes but remained clinically cured following removal of primary tumors. Historical observations indicated the life-long presence of occult tumor cells capable of forming metastasis [2,3]. Following sensitive tumor markers in many cases will show the elevation of these markers before identification of established tumor nodules, indicating tumor marker elevation represents a true event of tumor recurrence. Yet in some cases, elevation of sensitive tumor markers is only transient before eventually returning to baseline, suggesting that a short-lived tumor recurrence took place. Analysis of tumors with similar replication profiles has not identified any factor that predicts tumor recurrence and metastasis, supporting the assumption that the potential for tumor metastasis is actually similar among these tumors. Whether a metastasis will establish must be determined by other factor(s). The most likely candidate is the antitumor immunity that controls the establishment of tumor metastasis. Based on the interactions between tumor and antitumor immunity, we have previously proposed a model to explain the likelihood/risk of post-surgery tumor recurrence [4]. According to this window model (Figure 1), a malignant tumor will disseminate and deposit individual occult metastases in various locations of the patient during the course of primary tumor growth. These

metastases will establish continuously. When primary tumor is removed, the dissemination and deposit of tumor cells stops, but the establishment of metastases by previously disseminated tumor cells continues. On the other hand, the presence of antitumor immunity in the host will eliminate the newly established metastasis. Thus, whether a metastasis can establish is the balance of these two processes as illustrated in the figure. When antitumor immunity is adequate, regardless how many and how frequent tumor deposits turn into established tumor, this immunity will recognize and eliminate all of them. This is the situation in the protective window following removal of primary tumor by surgery. With time lags, the antitumor immunity decays to a level below ability to recognize and eliminate a newly established metastasis in-time to prevent its establishment due to lack of antigenic stimulation. Any metastases developed after this time point will likely become visible. This is the situation during the recurrence window in the figure. Based on this model, many clinical observations can be explained such as the variable time points recurrence takes place among individual cases. The variation of tumor's ability to form metastasis and the variation of antitumor immunity in each case will result in variation in metastasis formation pattern and time. Because that tumor deposits may form metastasis many years after primary tumor removal [2,3], the most critical factor that determines whether metastasis is formed would be the presence and absence of antitumor immunity. Clinical observation indicates that if a case has passed 5 years without recurrence, the possibility of recurrence would drop significantly to less than 10%. This observation thus indicates that either some tumor deposits exhaust before five year, or immune protection lasts more than five years in these cases or it is the combination of both. On the other hand, most post-surgery recurrence takes place between 1-3 years following resection of primary tumor, indicating that immune protection only lasted less than 3 years in these cases. Had immune protection been stronger, these cases may have been clinically cured.

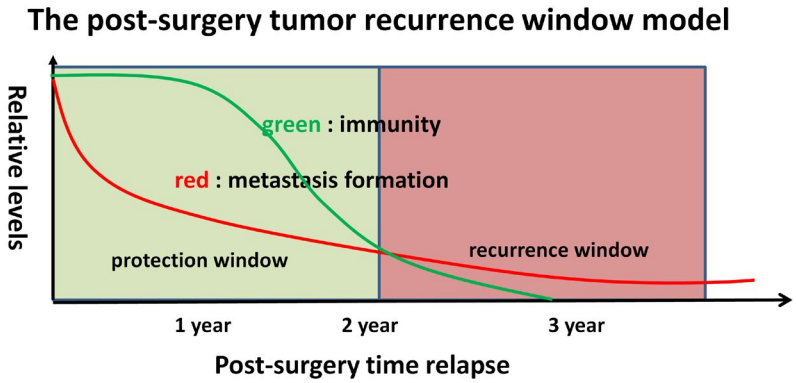

Figure 1: The post-surgery tumor recurrence window model. The horizontal axis shows the time lag after the removal of primary cancer. Th vertical axis shows the relative levels of establishment rate of residual tumor metastases (red line) and the levels of antitumor immunity (green line). The former reflects the frequency at which tumor metastasis appear after removal of primary tumor. This frequency becomes less frequent with time because all seeded tumor cells that can form metastasis will do so at the earliest time. With time, less and less such tumor cells remain till eventually almost none remaining. The antitumor immunity following removal of primary tumor will decay with time. This decay causes the gradual loss of protection against newly established metastasis until after a point this immunity can no longer recognize and eliminate newly established metastasis. This time point separates the two "windows" into protection and recurrence window.

Interestingly, some cases present recurrences not because lack of antitumor immunity, but because that the antitumor immunity are too strong at the time of surgery. Most of these cases present with local recurrence rather than distant metastases. The culprit behind this type of recurrence is tumor-expressed PDL1, an immune checkpoint ligand that interacts with PD1 on T cells to prevent immune destruction [5,6]. PDL1 expression is stimulated by IFN-g released by Th1 T cells when activated by tumor antigen. IFN-g is supposed to suppress tumor replication, but not in PDL1-exressing tumor cells that are often present with elevated tumor replication as witnessed by increased Ki-67 expression [7]. The effect of expression of PDL1 by tumor due to immune attack is the formation of stalemate between immunity and tumor that tumor is not eradicated by surrounding immunity whereas progression of the surrounded tumor is significantly slowed down and new metastasis is checked and eliminated by immunity. This situation often presents with highly elevated tumor marker without visible detection of tumor nodules (our unpublished observations). Tumor progression eventually become visible but often present with a single nodule. Even though such recurrence is totally different from recurrences due to lack of immune protection, not knowing so often leads to wrong clinical responses and loss of tumor control, which eventually causes patient death. Thus, this common misunderstanding is the reason attempt to claim that strong T cell infiltration seen in resected primary tumor is the single most accurate predictor of post-surgery recurrence and disease-free survival becomes difficult based on the surface of the data. In reality the relationship between levels of tumor-infiltrating T cells and recurrence becomes non-linear in that it takes the shape of a twisted bawl as illustrated in Figure 2. The reason for this upward rebound of the recurrence rate towards stronger immunity is the immunity-induced PDL1 expression as discussed above.

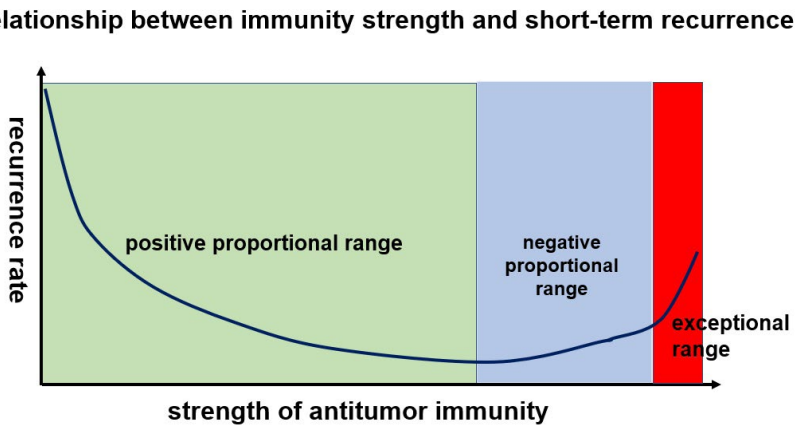

Figure 2: The relationship between the strength of antitumor immunity at the time of primary cancer removal and the short-term recurrence. The horizontal axis represents the increase of antitumor immunity at the time of removal of primary cancer. The vertical axis represents the likelihood of short-tern recurrence, which is recurrence taking place within a year of removal of primary cancer (often a few months). The drop of recurrence rate with increase of antitumor immunity is expected due to the protective feature of antitumor immunity (positive proportional range). With gradual increase of antitumor immunity, due to tumor expression of PDL1, the residual tumor metastasis is no longer eliminated by antitumor immunity and becomes visible (negative proportional range). This situation may become extreme with very strong antitumor immunity (the exceptional range).

Why is Recurred Cancer More Difficult to Manage Than Initially Diagnosed Cancer?

There are two answers for this question. The first answer is that compared to initially diagnosed cancer, most recurrent cancer lacks antitumor immunity (or they would not re-establish). Since the status of antitumor immunity has the most influential impact on patient survival [8], lack of immunity combined with replication active tumor often lead to quick loss of control and short survival. This is not a specific situation for recurrent cancer, because such lack of antitumor immunity may also be found in some initially diagnosed cancer cases. It is just that most recurrent cancer cases fall into this category while only some (about 30% or so) initially diagnosed cancer cases fall into this category. In addition, for recurrent cancer at the time of immunity decay, disseminated tumor cells have gone through long period of tumor variation to generate various metastases including potential immune escape variants while in a primary cancer setting, all disseminated tumor cells are more consistent with the major component of the primary tumor without extensive variation. Thus the overall prognosis of recurrent cancer is worse than that of overall initially diagnosed cancer. We have discussed in previous published works the significance of antitumor immunity in determining patient survival [8]. Without the support of antitumor immunity, most tumor reductive therapies cannot exhibit their maximal potential in tumor control [9]. Thus, many initially diagnosed cancer cases contain concomitant antitumor immunity, their responses to various therapies contribute positively to overall survival even if a case cannot be cured. In comparison, with recurrent cases lacking immune recognition, most tumor reductive therapies may not play full maximal potential in tumor control, and often may cause more damage to the recovery process of immune system, therefore making all treatments in vain.

The second answer is that recurrent cancer has various reasons that are not understood at all at the current clinical setting. Physicians tend to manage recurrent cancer cases by their own experiences and personal preference for therapy selection. These choices are often not based on the true reasons behind recurrence and are often ineffective. The progression by wrong choice of therapy leads to more random and desperate choices (for example, random application of immune check inhibitor therapy) which always get things worse and quick death of patients. On the other hand, if the true reason behind a recurrent cancer case is clearly defined, a proper management plan can be developed. There are only three most common reasons for cancer recurrence. By frequency, these are: 1) normal metastasis due to decay of immune protection following 1-3 years after removal of primary tumor; 2) residual tumor not eradicated by residual strong immunity due to PDL1 expression by residual tumor; 3) tumor variation-generated immune escape. For each of these three situations, the immune status behind is quite different. For example, recurrence due to decay of immune protection lacks antitumor immunity at the beginning of recurrence, but will likely resume immune recognition once tumor becomes well established. Not only will antitumor immunity recover following establishment of recurrent tumor, but it usually is stronger than before (at the time of primary tumor removal) (our unpublished observations). In comparison, if recurrence comes from development of tumor variant and immune escape clone, immune recognition is unlikely to establish with tumor growth (because it is an escape clone). Compared to these two situations, recurrence by residual tumor expressing PDL1 has strong antitumor immunity al the time. As discussed below, for each of these different recurrences, correct management strategies are also different.

How to Correctly Manage Recurrent Cancer Cases?

The first way to manage recurrent cancer cases is to identify the reason for recurrence behind each case. As discussed above, there

are three common reasons for cancer recurrence. The first type of recurrence is also the most common one that is due to decay of protective immunity. This type of recurrence usually takes place after a period of delay (>1 year) following removal of primary tumor. Because the recurrence is by disseminated tumor cells from the main components of the primary tumor, the recurrent tumor has similar structure to the primary tumor. Tumor replication may be slightly more or less active than that of the primary tumor, too. The most telling sign for this type of recurrence is the presence of multiple metastases in various locations other than the site of the primary tumor, including bone and brain metastases, metastases in other organs and body cavities. This recurrence with multiple metastases is because continued establishment of previously deposited tumor cells after the decay of protective immunity. In contrast, recurrence by immune escape variant is a rare event, often presents with a single metastasis. It is rare among all other recurrent metastases in a given patient, but not necessarily rare among all recurrences. Although not as common as recurrences due to decay of immune protection, this recurrence by immune variant/escape takes up around 10% of all recurrence cases (our unpublished observations). Different from recurrence by immunity decay, the immune escape recurrence is difficult to be controlled due to lack of immune recognition, even if it is often a single metastasis. The third type of recurrence due to tumor expression of PDL1 is more related to tumor type. For example, breast cancer always has strong antitumor immunity, and often presents with tumor expression of PDL1. Because that breast cancer often spread locally under skin, primary tumor surgery often leaves invisible residual local metastases coming into stalemate with antitumor immunity. As such, many breast cancer cases would present with local recurrence if left alone following removal of primary tumor. Nowdays such recurrence has decreased significantly since the introduction of local radiation combined with post-surgery chemotherapy. The residual tumor cells are often highly active in replication, a feature vulnerable for radiation-mediated killing. Other than breast cancer, many other solid tumors (such as some stomach cancer cases) may also present with residual and invisible tumor metastases that express PDL1 due to strong immune attack. Because local radiation therapy is not routinely performed in these tumor cases, the residual PDL1-expressing tumors always lead to recurrence within a year following removal of primary tumor. Compared with the other two situations, this recurrence has strong antitumor immunity accompanying the entire recurrence process.

The correct response to each recurrence requires correct identification of the reason behind each recurrence. Once the cause is identified, what response is correct and which one is wrong become clear. Knowing the actual cause of recurrence does not guarantee a successful cure for a case, but avoids mistake that may shorten the survival of the patient. The following are three cases representing the three types of recurrences mentioned above.

Case 1: Recurrence Due To Decay of Immune Protection Following Removal of Primary Tumor

A 53-year-old woman went to hospital for persistent coughing of over 5 months. CT exam revealed a left lung nodule (Figure 3A) with few nearby lymph node swelling, suspecting malignant tumor of the lung. Excluding other distant metastases, hospital arranged surgery to remove the lung nodule and nearby lymph nodes. Pathology analysis confirmed a medium differentiated adeno carcinoma of the lung. With three nearby lymph node metastases, the case was designated as stage 3A. Following removal of primary tumor, the patient followed guideline treatment plan for 4 cycles of adjuvant chemotherapy. Subsequently, the patient went into observation till 27 months later when a clavicular lymph node swelling was noted. PET-CT exam showed two separate lymph nodes with elevated SUV on the right-hand side of supra-clavicle and two mediastinal metastases in the right-hand side of the lung (Figure 3B). There was also a suspected brain metastasis. Thus, this case had become a recurrent case with multiple and distant metastases to the primary tumor. Upon recurrence, hospital arranged for continued systemic chemotherapy. After three cycles of chemotherapy, CT imaging showed stable disease. Patient refused to continue chemotherapy and went into observation. Six months later, the brain metastasis grew up and caused symptoms. Patient took radiation therapy and this brain metastasis was eradicated. Subsequently, recurrence progressed slowly and both sides of the lung had multiple nodules. The patient returned to more cycles of chemotherapy followed by multi-tyrosine kinase targeted therapy with small molecule drug (Anlotinib). Metastases continued to progress, albeit at a slow rate after three years of recurrence. Then, hospital suggested immune checkpoint inhibitor therapy with anti-PD1 antibody. The use of this therapy initially showed reduction of large metastases but continued treatments caused many new metastases in the lung (Fig 3C), supporting hyper-progression following ICI therapy [10]. Family member of the patient went to us again for help around this time. This case had come to our management before, soon after the removal of primary tumor. We had examined the tissue from primary tumor for the mode of tumor replication and status of antitumor immunity. Our observation (Figure 4) indicated that this was a medium-low differentiated tumor, mainly papillary adeno carcinoma with minimal interstitial space (Figure 4, HE). Tumor replication was active with Ki-67-positive cells ranged from 10-40% among tumor cells (Figure 4, Ki-67). There was a large number of T cells distributed in patches and threads in the tight interstitial space of the tumor (Figure 3, CD3). These T cells were mainly CD4 subtype, mostly showing activated state. Presence of T cell seemed to suppressed tumor replication (not shown). These observations supported the presence of a medium to high level of antitumor immunity that would be able to protect against establishment of metastasis following removal of primary tumor for a period of time. Because that there were local metastases at the time of surgery, our estimate was that this case had a tumor capable to spread but the antitumor immunity was able to provide protection until decay with time. Our conservative estimation was about 2 years before this protection lost effect. We hade suggested intermittent chemotherapy beginning 20 months following removal of primary tumor, but the patient and her physician refused to follow this advice. The actual recurrence seemed to take place around 24 months after surgery (or maybe sooner), quite close to our estimate. By the time the patient came back to our attention, there were large number of small lung metastases (Figure 3C). Because this is a case

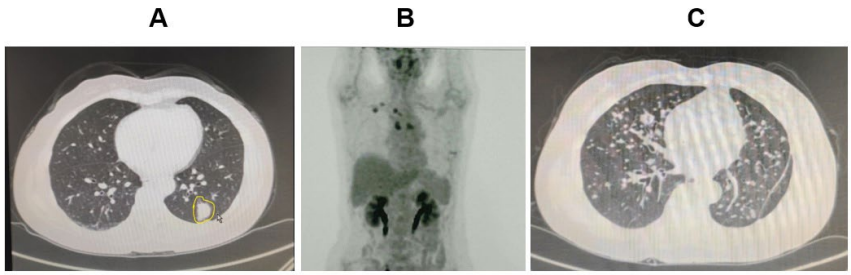

Figure 3: The change of tumor burdens at various time points for Case 1. Panel A shows the primary tumor (in the yellow circle) at the time of diagnosis by CT imaging. Panel B shows PET-CT detection of the initial recurrence after 27 months following the removal of primary tumor. Panel C shows the development of multiple lung metastases after repeated use of anti-PD1 antibody by CT imaging.

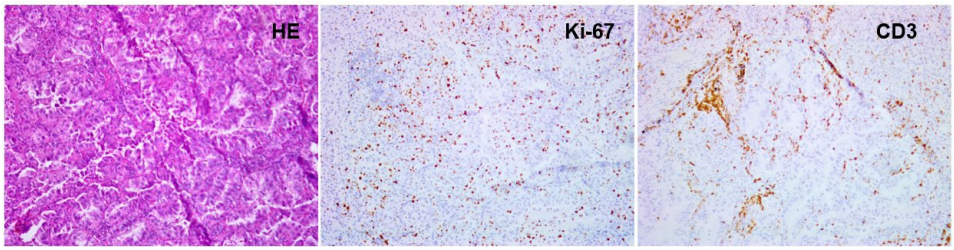

Figure 4: The tumor structure, replication and status of antitumor immunity in the removed primary tumor. This is a medium-low differentiated adeno carcinoma of the lung. Tumor replication was active with up to 40% of tumor cells stained positive for Ki-67. There were large number of T cell present in the thin interstitial space of the tumor. Most T cells are CD4 positive, and were in active state. We can see that presence of T cells suppressed tumor replication (not shown).

of recurrence by decay of antitumor immunity, we understood that the slow progression of recurred tumor was due to return of the previously decayed antitumor immunity once recurrence established and progressed. This returned antitumor immunity was responsible for supporting treatment efficacy by chemo and radiation therapy, for example, the eradication of brain metastasis. Yet this immunity was not highly activated by these therapies to eradicate all tumor burden. Instead, this immunity was partially deleted by repeated ICI therapy, leading to rapid establishment and progression of large number of metastases in the lung. Once further anti-PD1 antibody stopped, this depleted immunity would return after 2-3 months. The immediate goal was to hold further establishment of metastases and wait for the re-establishment of antitumor immunity. With this design, we advised intermittent chemotherapy for further treatments. Subsequent treatments indicated the return of antitumor immunity because sensitive tumor markers continued to drop even after 8 weeks of chemotherapy. To further enhance the activated immunity, we also advised the use of interleukin 12 [11]. These treatments lowered overall tumor burden but did not prevent new metastases from establishing, indicating presence of immune escape variants. In order to confirm the presence of antitumor immunity and look for other means of control (for example, possibility of targeted therapy on new mutations), we advised biopsy of the lung metastases. Biopsy samples showed a medium differentiated papillary tumor, clearly different from the primary tumor with more interstitial space (Figure 5, HE). Tumor replication was not active with about 10-20% Ki-67 positive cells (Figure 5, Ki-67). There were some T cells distributed unevenly in the tumor, mostly not in the interstitial space (Figure 5, CD3). T cell infiltration was much less intense than what was seen in the primary tumor (compare to Figure 4). These T cells were still mainly CD4 subtype, but not activated. There was no clear sign of suppression of tumor replication by T cells, but destruction of tumor structure was present. These observations indicated that there was presence of antitumor immunity in the recurrent metastases, but the immunity level was low. Genetic screen showed the presence of ALK mutation (abundance ratio about 7%), a mutation not found in the primary tumor. This finding also indicated presence of tumor variation, explaining the mixed response following chemotherapy with some metastases disappearing while other new ones establishing. These newly established components are likely driven by new driver mutations (such as ALK fusion gene). They had a medium differentiated structure, low autonomous replication driving large non-autonomous replication, and were not recognized by previously established antitumor immunity. Testing with ALK-targeted therapy did show response of some sensitive markers. Because of the mixed presence of tumor components, neither immunity nor targeted therapy can obtain complete control of such tumor mixture. The correct way to give targeted therapy is intermittent instead of continuous use. This intermittent use of targeted therapy has brought persistent response in our hands in a number of cases where antitumor immunity controlled other non-target components (our unpublished results). As expected, the subsequent use of intermittent targeted therapy brought graduate reduction of tumor burden to almost non-visible (Figure 6).

This case went through surgery to remove primary tumor and

recurrence. Although there were some lymph node metastases at the time of surgery, all visible tumor burden was successfully removed. In this aspect, the subsequent recurrence was true recurrence in that established tumor was from the main component of the primary tumor. The two years between removal of primary tumor and recurrence was the time period of immune protection by the immunity seen at the time of surgery. This was supported by the observation that the initial three years after recurrence, tumor progression was slow and chemo and radiation therapies seemed effective in holding tumor progression. Had this management path continued, this case would have remained a slow balance between multiple metastases and antitumor immunity for a while before final development of tumor variation and immune escape variant. This process was accelerated by the repeated use of ICI therapy, which caused hyper-progression due to over depletion of antitumor T cells [7,10]. The fortunate part of this tragedy was that variant metastases had ALK mutation that could be targeted by small molecule tyrosine kinase inhibitor drug. The use of targeted therapy alone is not the reason that this case was brought to a satisfactory ending with nearly complete tumor eradication. It is the addition of antitumor immunity to control the non-targeted components that brought the success. Although this case had a satisfactory ending, the history and handling of this case by main stream medicine and by us still demonstrated the sinister nature of recurrence cancer. For example, unlike the primary cancer, this recurrent cancer had multiple metastases to begin with, reflecting a difficult challenge for tumor reduction. On the other hand, because that this case had antitumor immunity to begin with in the primary tumor, once antigen returned due to recurrence, this immunity would return as well. As long as this immunity is used correctly, tumor progression may be well controlled if not reversed. In this aspect, antitumor immunity was correctly used in this case through the intermittent use of targeted therapy. The mechanism behind this intermittent use of targeted therapy under presence of antitumor immunity is not well understood, but seems to involve transient inhibition of antitumor immunity and release of this inhibition seems to activate the antitumor immunity transiently as well. We will be discussing this phenomenon in a future article.

Many recurrent cancer cases present with distant metastases such as multiple bone metastases, multiple brain metastases and sometimes metastases in other organs such as liver. This is typical of recurrence due to decay of immune protection. This case had also a brain metastasis that was eradicated with radiation. Although checked regularly and sometimes vigorously, recurrence with multiple metastases is still a common outcome of cancer recurrence. This fact alone, if viewed from the window model in Figure 1, indicates how frequent disseminated tumor seeds spring up even after 1-3 years. This fact also underlines the protective power of antitumor immunity when it is effective before significant decay. Therefore, the most effective way to prevent recurrence would be to raise the immunity at the time of primary tumor removal to as high as possible or to maintain its active state as long as possible after the removal of primary tumor. In this regard, neoadjuvant chemotherapy before surgery can elevate antitumor immunity that translate into longer protection after removal of primary tumor [9] and vaccination with tumor antigen post removal of primary tumor would serve the purpose of maintain antigen presence and thus immune activation. In every case, such immune manipulations should be considered before removal of primary tumor, even before any treatment begins. It is not yet adapted in cancer clinic today, but certainly is a goal for improvement tomorrow. If recurrence still occur, we should know how to deal with it. Fortunately, the decayed antitumor immunity often returns upon recurrence establishes. This is a natural consequence of immunity due to its antigen-driven feature. Thus, determining the status of antitumor immunity in recurrent tumor becomes the most critical diagnostic task. Only with the return of antitumor immunity, routine tumor reductive therapy such as chemo and radiation treatments become fully effective. This is the reason why timing becomes ever more critical in dealing with recurrent cancer. Too aggressive chemotherapy too early is a most common mistake in dealing with recurrent cancer. This prevents the fully return of antitumor immunity and only get things worse once chemotherapy stops. On the other hand, selecting proper therapy and timing may facilitate the return and elevation of antitumor immunity. ICI therapy, if used properly, represents a highly effective mean to activate antitumor immunity. But abusive use of this therapy has brought many tragedies in the clinic [7,10] including this case. In our hands, careful and individualized management of recurrent cancer can also bring long term survival (3-7 years). In all of such cases, immunity support is the most contributing factor. The moment immune escape takes place, a case has entered the final stage of accelerated tumor progression and death. In this regard, recurrent cancer is still more difficult to conquer than the primary cancer even with everything done right.

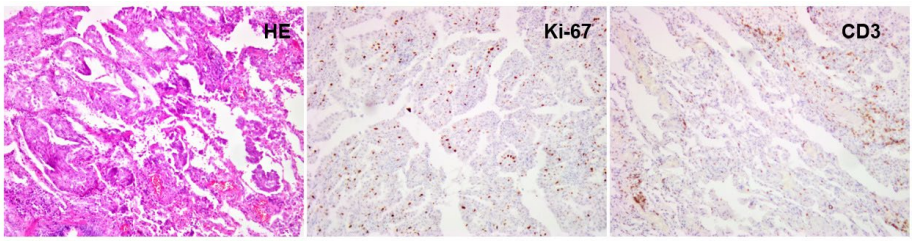

Figure 5: The tumor structure, replication and status of antitumor immunity in the biopsy sample taken after chemotherapy and mixed responses of Case 1. Compared to the primary tumor (Figure 4), the recurrence tumor has a medium-differentiated structure. Autonomous tumor replication as indicated by Ki-67 was less active than that in the primary tumor. Presence of T cells showed an uneven distribution with some parts of the tumor sample showed accumulated T cells inside the tumor (not in the interstitial space) while other parts of the tumor did not have T cell presence. Presence of T cells did not seem to suppress tumor replication.

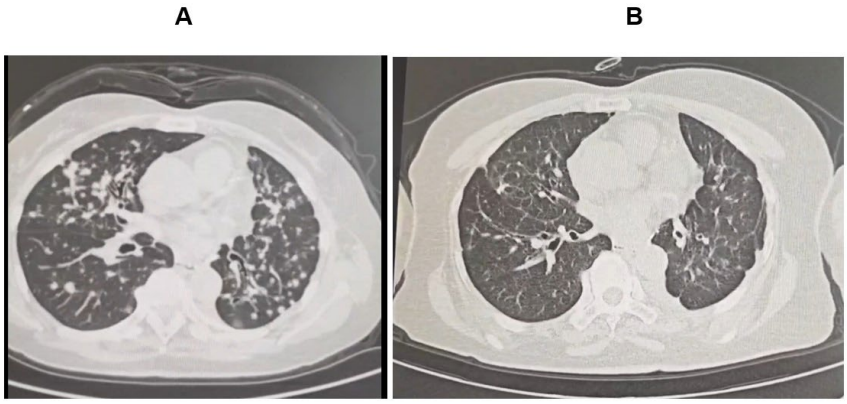

Figure 6: Comparison between lung metastases before and after intermittent ALK mutation-targeted therapy. Panel A shows the representative intra-lung tumor burden before beginning of ALK-targeted small molecule drug (Clozotinib). Panel B shows the same section of the lung by CT imaging 6 months later.

Case 2: Recurrence Due to Residual Tumor Expressing Pdl1

A woman of 54-year-old went to hospital after she felt a lump in the right-hand side breast. After a significant delay of a year of alternative medicine, CT and ultrasound imaging found the primary tumor growing to >8CM large and swelling lymph nodes under arm pit. Biopsy confirmed the presence of low differentiated malignant tumor of the breast duct cell. Immunopathological staining showed the tumor to be ER/PR negative. Upon diagnosis, the hospital arranged for neoadjuvant chemotherapy followed by surgery. Post-surgery pathology found two local lymph node metastases. A family member went to us for advice. Since her sensitive tumor markers showed persistent responses during chemotherapy that signaled activation of antitumor immunity, we compared her biopsy sample with surgery sample for signs of immune activation. This comparison showed that there were only few T cells in the biopsy sample taken at the time of diagnosis, and the presence of T cells increased significantly to a moderate level at the time of surgery. Most of these T cells showed activated state, consistent with elevation of antitumor immunity by neoadjuvant chemotherapy. We estimate that this immunity was able to provide 2 years of protection against recurrence. The patient went into observation following 5 cycles of post-surgery chemotherapy without radiation treatment. However, the sensitive tumor markers did not return to normal range following surgery and post-surgery chemotherapy. Two months later they showed rapid rebound, indicating recurrence. Another month later, a rapidly progressing nodule (>4 cm) was identified near the surgery site under skin. Under the observed antitumor immunity, we thought that this recurrence would represent an immune escape varient, thus recommended to have it resected and to save the tumor for vaccination to raise immunity against recurrence. Analysis of the resected recurrence (Figure 7) showed that the recurrent tumor had the same structure as the primary tumor (HE) with much more active tumor replication (Ki-67). Surprisingly, this tumor was not an immune escape. Large number of highly activated T cells were present inside the tumor (CD3). These observations ruled out the possibility that this recurrence came from an immune escape variant. Since no immune-recognized metastasis can establish under such strong immune surveillance, we had to consider this recurrence as an already established metastasis at the time of removal of primary cancer, only not visible. The tumor tissue from the second surgery was later used to make tumor vaccine, and vaccination showed robust local DTH response, supporting immune recognition already present before vaccination, consistent with observed antitumor immunity in the resected recurrent tumor. Despite this strong immunity, a second recurrence appeared few months later after second surgery. We realized that this recurrence would be the same as the previous one in that it was from residual metastasis. This repeated recurrence under strong immunity led to the suspicion of tumor expression of PDL1 as the culprit for inhibition of immune destruction. We went back to stain the tumor sample from second surgery and confirmed the high expression of PDL1 by highly replicating tumor cells (Figure 7, PDL1). At the time, our knowledge about the checkpoint inhibition therapy with antibody blocking was still based on the blocking mechanism adapted by the mainstream, we therefore used anti-PD1 antibody to treat the patient. After one dosing, sensitive tumor markers dropped quickly and the recurrence disappeared completely. The patient remained recurrence-free till now, over 5 years after the last treatment.

There are two critical points to be discussed about this case. First, this is a typical example of recurrence by residual metastasis not resected by surgery. When residual antitumor immunity attacks these residual metastases, the immune-released IFN-gamma stimulate tumor expression of PDL1, causing their resistance to immune eradication. This interpretation is consistent with our observation in this case that the recurrence was accompanied by strong presence of T cells and the use of ICI therapy led to clinical cure. This case has well illustrated what we have presented in Figure 2 that stronger immunity is actually associated with short term recurrence. Triple negative breath cancer, which possesses stronger antitumor immunity among solid tumors, often has post-surgery recurrence before post-surgery radiation was adapted for adjuvant therapy. Historical approach to this recurrence has been extension of surgical area without clear benefit. Since the adaptation of radiation, recurrence has dropped significantly. The mechanism, however, was never revealed. Our analysis provides

an explanation in that tumor cells expressing PDL1 always have elevated replication (Figure 7, Ki-67) that made them highly sensitive to killing by radiation. Secondly, what is not consistent with the mainstream-adapted mechanism for the checkpoint inhibition is the inhibition on T cells by tumor expressed PDL1. Instead, direct observation showed large number of highly activated T cells present with recurrent tumor. By function, if T cell response was inhibited, we should only see decreased T cell number, loss of activated state, and appearance of distant metastasis. None of these took place in this case (or any other similar cases as fact). Therefore, the claim of T cell function inhibition by tumor-expressed PDL1 is not supported by in vivo evidence. Instead, our observation indicated that tumor cell expression of PDL1 only made them "resistant" to immune-mediated killing, most likely the inhibition of replication by IFN-gamma and other factors. This interpretation is consistent with the ability of residual T cells to protect against newly established metastasis due to the immediate killing by immunity before these cells have a chance to express PDL1. On the other hand, without a strong antitumor immunity and tumor expression of PDL1, post-surgery radiation may not be necessary or may even harmful due to inhibition of immunity. Thus, whether to select post-surgery radiation for a case should be based on whether there are residual tumor metastases and whether these metastases express PDL1 under immune attack. The use of ICI therapy in this case to eradicate repeated recurrence was based on the mainstream selection criteria of tumor expression of PDL1. Although successful, this decision was not based on the correct depletion model we have recently proposed [7]. It is just that the tumor structure and T cell infiltration pattern for this case also met the correct selection criteria based on the depletion model. Readers should be aware of this issue.

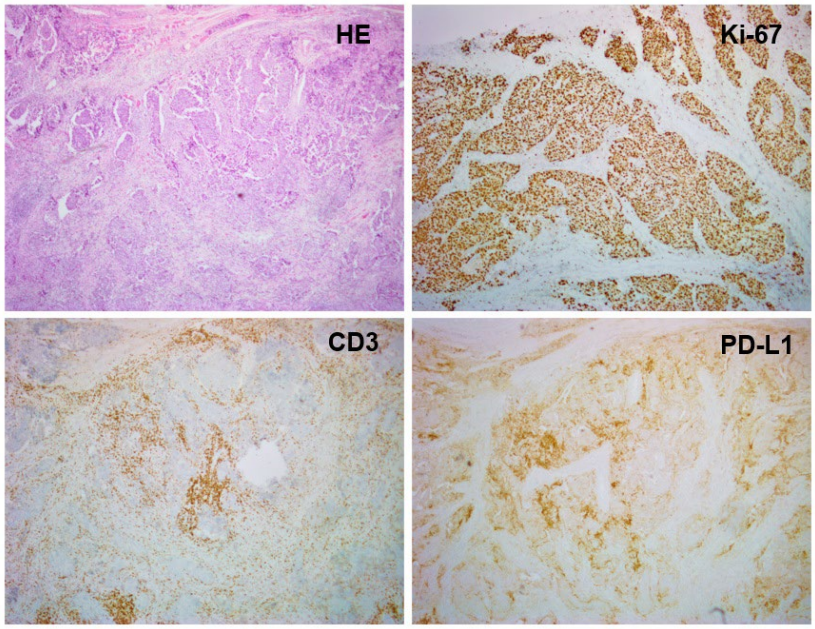

Figure 7: Tumor structure, replication, status of antitumor immunity and tumor expression of PDL1 in the 2nd surgery sample. The tumor is still a lowly differentiated carcinoma (HE). Tumor replication was very active with >90% of tumor cells stained strong with Ki-67. There were large number of T cells accumulate in patches or evenly infiltrating the tumor (CD3). T cells were the CD8 subtype, showing mostly activated state. More than 50% of tumor cells expressed PDL1.

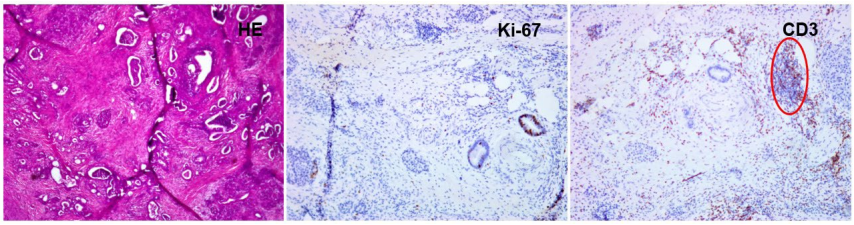

Figure 8: Tumor structure, replication and status of antitumor immunity in the primary tumor. Tumor structure shows small adeno-like tumors buried in large area of interstitial space, typical of pancreatic adeno carcinoma. Tumor replication was not active, only few lustered tumor cells showed Ki-67 positive stain, while many tumor cells stained positive for PCNA (not shown). There were large number of T cells present in the tumor, mostly in the interstitial space, surrounding and destroying tumor structure. These were mainly CD8 T cells, mostly not showing activated state. They formed tertiary lymph node structure (red circle), indicating presence of strong antitumor immunity.

Case 3: Recurrence Due to Variant Tumor Escape

A 60-year-old women went for physical check-up. Tumor marker tests showed elevated CA199 (>220) without symptoms. Imaging by MRI indicated presence of a nodule at the pancreatic tail. PET-CT indicated this nodule had increased SUV (>7), supporting presence of a malignant cancer. Excluding visible metastasis, the hospital arranged surgery to remove this lesion. Pathology analysis confirmed it to be adeno carcinoma with 1/19 removed lymph node showing metastasis. Adjuvant chemotherapy was arranged for a total of 7 cycles in 6 months following by two months of oral chemotherapy with S1. By the time of the end of chemotherapy, CA 199 had dropped below normal range. Three months later, CA 199 began to rise slowly, In the next year, CA199 increased to the pre-surgery level. Yet not imaging test found any recurrence. Thereafter, CA199 increase accelerated, thus by the next year, it reached a level of over 8000, still no recurrence was identified by repeated PET-CT. Eventually, a small nodule of <2cm was seen in the right liver. By this time, a family member went to us for advice. We asked to look into the primary tumor for a clue of recurrence. As Figure 8 shows, this was a typical pancreatic tumor with adeno carcinoma structure buried in large interstitial area (HE). Tumor replication was not highly active with Ki-67 positive cells take up about 10-30% of entire tumor population (Ki-67). PCNA staining showed nearly 90% tumor cells positive (not show), indicating presence of large number of non-autonomously replicating tumor cells. There are large number of T cells in the area surrounding tumor structure (CD3). Most of these are CD8 T cells. Most were not activated. T cell seem to be able to destroy tumor structure and suppress tumor replication, indicating that they were functional. They formed a few tertiary lymph node structures in the tumor, too. These observations showed a case of typical pancreatic duct cell cancer with low autonomous replication and strong antitumor immunity. This is consistent with the lack of multiple metastasis seen in the pathology report. This level of immunity should provide at least two years of protection against recurrence, ruling out recurrence as the result of immunity decay. Since we did not see elevated tumor replication associated with T cell attack, we did not suspected recurrence by residual PDL1-expressing tumor cells. We therefore suspected that this single live metastasis was an immune escape variant. Its source of generation was not clear, could be due to the large number of non-autonomous replicating cells mutated during post-surgery chemotherapy, a typical rare event we have seen in multiple cases (our unpublished observations). Immune escape tumors have the typical response to chemotherapy with immediate drop lasting about 3-4 weeks before rebounding. We therefore suggested one round of chemotherapy to test this explanation. The change of CA199 showed expected drop and rebound following chemotherapy, confirming the lack of immune recognition. Once the nature of this recurrence was identified, we recommended quick and complete eradication of this lesion by surgery. Yet our recommendation was rejected by the patient and her physician. Instead, they wanted to do radiation frequency abolition (RFA) therapy. We explained that RFA is not suitable for lesions that has no immune recognition because there are always residual cells not killed by RFA and these cells rebound to generate satellite lesions. The patient chose to accept RFA therapy anyway and developed satellite lesions as expected. Subsequently, the patient went through other therapies including chemotherapy, ICI therapy, intervention therapy. None of these therapies had controlled tumor progression. Three years after, three lung metastases developed, indicating decay of immune protection. However, these lung metastases were effectively controlled by intermittent chemotherapy while no more new metastases developed thereafter. But the liver metastasis had continued to grow from an initial small and single nodule to a large size fused by multiple satellite lesions (Figure 9). The patient is still alive 5 years after removal of the primary tumor.

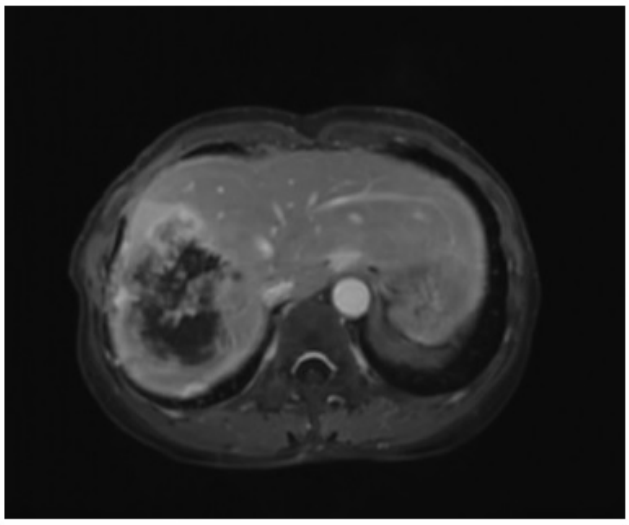

Figure 9: The MRI image of the single recurrence after three years of its appearance as a <2cm lesion in the liver.

There are few points to be noted. First, this case, although being pancreatic cancer, had strong antitumor immunity at the time of diagnoses. Without recurrence by variant, this case should have much better prognosis if not cured. The presence of tertiary lymph node structure, which is a feature present in this case, has been found to correlate with significantly better cancer survival [12]. Secondly, the generation of immune escape variant in this case proved to be a rare event by time (a single one in three years), indicating that it was not from one component in the primary tumor that was not recognized by immunity. We suspected that it was from the post-surgery chemotherapy-induced mutation in the non-autonomously replicating tumor cell. We had reported a case of chemotherapy-induced metastasis in an ovarian cancer previously [13]. Had we examined the primary tumor sample soon after surgery, we would not have recommended extensive chemotherapy, but resting with monitoring tumor marker movement. Thirdly, the three-year time for the presence of this single liver metastasis in this case again raised the question of secondary metastasis (i.e., metastasis coming from spread of a single metastasis). This is a very important question affecting therapy selection directly (for example we recommended surgery to remove the recurrence), but never even raised by mainstream medicine, less to say analyzed for answer. By our experience in the past 9 years of individual management of cancer cases, we have not found convincing evidence for the presence of secondary metastasis. Maybe in one or two cases, intra-organ secondary metastasis seemed likely, but never confirmed. The reason why metastasis cannot provide the source for further metastasis is not clear. There are only two critical steps for metastasis formation: the ability to spread to other location and the ability to form blood supply. It seems that tumor cells from a metastasis may have lost the ability to seed, but not to spread (circular tumor cell analysis can confirm this). Fourthly, the meaning of tumor marker has never been well identified. Most physicians even refuse to acknowledge tumor marker as tumor marker because they cannot deduce reliable information from them. For example, the over 30-times high CA199 over the level at diagnoses with clear primary tumor burden before a recurrence was detected in this case was confusing, but at least demonstrated that it cannot be used to reflect size of tumor burden. Then what is tumor marker reflecting? Based on our experience, tumor markers mainly reflect the replication "rate" of a given component in a tumor. In other words, tumor marker does not reflect how many tumor cells are replicating, but how active few replicating cells are replicating. In this case, for example, tumor replication in the primary tumor was clearly suppressed by the concomitant immunity, thus we saw the relatively low level of CA199. With the recurrence, extremely high CA199 reflected increase of tumor replication, but not increase of tumor size. The increase of tumor size was the result of continued tumor replication and continued variation by selection of most actively replicating tumor component. This interpretation of the meaning of tumor marker has not been proven, but not disproven, either. On the other hand, different tumor markers represent different components of the tumor, and the change of each marker only reflect the replication of its representing component. Also, the level of a given tumor marker is not absolute in that different tumor even having the same tumor marker may have different levels to reflect its replication. With these limitations in mind, we often can accurately interpret the change of tumor markers during disease course for a given case.

Summary

Cancer recurrence is a serious clinical challenge. Not only is it generally more lethal than the primary cancer, but also it is less predictable for behavior/prognosis as a group. No treatment guideline based on the TNM staging system has been established and could be established for recurrent cancer due to these features. In this review, we have summarized our understanding and our management approach for cancer recurrence, based on our own research and experiences in the past 9 years since we started individualized management for cancer cases. Although not adequate and proven, our views do explain some of the perplexing clinical observations on recurred cancer cases and provide answers to the most basic questions. The most basic reason for the general bad prognosis for recurrent cancer is the lack of adequate concomitant antitumor immunity. Recurrence would not take place when there is sufficient immune surveillance except for those residual metastases expressing PDL1 under strong immune attack. Although primary cancers also go through the period of lack of immune surveillance to become established, they do not have metastases all over the body at the time. The problem with recurrent cancer is that when immune surveillance is gone, all of the previously disseminated cancer cells in any part of the body may establish independent metastases. Despite in some cases, immunity may recover following establishment of recurrence, it is often too late for recovered immunity to hold disease progression. In addition, active tumor replication by recurrent cancer, always bring various variants that have different replication driven mechanism and different immunogenicity. The lagging immunity never has chance to catch up with this rapid change of tumor profile. This is a grim picture indeed, but it is the reality of cancer recurrence. To understand the challenge by recurrent cancer, one must focus on the status of antitumor immunity before and after recurrence.

The second confusing feature of recurrent cancer is the unpredictable behavior of the recurrence process. Sometimes, one sees one single recurrence persisting for years without other recurrences; other times, one sees multiple recurrences quick grow out of control. What dictates the behavior of each recurrence? Is it the biology of the given tumor or something else? Our analysis indicated that although tumor biology does contribute to the distribution of recurrence (for example, single or multiple, organ preference, etc.,), the most critical factor dictating the number of recurrent tumors is immune recognition. Under broad immune surveillance, no metastasis can be established regardless the biology nature of the tumor. On the other hand, when such surveillance is missing, the number of established metastases may vary from tumor to tumor, but often being more than one during a 6-month period, reflecting the frequency of previously seeded

cancer cells become vascularized and established as a focus of growth. This frequency, of course, is not constant but slows down with time as depicted in Figure 1. One needs to take this kinetics into consideration when anticipating coming metastasis in the absence of immune surveillance.

Correct management of recurrence not only possible, but could be highly effective. The most important step is to identify the reason for recurrence. As we have lined up in this writing, there are only three most common reasons for recurrence. Among these three types of recurrence, recurrence by residual tumor metastasis expressing PDL1 under strong immune attack is not a true "recurrence" as the metastasis already existed before removal of primary tumor, It is just invisible due to immune suppression that does not lead to expression of PDL1 in the presence of primary tumor. The reason why such occult metastases can stay invisible before removal of primary cancer is not clear. Maybe only small number of available immune cells is distributed to these metastases before surgery and large number of T cells become available after removal of primary tumor. Regardless, we have seen many such cases, more common than recurrence due to down regulation of pre-surgery immunity by residual tumor burden. The most distinct feature of these recurrences is strong antitumor immunity associated with primary tumor that induced tumor expression of PDL1. This strong immunity if accompanied by multiple lymph node metastases following surgery, almost point to recurrence by residual metastases. The other two recurrences are all due to lack of immune control, therefore are likely "true" recurrence in that they can establish as long as tumor growth allows. The biggest difference between them is the number of recurrent metastases. Recurrence due to decay of immunity often has multiple metastases whereas recurrence by immune escape variant often has only one metastasis. The other difference is that because the former recurrence takes place after decay of previously effective immunity, with recurrent tumor growing up, the decayed immunity would return. Not only does the immunity return, it is usually stronger than previous level at the time of primary tumor removal. This return of antitumor immunity is the basis for good prognosis for these cases. In contrast, recurrence by tumor variation has lost the ability to be recognized by previously established immunity, thus the growth of the variant metastasis often remains unrecognized by immune system. As such, this recurrence is more difficult to eradicate other than by resection. Unfortunately, most time when it happens, the treating physician refuses surgical approach for fear of inducing other metastases. Thus, comparing management of primary cancer, the management of recurrent cancer requires more careful selection of therapy as well as timing for each therapy. For example, for recurrence due to decay of immunity, until the full return of decayed immunity, any tumor reductive means would not be highly effective due to the lack of immunity support. In these cases, waiting and making sure that immunity has returned is the best "treatment". With sensitive tumor markers to monitor, this is not difficult to carry out. Yet there is almost no such thing as waiting in today's clinical setting for any cancer management, primary or recurrent cancer. Once a tumor is identified, rushing to the earliest treatment seems always correct by mainstream medicine. This "early detection and early treatment" mentality is generally good for management of primary cancer, but not necessarily good for the management of recurrent cancer, which in many cases are discovered and treated early, but rarely with satisfactory results. The complicated nature of recurrent cancer requires correct identification of its cause, correct selection of therapy and correct timing of treatments for successful management. The general lack of these knowledge by physicians in the field is the key reason recurrent cancer seems more lethal and more difficult to manage for now.

References

1. Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, et al. (2012) EMT and dissemination precede pancreatic tumor formation. Cell (1-2):349-361.
2. Dunphy JE (1950) Some observations on the natural behavior of cancer in man. N Engl J Med 242(5):167-172.
3. MacKie RM, R Reid, B. Junor (2003) Fatal melanoma transferred in a donated kidney 16 years after melanoma surgery. N Engl J Med 348(6):56756-8.
4. Chen X, Wang Q, Tsung K (2020) Antitumor Immunity as Determining Factor for Prevention of Post-Surgery Cancer Recurrence. Journal of Clinical & Experimental Immunol 5(1):1-11.
5. Abiko K, Hamanishi J, Matsumura N, Mandai M (2015) IFN-gamma from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. Br J Cancer 112(9):1501-1509.
6. Garcia-Diaz A, Shin DS, Moreno BH, Saco J, Escuin-Ordinas H, et al. (2017) Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. Cell Rep 19(6):1189-1201.
7. Tsung K, Zhang Xu, Zhanghui, Tanlun Research Participants Group (2022) The Blocking vs Depletion Model of Immune Checkpoint Inhibitor Therapy for Cancer. J Cancer Research Reviews & Reports 4(2):4.
8. Tsung K, Zhang Xu, Zhang Hui, Tanlun Research Participant Group (2023) On the Individualized Cancer Management. Medical and Clinical Research 8(10):1-9.
9. Guo H, K. Tsung (2017) Tumor reductive therapies and antitumor immunity. Oncotarget 8(33): 55736-55749.
10. Tsung K, Zhang Xu, Zhang Hui, TANLUN Clinical Research Participant Group (2023) Supporting Cases for the Depletion Model of Immune Checkpiont Inhibitor Therapy in Cancer. Journal of Cancer Research Reviews & Reports 5(5):1-12.
11. Le HN, Lee NC, Tsung K, Norton JA (2001) Pre-existing tumor-sensitized T cells are essential for eradication of established tumors by IL-12 and cyclophosphamide plus IL-12. J Immunol 167(12):6765-6772.
12. Schumacher T.N, D.S. Thommen (2022) Tertiary lymphoid structures in cancer. Science 375(6576):eabf9419.

13. Tsung K, Zhang Xu, Zhang Hui (2020) Existence and Significance of Non-Autonomous Cancer Replication for Clinical Management of Cancer: Observations and Hints from Ovarian Cancer Cases. J Pathology Res Review and Reports 2(2): 1-8.