

Morphological and Functional Remodeling of the Thymic-Lymphatic System Following Tumor Resection

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ABSTRACT

Surgical removal of the primary tumor remains one of the main methods of therapeutic intervention in the tumor process. Removal of tumor tissue is necessary for eliminating the tumor's immunosuppressive effects and usually has a beneficial effect on the course of the tumor. In some cases, however, the appearance and rapid growth of metastases is observed early after surgery. Apparently, surgical intervention affects the entire body, affecting the state of its protective adaptive and regulatory systems, among which the immune system plays a key role. It can be hypothesized that the reduction or, conversely, the development of resistance to metastases after tumor removal depends on the timing and degree of repair of various lymphoid organs and lymphoid cell populations responsible for cellular and humoral immune responses. It is important to keep in mind that the process of structural and functional restoration of the morphological substrate of the immunocompetent system after tumor removal occurs under various conditions, often complicated by the development of relapse or metastases.

Keywords: *Thymic regeneration, Lymphatic remodeling, Post-oncologic surgery*

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1. INTRODUCTION

The study of the recovery process in the immunocompetent system after surgical removal of the tumor is of primary importance for the choice of postoperative treatment tactics; establishing the optimal timing and doses of radiation therapy, chemotherapy, and the choice of timing and methods of immunotherapeutic intervention on the body.

Purpose and objectives of the study. The purpose of this study was to identify a correlation between the processes of restoration and activation of various structural and functional elements of the thymic-lymphatic system and the development or reduction of antitumor resistance in the postoperative period. Accordingly, the following objectives were set.

- 1) To study the structural and functional changes in the thymic-lymphatic apparatus during the growth of a transplanted and induced tumor;
- 2) To study the reaction of the thymic-lymphatic apparatus to surgical trauma - tumor removal;
- 3) To establish a correlation between the restoration of various structural and functional elements of the lymph node and changes in the thymus after tumor removal;

To identify a correlation between changes in the thymic-lymphatic apparatus after tumor removal and the occurrence of relapses and metastases.

Scientific Novelty. The literature lacks necessary and sufficient information on the changes that occur in the lymphoid system after tumor resection and their role in the mechanisms of enhanced metastasis or the development of resistance. Clinical studies examining the morphological substrate of the immune system in cancer patients focus solely on the static state of regional lymph nodes at the time of surgery and its correlation with postoperative prognosis. The dynamics of changes in lymph nodes and other immune system organs during the postoperative period, including recovery processes, are poorly understood. Available literature- we found three works devoted to the problem of restoration of the morphological substrate of the immunocompetent system - lymphoid organs . However, these studies lack data on the course of recovery processes depending on the individual's age, the size of the removed tumor, the development of relapses and metastases. The dynamics of recovery of various structural and functional elements of the lymphoid apparatus have not been studied, nor have the interrelationships between the recovery processes of central and peripheral

lymphoid organs been explored. We took this into account when setting the objectives of this study.

For the first time, the thymus and lymph nodes of various locations (regional to the tumor, symmetrical, and distant) were dynamically studied morphologically (using morphometric methods) after tumor removal in young and old animals of varying sizes. An analysis was conducted of the relationship between the development of relapses and/or metastases and changes in immunocompetent organs during the postoperative period. The study also yielded original data that allow us to understand the general patterns of the thymic-lymphatic system's response to surgical trauma and the correlation between the processes of structural and functional restoration of its various components after tumor removal.

Scientific and practical significance of the work. The experimental data presented in this dissertation expand and deepen existing understanding of the processes that occur in the immune system following surgical treatment, emphasizing the correlations between the restoration of central (thymus) and peripheral (lymph nodes) lymphoid organs and various precursor zones following surgical removal of humoral and cellular immunity in these organs. The results of the study, which confirmed the correlation between changes in the thymic-lymphatic apparatus and tumor progression, in particular metastasis, can find application in the further development of some theoretical issues of the "tumor-organism" problem.

In practical terms, the data we obtained allow us to consider the study of the immunological status after radical removal of the tumor to be very important for determining the postoperative prognosis in cancer patients.

The obtained results confirm the need to search for regimens and doses of postoperative chemotherapy and radiation therapy that have the least pronounced immunosuppressive effect.

Taking into account the data obtained in this study on the dependence of the structural and functional restoration of lymph nodes on the restorative processes in the thymus, it should be considered appropriate to prescribe thymus preparations (thymosin, thymoline, etc.) in combination with other immunotherapeutic measures in the early postoperative period after tumor removal.

In some oncological diseases (connective tissue tumors, melanoma), to determine the degree of restoration of the morphological substrate of humoral and cellular immunity, it is advisable to conduct a morphological (morphometric) study of biopsy material from regional or symmetrical lymph nodes, which is important for choosing the optimal timing of non-specific and specific local immunotherapy in the postoperative period.

RESULTS

1. Changes in the thymic-lymphatic apparatus in Wistar rats aged 4-6 months after removal of PC-I carcinoma a. The structure of the thymic-lymphatic apparatus in intact Wistar rats aged 4-6 months and its changes after limb amputation e dynamics b. Changes in the thymic-lymphatic apparatus in rats with a tumor 2 cm in diameter before and after its removal in dynamics c. Changes in the thymic-lymphatic apparatus in rats with a tumor 5 cm in diameter before and after its removal in dynamics . Changes in the thymic-lymphatic apparatus in rats with a tumor 8 cm in diameter before and after its removal in dynamics e.

2. Changes in the thymic-lymphatic apparatus in Wistar rats aged 18-20 months after removal of carcinoma PC-I 82 a. The structure of the thymic-lymphatic apparatus in intact Wistar rats aged 18-20 months and its changes after limb amputation in dynamics . Changes in the thymic-lymphatic apparatus in rats with a tumor 2 cm in diameter before and after its removal in dynamics c. Changes in the thymic-lymphatic apparatus in rats with a tumor 5 cm in diameter before and after its removal in dynamics d. Changes in the thymic-lymphatic apparatus in rats with a tumor 8 cm in diameter before and after its removal in dynamics e. Changes in the thymic-lymphatic apparatus in rats with a relapse of the tumor after its removal

3. Changes in the thymic-lymphatic apparatus in Wistar rats aged 8-10 months after removal of sarcoma induced by DMBA a. The structure of the thymic-lymphatic apparatus in intact Wistar rats aged 8-10 months and its changes after limb removal in dynamics b. Changes in the thymic-lymphatic apparatus in rats with a tumor 2 cm in diameter before and after its removal in dynamics c. Changes in the thymic-lymphatic apparatus in rats with a tumor 5 cm in diameter before and after its removal in dynamics d. Changes in the thymic-lymphatic apparatus in rats with a tumor 8 cm in diameter before and after its removal in dynamics.

DISCUSSION

Based on our data, after tumor removal, structural restoration of the thymus and the morphological substrate of cellular immunity in the lymph nodes occurs at varying times after surgery, depending on the size of the primary tumor lesion, the tumor type, and the age of the tumor-bearing host. Simultaneously, or somewhat earlier, signs of activation of humoral immune representative zones in the lymph nodes and the histiocytic reaction in the sinuses disappear. Restorative processes in the thymic-lymphatic system develop due to the elimination of the tumor's suppressive effect on the immune system after radical surgery. It is known that tumors, as they grow, exert an immunosuppressive effect on the body. This property is due, in particular, to the fact that tumor cells secrete substances into the blood, the so-called toxohormones, which suppress the function of lymphocytes by disrupting their intracellular metabolism [8, 16, 21, 70, 72, 94, 95, 130, 303]. It has recently been discovered that tumor cells are capable of synthesizing prostaglandins, which suppress the body's immunological response [154, 185]. In addition, the tumor has an immunosuppressive effect on the body through immunological mechanisms: the development of tolerance caused by an excess of tumor antigens; blocking the effector link of the immunocompetent system by circulating tumor antigens, antibodies and antigen-antibody immune complexes; activation of the activity of suppressor T-lymphocytes and macrophages [7, 21, 38, 65, 66, 93, 134, 145, 162, 173, 233].

In light of the above, it becomes clear that the immunosuppressive effect of a tumor on the body can be eliminated, at least at present, only by radical surgery [304].

Our results show that early after removal of a tumor-bearing limb, the lymph nodes exhibit signs of activation of humoral immune representative zones, a histiocytic reaction in the sinuses, and depletion of the morphological substrate for cellular immunity. These changes are most pronounced in the regional lymph nodes. Accidental thymus involution is also observed. We attribute these changes to the effects of surgical stress and the absorption of tissue breakdown products from the surgical wound.

G. Selye was the first to describe that stress causes involution of the thymic-lymphatic apparatus, caused by the secretion of ACTH and glucocorticoid hormones of the adrenal cortex [77]. We have shown that in the early stages after surgery, along with the involution of the thymic-lymphatic apparatus, a number of signs are morphologically revealed indicating an increase in the glucocorticoid function of the adrenal cortex; expansion of the fascicular zone, an increase in the size of the nuclei of its cells; depletion of their cytoplasm of lipids, ascorbic acid and glycogen. Moreover, the larger the tumor, the more pronounced these signs are [87]. Changes in the thymus and lymph nodes under conditions of surgical trauma similar to our data were also observed by other researchers [74]. In old animals, the reaction of the lymphoid apparatus to surgery is comparatively less pronounced than in young animals. Apparently, this is due to a weaker response of the pituitary-adrenal axis to surgical stress. Restoration of the morphological substrate of cellular immunity occurs later in older animals compared to younger ones. Furthermore, in young animals, unlike older animals, after restoration of thymus structure, signs of activation of its activity are observed, coinciding with the restoration of the morphological substrate of cellular immunity in peripheral lymphoid tissue. In all cases, regardless of tumor size, type, and age, structural restoration of the thymus precedes restoration of the cellular immune representation zone in the lymph nodes, with the exception of the thymus of older animals with large tumors removed, in which the thymus structure does not recover after surgery.

Following removal of a limb with DMBA-induced sarcoma, morphological signs of humoral immunity substrate activation and cellular immunity substrate suppression, as well as the histiocytic reaction of the sinuses in the lymph nodes, persist in the postoperative period significantly longer than in animals with resected PC-I carcinoma. The thymus structure is also restored later after surgery. This may be due to the pronounced dissemination of tumor cells after sarcoma removal and the prolonged circulation of tumor antigens and immune complexes in the blood. Clinical and experimental observations have demonstrated the entry of a large number of tumor cells into the bloodstream after excision of the primary tumor node [27b].

We observed tumor recurrence after removal of PC-I carcinomas and induced sarcomas in approximately the same percentage of cases. Recurrences occurred somewhat more frequently in older animals than in younger ones. This is likely due to the fact that restoration of the morphological substrate for cellular immunity occurs relatively more slowly in older animals than in younger ones. Recurrences occurred comparatively less frequently after removal of small tumors than after removal of large and medium-sized ones.

We observed the development of metastases after radical tumor removal only after the removal of induced sarcomas.

In the group of animals with relapses, metastases developed significantly more frequently than in animals without relapses. The patterns revealed in our material concerning the dependence of the process of postoperative metastasis on the size of the removed tumor and the presence of relapses were also observed by other authors [4, 19, 59, 98, 138, 141]. The effect of stimulation of metastasis growth after removal of the primary tumor is well known [19, 45, 141, 189, 207]. Existing concepts explaining the possible mechanism of increased metastasis after radical surgical removal of tumors have been analyzed in detail in a number of studies [3, 28, 155[^]. In them, a significant place is given to immunological processes [26, 190, 207, 250]. Our data confirm the role of changes in the immunocompetent system after tumor removal in the occurrence and prevention of metastasis in the postoperative period.

The development of metastases after removal of induced sarcomas always occurs against a background of severe thymus atrophy, with a sharp reduction in the lymphoid component of the paracortical zone of lymph nodes, and simultaneous hyperplasia of cortical follicles and plasmation of the medullary cords. We believe that one of the factors contributing to the development of metastases after tumor removal is accidental thymus involution and a reduction in the morphological substrate of cellular immunity in the lymph nodes, caused by surgical stress. The development of metastases is also facilitated by delayed or absent structural restoration in the thymus-paracortical zone of lymph nodes and activation of humoral immunity representative zones of the lymphoid system, often associated with an increased risk of relapse. In animals with relapsed PC-1 carcinoma or induced sarcoma,

structural restoration of the thymus and T-dependent zones of the lymph nodes is delayed. Concurrently, hyperplasia of cortical follicles and plasmation of the medullary cords are observed in the lymph nodes. These abnormalities likely contribute to the development of metastases.

The fact of atrophy of the lymphoid tissue of the thymus and paracortical zone of the lymph nodes in the early stages and its structural restoration in the late stages after tumor removal is of great importance for clinical practice.

The data we obtained indicate the importance of immunological studies in the postoperative period in cancer patients, in particular for determining the prognosis of the disease.

It is known that lymphoid tissue, which normally exhibits high cellular proliferative activity, is particularly sensitive to the toxic effects of chemotherapy and radiation therapy [9, 52, 63]. The need for cautious postoperative chemotherapy and radiotherapy, taking into account the dynamics of immunological changes after tumor resection, is becoming evident. The search for new regimens and doses of chemotherapy and therapeutic radiation in the postoperative period that would have the least pronounced immunosuppressive, or even immunostimulating, effects is becoming increasingly important.

Taking into account the data obtained in the present study on the dependence of the structural and functional restoration of the morphological substrate of cellular immunity of the lymph nodes on the restorative processes of the thymus after tumor removal, it should be considered appropriate to prescribe thymus preparations (thymosin, thymolin, embryonic thymus transplantation in a diffusion chamber) in the early postoperative period. Research on the use of thymus preparations in cancer patients has been conducted in recent years by a number of authors [23, 31, 90, 153, 240]. However, these preparations are mainly prescribed to patients with advanced forms of the disease, when all other methods of tumor therapy have been exhausted.

The severity of changes in the morphological substrate of humoral and cellular immunity in lymph nodes after tumor removal and their high informative value for assessing the body's

immune reactivity in the postoperative period suggest that morphological (morphometric) examination of biopsy material from regional or symmetrical lymph nodes after surgical tumor removal is promising. The information obtained will help determine the optimal timing and methods of local immunotherapy in the postoperative period.

A comparative analysis of morphological, including morphometric, parameters characterizing the state of substrates of cellular and humoral immunity in the lymph nodes and thymus in young animals with PC-1 carcinoma revealed the following changes.

As the tumor grows, signs of activation of humoral and cellular immune substrates are observed in regional lymph nodes. These signs are most pronounced with medium-sized tumors, and a histiocytic reaction in the sinuses is added. As the tumor grows, signs of activation in the paracortical zone disappear, signs of activation of humoral immune representative zones weaken, and the histiocytic reaction in the sinuses remains unchanged. Symmetrical and distant lymph nodes with small tumors show no noticeable changes. With medium-sized tumors, signs of activation of morphological substrates of cellular and humoral immunity are observed, but are less pronounced than in regional lymph nodes. With large tumors, signs of cellular immune substrate activation disappear, humoral immunity remains active, and a histiocytic reaction appears in the sinuses. In the thymus, no significant changes are observed with small tumor sizes. Morphological signs indicating increased functional activity are observed with medium-sized tumors. As the tumor reaches large sizes, moderate signs of accidental involution are observed.

Following removal of a limb with PC-1 carcinoma in young animals, signs of activation of the morphological substrate of humoral immunity and a histiocytic reaction in the sinuses are observed in the regional lymph nodes and, to a much lesser extent, in symmetrical and distant lymph nodes within 1-20 days after surgery. These signs weaken in the following days and completely disappear by 30-40 days after removal of small and medium-sized tumors, and by 60-80 days after removal of large tumors. Signs of suppression of cellular immunity are simultaneously observed, most pronounced in the regional lymph nodes. Complete restoration of the structure and cellular composition of the paracortical zone of the lymph

nodes is observed by 30-40 days after removal of small and medium-sized tumors and by 60-80 days after removal of large tumors. Postoperatively, the thymus gland exhibits signs of accidental involution, most pronounced in the immediate post-removal period (1-7 days). These signs are superimposed on existing pre-operative changes and are most pronounced in animals after removal of large tumors. Postoperative restoration of the structure and cellular composition of the thymus cortex and medulla occurs by 14-20 days after removal of small and medium-sized tumors, and by 30-40 days after removal of large tumors. In animals after removal of small and medium-sized tumors, morphological signs of thymus activation are also observed on days 30-40, coinciding with the restoration of the cellular immune substrate in the lymph nodes.

Following limb amputation, intact control rats develop changes in the lymphoid organs similar in nature and timing to those seen in animals with limbs amputated containing tumors with an average diameter of 2 and 5 cm. However, these changes are comparatively less pronounced in intensity. Compared to animals with limbs amputated with tumors measuring 8 cm, these changes are significantly less pronounced in intensity and resolve 30-40 days earlier.

Analysis of morphological parameters characterizing the intensity of cellular and humoral immunity in the lymph nodes, as well as the state of the thymus in old animals with transplanted PC-1 carcinoma, revealed the following changes compared to young animals.

In animals with growing tumors, no signs of activation of the morphological substrate of cellular and humoral immunity are observed, except for medium-sized tumors, when signs of some activation of humoral immunity appear in the regional lymph nodes. Signs of thymus activation at this time, unlike in young animals, are not detected. Changes in the thymus correspond to age-related involution. As the tumor reaches a large size, signs of activation of humoral immunity representative zones in the regional lymph nodes disappear, and suppression of cellular immunity indicators is observed in regional and, to a lesser extent, in symmetrical and distant lymph nodes. The histiocytic reaction of the sinuses remains at the

same level. The thymus is in a state of profound involution. Age-related changes are accompanied by signs of accidental involution.

Following removal of a limb with PC-1 carcinoma, signs of activation of humoral immune representative zones and a histiocytic reaction in the sinuses are observed in the regional lymph nodes in the first 1-20 days after surgery in older animals. These changes are less pronounced than those observed during the same time period in young animals. These changes weaken and completely disappear within the same timeframes as in young animals: 30-40 days after removal of small and medium-sized tumors, and 60-80 days after removal of large tumors. Concurrently, signs of suppression of the morphological substrate of cellular immunity are observed in the regional lymph nodes during the postoperative period. Compared to young animals, these changes are less pronounced in intensity. The restoration of the morphological substrate of cellular immunity in the lymph nodes of old animals compared to young animals is observed later: after the removal of small and medium-sized tumors by 60-80 days, and after the removal of large tumors it is noted by 100-120 days.

In symmetrical and distant lymph nodes, similar changes are observed only after removal of large tumors. In the thymus gland, age-related changes are accompanied by signs of accidental involution after surgery. Restoration of the structure and cellular composition of the thymus cortex and medulla to baseline values occurs after removal of small and medium-sized tumors by 30-40 days; this does not occur with removal of large tumors within the studied timeframe (up to 120 days). Morphological signs of thymus activation, as observed in young animals after restoration of the organ's structure, are not observed in older animals.

Following limb amputation in intact rats of the same age, changes in the lymphoid organs develop similarly to those seen in animals after removal of a limb containing a tumor. However, these changes are comparatively less intense and reverse more quickly.

An analysis of morphological parameters of the cellular and humoral immune substrates in the thymic-lymphatic system of animals with DMBA-induced sarcoma revealed the following differences compared to animals with transplanted PC-I carcinoma. Morphological signs of cellular and humoral immunity activation are observed in regional lymph nodes at times

corresponding to small tumor sizes. Cellular immunity activation is less pronounced than in similarly sized animals with transplanted PC-I carcinoma. Signs of cellular immunity morphological substrate activity disappear in regional lymph nodes at times corresponding to medium tumor sizes. Humoral immunity representative zone activity decreases, but the difference compared to intact animals remains. A histiocytic reaction is observed in the sinuses. As the tumor reaches large sizes, depletion of the cellular immune substrate and disappearance of signs indicating humoral immunity activation are observed. Symmetrical and distant lymph nodes with small and medium-sized tumors show no significant changes. As the tumor grows larger, signs of humoral immune activation and a histiocytic reaction in the sinuses are observed. In the thymus, moderate signs of accidental involution are observed with medium-sized tumors; in the presence of a large tumor, severe accidental involution is observed.

Following removal of a limb with induced sarcoma, signs of humoral immunity activation and a histiocytic reaction in the sinuses are observed in animals within 1-40 days after surgery in regional lymph nodes and, to a lesser extent, in symmetrical, distant lymph nodes. These signs weaken in the following days and completely disappear with the removal of small and medium-sized tumors by 60-80 days, and for large tumors by 100-120 days after surgery. Concurrently, signs of suppression of the substrate of cellular immunity are observed between 1 and 20 days after surgery, most pronounced in the regional lymph nodes. Complete restoration of the morphological substrate of cellular immunity occurs with the removal of small tumors by 30-40 days, medium tumors by 60-80 days, and large tumors by 100-120 days after surgery. In the thymus gland, accidental involution increases in the days following surgery. These changes are first detected during the removal of small tumors, while those of medium and large tumors are superimposed on preoperative changes. Complete restoration of thymus structure occurs 14-20 days after the removal of small tumors, 30-40 days after the removal of medium tumors, and 60-80 days after the removal of large tumors. Morphological signs of thymus activation are observed after the removal of small and medium-sized tumors, 30-40 and 60-80 days, respectively.

A comparative analysis of key morphological parameters in young and old animals with recurrent PC-1 carcinoma and DMBA-induced sarcoma compared with animals of similar age, tumor size, and time since surgery revealed the following: When tumor recurrence develops relatively early after tumor removal, no significant changes in the cellular and humoral immune representative zones in the lymph nodes and thymus are observed compared to animals without recurrence.

When relapses occur late after tumor removal, restoration of thymus structure and cellular immune substrate in the lymph nodes is delayed, and thymic activation is not observed, unlike in animals without relapse. Signs of humoral immune substrate activation may also be evident, whereas in animals without relapse, these signs disappear in the lymph nodes within this timeframe.

In animals with sarcoma metastases, early postoperatively, a more pronounced suppression of the morphological substrate of cellular immunity and accidental thymus involution are observed compared to animals without metastases. Later, a delay in structural restoration of the thymus and the substrate of cellular immunity in the lymph nodes is observed. The lymph nodes simultaneously show signs of activation of humoral immune representative zones.

5. CONCLUSIONS

1. Following removal of a limb with PC-1 carcinoma, morphological signs of activation of humoral immunity representative zones and a histiocytic reaction in the sinuses are observed in peripheral lymphoid organs (lymph nodes of various locations). Simultaneously, accidental thymus involution and a reduction in the morphological substrate of cellular immunity are observed in the lymph nodes. These changes are most pronounced in regional (inguinal, lumbar) lymph nodes.

2. In older animals, the response of the thymus and lymph nodes to surgical stress is comparatively less pronounced than in young animals. Restoration of the morphological substrate of cellular immunity in older animals occurs 2-2.5 times slower than in young animals.

3. After limb removal in animals with DMBA-induced sarcoma, morphological signs of humoral immunity substrate activation persist significantly longer in the postoperative period than in animals with transplanted PC-1 carcinoma. Structural and functional recovery of the thymus and cellular immune representative zones is also delayed.
4. Regardless of tumor size, type, and age, thymus recovery occurs faster than the recovery of the paracortical lymph nodes, with the exception of older animals with large (8 cm or more) tumors, in which the thymus does not recover until 100-120 days of observation. Furthermore, young animals show morphological signs of thymus activation, coinciding with the recovery of the morphological substrate for cellular immunity in the regional lymph nodes.
5. Structural and functional restoration of the thymic-lymphatic apparatus after tumor removal is an important condition for preventing postoperative recurrence and metastasis.
6. In the development of relapses in animals with removed PC-1 carcinoma or DMBA-induced sarcoma, regardless of the age of the animal and the size of the removed tumor, the structural and functional restoration of the thymus and T-dependent zones of the lymph nodes is delayed compared to animals without relapses.
7. The development of metastases after removal of induced sarcoma always occurs against the background of pronounced atrophy of the thymus, with phenomena of a sharp decrease in the lymphoid component of the paracortical zone of the lymph nodes, in conditions of simultaneous hyperplasia of the follicles of the cortical layer and phasmatization of the pulpal cords.
8. One of the factors contributing to the occurrence and growth of metastases after tumor removal is accidental involution of the thymus and reduction of the morphological substrate of cellular immunity in the lymph nodes, caused by the influence of surgical stress on the lymphoid tissue of the body.
9. The occurrence and growth of metastases after tumor removal are facilitated by disturbances in structural restoration in the links of the thymus system - T-dependent zones

of the lymph nodes, as well as the activation of zones representing humoral immunity in the lymph nodes, often associated with an increase in relapse.

10. The obtained results confirm the necessity and importance of a thorough study of the immunological status of cancer patients after surgery in dynamics in order to determine the prognosis, develop the correct tactics for prescribing chemotherapy drugs and radiation therapy with an immunosuppressive effect, as well as select the methods and optimal timing of immunotherapy.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

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