Review Article

A narrative review on the research progress of gonadal function protection in children with cancer

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Background and Objective: The global incidence of malignant tumors in children (0–14 years) and adolescents (15–19 years) ranges between 95 per 1 million and 255 per 1 million, which seriously affects the survival of patients. In the past 30 years, with the application of comprehensive treatments (including surgery, chemotherapy, radiotherapy, and bone marrow transplantation), great progress has been made in the treatment of malignant tumors in children and adolescents. The 5-year survival rate now exceeds 80%, and most patients can smoothly enter adolescence or the reproductive period. However, due to the particular age of patients with malignant tumors in children and adolescents, treatment may cause abnormal growth of the patient's height, bones, and some vital organs (such as the pituitary gland and reproductive organs). Treatment may also cause abnormal secretion of growth hormones, thyroid hormones, and sex hormones. These complications seriously affect the quality of life of tumor patients. In the past ten years, countries have established long-term follow-up specifications for children with tumors. These programs have found that, in adulthood, 67% to 75% of children who survived having tumors have at least one treatment-related complication. Among patients receiving chemotherapy, gonadal dysfunction is the most common related endocrine dysfunction.

Methods: This paper reviews the literature on fertility protection services for cancer patients in foreign countries was conducted to provide a reference for developing gonadal protection services for cancer patients and for establishing consensus or guidelines on gonadal protection in China.

Key Content and Findings: In the treatment of childhood cancer, the assistance of reproductive technology can effectively reduce the occurrence of complications from treatment.

Conclusions: Therefore, minimizing the effects of radiotherapy and chemotherapy on the growth and endocrine of children and adolescents while treating tumors is a new challenge for oncologists.

Keywords: Gonadal function; malignant tumor; children; adolescents; functional protection

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Introduction

The global annual incidence of cancer in children and adolescents is 186.6 per million. About 1 in 285 children are diagnosed with cancer before the age of 20, and only 1 in 530 people aged 20 to 39 is a survivor of childhood cancer (1,2). As childhood cancer survival rates increase, so does the number of survivors suffering from long-term complications. Gonadal dysfunction is one of the important late complications experienced by cancer survivors. Among adult survivors of childhood lymphoma, 11% of men and 44% of

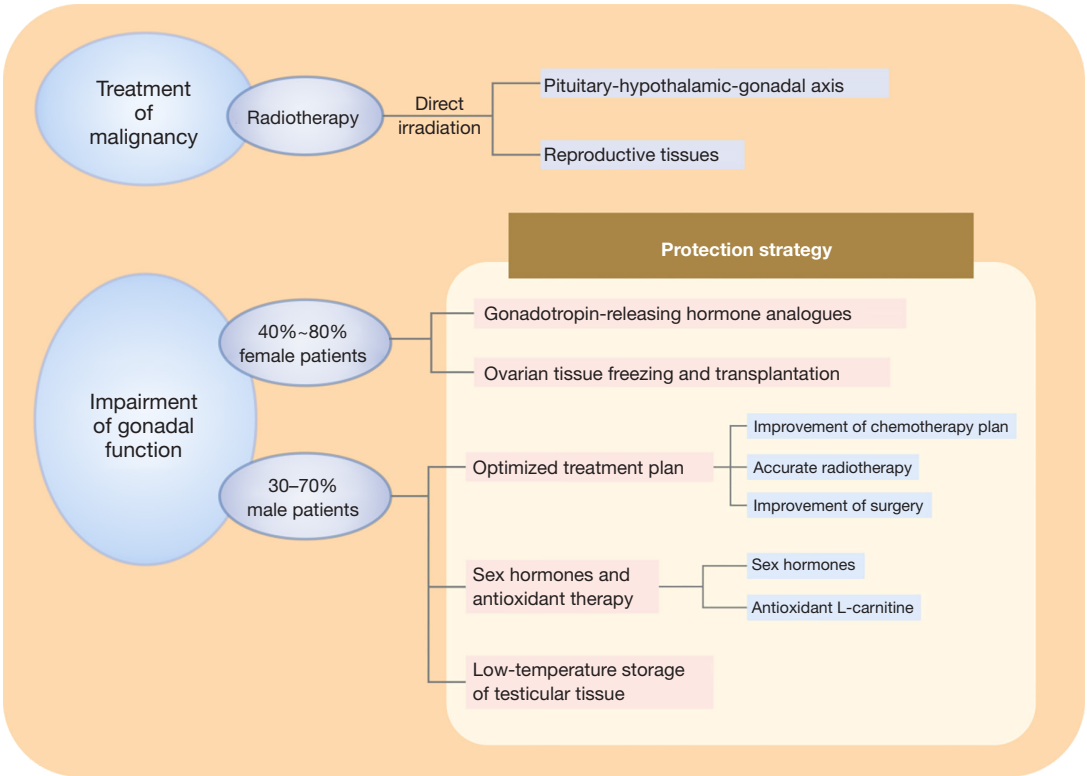

Figure 1 Treatment of malignancy and protective strategies for impaired gonadal function.

women reported gonadal failure. Among female pediatric cancer survivors, the risk of premature menopause is 13.2 times higher than that of their siblings (3). At the same time, one study has shown that 25% of childhood cancer survivors treated with alkylating agents have azoospermia (4). However, there is currently no effective method to protect children's gonadal development from tumor treatment. But one study has mentioned that cryopreservation of ovarian and testicular tissue can be used for fertility protection (5). Therefore, this study reviewed the relevant literature on the impact of tumor treatment on children's gonadal function. The results of the treatment and related protection strategies are shown in *Figure 1*. This study aimed to provide a reference for the treatment of children and gonadal dysfunction caused by tumor therapy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-681/rc).

Methods

This paper reviews the literature on fertility protection services for cancer patients in foreign countries was conducted to provide a reference for developing gonadal protection services for cancer patients and for establishing consensus or guidelines on gonadal protection in China. The search strategy summary as shown in *Tables 1*,*2*.

The impact of tumor treatment on gonadal function

Gonadal dysfunction is a side effect characterized by severe toxicity and caused by the treatment of malignant tumors. One study has shown that 40–80% of female children with tumors and 30–70% of male children with tumors have the risk of infertility (6). The main reason for infertility is that clinical radiotherapy for tumors is directly irradiated on the pituitary-hypothalamic-gonadal axis or reproductive tissues and results in damaged gonadal function (7). The degree of influence of chemotherapy and radiotherapy on gonadal function depends on various factors such as the size and location of the target area of the chemotherapy drugs or the target area of radiotherapy, the total dose, dose intensity, administration methods (oral and intravenous), disease

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	2021.8.2–2022.1.28
Databases and other sources searched	CNKI, VIP databases, PubMed
Search terms used (including MeSH and free text search terms and filters)*	Gonadal function; malignant tumor; children; adolescents; functional protection
Timeframe	1990–2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Related to gonadal function; malignant tumor; children; adolescents; functional protection
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Ruolan Hu conducted data search with the assistance of other authors
Any additional considerations, if applicable	None

*, please use an independent supplement table to present detailed search strategy of one database as an example.

Table 2 Search in CNKI

Search terms used in CNKI: gonadal function; malignant tumor; children; adolescents; functional protection
Inclusion criteria: related to gonadal function; malignant tumor; children; adolescents; functional protection

type, age, and gender. Due to the different mechanisms of gametogenesis, women are more affected than men (8).

For male children with tumors, the disease itself (such as testicular cancer and Hodgkin's lymphoma), anatomical problems caused by treatment (such as retrograde ejaculation or no ejaculation), and damage to reproductive stem cells can impair gonadal function. The markers of gonadal injury mainly include changes in testicular volume, routine analysis of semen, and abnormalities of serum endocrine such as follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone and inhibin B. At present, inhibin B is the main evaluation standard of male fertility. Radiation doses as low as 0.1–1.2 Gy can cause damage to spermatogonia, which can lead to oligospermia, while radiation doses greater than 4 Gy can directly lead to infertility. When the radiation dose is greater than 20 Gy, the testicular stromal cells of male children will also be damaged, and this damage is irreversible. The negative effects of cytotoxic drugs on spermatogenesis have been extensively studied. The most harmful drugs are nitrogen mustard derivatives, such as melphalan, and alkylating drugs, such as cyclophosphamide and procarbazine (9). For female children with tumors, any tumor treatment that reduces the number of primordial follicles and affects the balance of hormones or interferes with the function of the ovaries, fallopian tubes, uterus, or cervical function may impair fertility. The anatomy or vascular changes of the uterus, cervix, and vagina caused by surgery or radiotherapy will also reduce the probability of natural conception, so assisted reproductive technology is required (10).

Cranial (spinal cord) radiotherapy can damage the hypothalamic-pituitary axis and affect various endocrine functions, including ovarian function. Low-dose (<10 Gy) cranial radiotherapy often leads to precocious puberty, while a high-dose (>24 Gy) can lead to decreased levels of gonadotropins, including LH and FSH, delayed pubertal development, and the need for sex hormone replacement therapy (11). Bath *et al.* (12) reported that acute leukemia survivors after cranial radiotherapy with a dose of 18–24 Gy had decreased LH secretion and a shortened luteal phase. Similar to this report, after chemotherapeutic drugs enter the body, in addition to damaging gonadal function and causing disruption of ovarian function in response to damage to the hypothalamic versus pituitary system, it can also directly damage the ovaries (13,14). Most anti-cancer drugs can directly affect the ovaries and cut off the replenishment and development of follicles while reducing the number of primordial follicles. Therefore, once the ovaries are injured, menopause will occur, which may cause ovarian failure (15,16). At this stage, the effective chemical drugs in the treatment of female malignant tumors have a certain toxicity, which directly affects the epithelial cells and

follicles and weakens the ovarian function (17,18).

Protective strategies for gonadal function in female children

Gonadotropin-releasing hormone analogues (GnRH-a)

GnRH-a has a higher receptor affinity and lower enzymatic degradation ability than natural gonadotropin-releasing hormone (GnRH) molecules. Multiple clinical trials and meta-analyses have shown that, compared with patients who did not receive chemotherapy, premenopausal women who used GnRH-a to suppress ovarian function during chemotherapy were less likely to develop ovarian failure and had a higher chance of menstrual recovery (19,20). At the same time, one study has confirmed that, under the premise that the chemical efficacy will not be affected, the combined use of GnRH-a and chemotherapy drugs can increase the probability of patients returning to normal ovarian and reproductive function by 65–68% (21).

Several studies have shown that GnRH-a can reduce the damaging effects caused by chemotherapeutic drugs because of the following mechanisms: (I) GnRH-a can reduce the concentration of GnRH in the blood, thereby reducing the secretion of FSH and interrupting FSH-induced follicular recruitment and atresia process (22), and induce ovarian quiescence and protect follicles in the initial state of development, thereby reducing the exposure of follicles to gonadal toxic drugs (23); (II) GnRH-a can reduce uterine ovarian perfusion, thereby reducing the amount of gonadal toxic chemotherapeutic drugs that accumulate in the ovaries (24); (III) the activation of GnRH receptors reduces cell apoptosis; and (IV) sphingosine-1-phosphate (S-1-P) can potentially reduce the damage of chemotherapeutics to the ovary vitro or in the ovary, and GnRH-a can up-regulate the content of S-1-P in the ovary, thereby protecting ovarian stem cells (25).

Clinical practice found that GnRH-a inhibits (ovarian function) because it competes for receptors. In a study to prevent early amenorrhea, all subjects were hormone receptor positive. The amenorrhea rates of subjects who used GnRH-a in combination with chemotherapy and chemotherapy alone were 8.0% and 22.0%, respectively ($P<0.05$) (19). In another study, 80.0% of subjects were hormone receptor negative, the amenorrhea rates were 8.9% and 25.9% ($P<0.01$) (26). PROMISE-GIM6 Phase III experimental results showed that a brief period of ovarian suppression during chemotherapy can reduce the efficacy of amenorrhea and increase the adverse effects of GnRH-a decline, such as fever, headache, sweating, osteoporosis, and vaginal dryness. Data showed that the combined application of GnRH-a and chemotherapy protected ovarian function and reduced the probability of premature ovarian failure. However, some data and meta-analyses showed different results. One study has found that the use of GnRH-a had no benefit in protecting ovarian function and fertility (27). Therefore, the use of GnRH-a during chemotherapy is considered to be an experimental strategy that may protect gonadal function and fertility. However, it may have a negative effect on prognosis due to the lack of long-term experimental data (28,29).

Freezing and transplantation of ovarian tissue

The low-temperature preservation of ovarian tissue allows hundreds of primordial follicles to be preserved in situ. This technique has several advantages: it does not require ovarian stimulation, it does not require delaying chemotherapy in patients, and a large number of germ cells can be preserved. Due to the small size of primordial follicles, their low metabolism, and their lack of zona pellucida, they are not easily damaged during the freezing and thawing process (30). After tumor treatment, the ovarian tissue can be transplanted orthotopically or heterotopically or cultured *in vitro* (31). If the fallopian tube is functioning well, after orthotopic autotransplantation, the ovaries can ovulate spontaneously or after stimulation, and pregnancy can be spontaneous. Heterotopic transplantation is mostly transplanted to the subcutaneous tissue of the forearm or abdomen. It is minimally invasive, reversible, reproducible, and easy to monitor. However, due to the difference in body temperature and the pressure of the subcutaneous tissue, the development quality of ovarian tissue follicles after transplantation into the subcutaneous tissue may be affected, and the patient's fertility can only rely on assisted reproductive technology (32,33). Isolation of primordial follicles refers to the separation of primordial follicles and low-temperature preservation after ovarian tissue is surgically removed. Its advantages are the same as the low-temperature preservation of immature oocytes, and it can also exclude ovarian tissue carrying cancer cells. Abir *et al*. (34) punctured and extracted immature eggs from the ovaries of 42 tumor patients who were 2–18 years old who were going to undergo ovarian tissue cryopreservation (OTC), and at the same time filtered the liquid for ovarian sectioning, and finally successfully preserving frozen eggs

in 28 cases. The number of frozen eggs obtained by this method was positively correlated with age. The older the age, the greater the number of frozen eggs obtained. However, primordial follicles are easily damaged after isolation, and *in vitro* incubation techniques are not yet mature (35,36).

It is worth noting that the loss of follicles due to ischemia during transplantation is as high as 66%, so it is not suitable for patients with a small volume of frozen ovarian tissue (37). The second worrying issue is that the transplantation of ovarian tissue may re-transplant remaining malignant tumor cells into the body, leading to cancer recurrence. It is hoped that, with the development of technology in the future, related issues can be overcome one by one and bring hope to young cancer patients.

Protective strategies for gonadal function in male children

Optimize treatment regimens

Improvement of chemotherapy regimens

Children who use nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) regimens for chemotherapy have a higher probability of infertility, while children treated using doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) are less likely to suffer from infertility. Bujan *et al.* (38) found that, after 24 months of treatment, more than 90% of patients using ABVD chemotherapy could return to normal gonadal function, but, after using cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP), only 61% of patients returned to normal gonadal function after treatment.

Currently, in the selection of chemotherapy regimens, the influence of alkylating agents on gonadal function is less than before. Under ABVD chemotherapy regimens, sex hormone (FSH) levels can be at normal levels of 50–75% for children (39). Meissner *et al.* (40) reported on the treatment of two large-scale clinical trials that analyzed the reproductive results based on CHOP chemotherapy and found that children who used CHOP chemotherapy had slightly higher FSH than men of a normal age and reproductive period (41.8% *vs.* 32.6%). In addition, 80% of children treated with an increasing dose of the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine procarbazine, and prednisone (BEACOPP) regimen had higher inhibin and FSH hormone levels than infertile men after the end of BEACOPP treatment (35).

Precision radiotherapy

Radiotherapy and three-dimensional conformal radiotherapy are precision radiotherapies widely used in clinical practice. Precise radiotherapy for cancer lesions can reduce the scattered dose received by the gonads, thereby reducing the damage to the gonads (41). Xu *et al.* (42) found that, after three-dimensional conformal radiotherapy for testicular seminoma, the local control rate could be guaranteed, and the acute radiation reaction could be reduced. In addition, for patients undergoing radiotherapy, most doctors will choose to use baffles, such as lead plates, to protect the gonads. In the study by Deng *et al.* (43), for the radiotherapy of testicular seminoma, precision radiotherapy was superior to traditional radiotherapy in all aspects, and they emphasized the necessity of using a lead spoon to protect the contralateral testicle.

Improvements in surgery

With the development of surgical techniques, the protection of nerves during surgery greatly reduces the risk of ejaculatory dysfunction (44). The rapid development of laparoscopic surgery and robotic surgery allows surgeons to more accurately remove diseased tissues, resulting in normal gonadal tissue being not or less damaged. For example, for benign testicular tumors, partial orchiectomy with testicular preservation can maximize the protection of the patient's fertility (45) and reduce gonadal damage caused by human factors so that the patient's fertility-related tissues and organs can be completely preserved.

Sex hormones and antioxidant therapy

Sex hormones

The inhibitory effect of sex hormones can allow the testes to enter the resting phase, reducing the toxic effect of treatment on the gonads (46). When a large amount of exogenous testosterone enters the body, through the negative feedback effect of the hypothalamic-pituitary-testicular axis, testosterone secretion decreases, and a large amount of estrogen can antagonize testosterone. This can also inhibit the function of the testicles, thereby slowing down or stopping causing the occurrence of sperm. Glode *et al.* (47) reported for the first time the protective effects of exogenous testosterone and estrogen on rat testicular spermatogenesis during chemotherapy, but this method can only protect undifferentiated spermatogonia; differentiated spermatogonia and spermatocytes cannot be protected. One study has also shown that gonadotropin-releasing hormone

analogues or stimulants can also reduce the secretion of FSH and LH through the negative feedback effect of the hypothalamic-pituitary-testicular axis and reduce intratesticular testosterone in the testes, thereby protecting the spermatogenic function of the testicles (48).

Antioxidant levocarnitine

Levocarnitine is an endogenous mitochondrial membrane compound that plays an important role in promoting the transport of long-chain fatty acids into the β-oxidation pathway into mitochondria. One study has shown that levocarnitine reduces oxidative stress and prevents fatty acid stress and apoptosis induction by inhibiting mitochondrial swelling and reducing the release of cytochrome c (49). In human experiments, research has been found that levocarnitine can counteract apoptosis by enhancing its antioxidant effects, thereby improving sperm production and vitality (50). Recent studies have shown that the addition of levocarnitine to sperm cultivation can improve sperm motility. The addition of levocarnitine to semen samples used in low-temperature preservation and assisted reproduction has also been found to improve the quality of semen (51,52). Zhu *et al.* (53) used cyclophosphamide to induce rats and compared the sperm survival rate, sperm motility, and testosterone levels between the cyclophosphamide group and the cyclophosphamide and levocarnitine group, and found that levocarnitine helps to inhibit cell apoptosis and autophagy and can protect from testicular damage induced by cyclophosphamide.

Low-temperature storage of testicular tissue

Low-temperature storage of immature testicular tissue is a technology that is still in the experimental stage. It mainly treats diploid spermatogonial stem cells in the form of tissues or single cells with drugs and then uses low-temperature technology to temporarily enter the quiescent phase. In the future, when appropriate, diploid spermatogonial stem cells will mature *in vitro* and transplanted (54). Sato *et al.* (55) found that the newborn mouse testicular tissue can obtain sperm after being cultured *in vitro* and the mouse testicular tissue still have the complete spermatogenic capacity after freezing and thawing. Baert *et al.* (56) detected the markers of pericyte-like myocytes, interstitial cells, and Sertoli cells in the frozen testicular tissue and fresh tissue and found that there was no significant difference between the two. Xenotransplantation of low-temperature preserved testicular tissue demonstrates the feasibility of maturation and proliferation of spermatogonia in vitro. Immature testicular tissue can still retain its function after low-temperature preservation. The low-temperature preservation of testicular tissue preserves the contact between germ cells and cells and maintains the niche of stem cells necessary for their survival. Frozen and thawed testicular tissue blocks can be used for testicular xenotransplantation and autologous transplantation.

Prospective

As the survival time of children with tumors continues to extend, doctors are not only concerned about treatment for children but also about achieving a disease-free state after treatment. Increasing attention has been paid to curing patients, improving the quality of life, and achieving an optimal state of life after cancer treatment, which also makes doctors pay more attention to the long-term adverse reactions after cancer treatment. Due to the increased effectiveness of novel tumor treatment methods, such as radiotherapy and chemotherapy, the survival rate of tumor patients has steadily increased (57). However, these treatments can impair the patient's reproductive ability and may lead to premature ovarian failure in women and azoospermia in men. Therefore, in clinical cancer treatment, it is recommended that reproductive physicians and oncologists jointly decide on the treatment plan based on the age of the patient, the type and characteristics of cancer, the cytotoxic treatment plan.

Although there are different options for reproductive protection, some technologies are still in the experimental stage, so there are still many difficulties in the current implementation, and further research is needed. In the treatment of childhood cancer, the assistance of reproductive technology can effectively reduce the occurrence of complications from treatment. However, it is still necessary to further consider the effective combination of cancer treatment and reproductive technology to provide successful strategies for the clinical treatment of childhood cancer.

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-681/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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