

# Klinefelter Syndrome and Cancer

Recommendations from the society for diagnosis and therapy of  
haematological and oncological diseases

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## 1 Summary

- Men with Klinefelter syndrome do not have an increased overall risk of acquiring malignant neoplasias.
- However, they have an increased incidence of breast cancer and extragonadal germ-cell tumors mostly localized in the mediastinum. Breast cancer occurs rather late in life, whereas germ-cell tumors appear mostly before the patient reaches the age of 30 years.
- The data on the increased incidence and/or mortality of hematological neoplasias and lung cancer are not unequivocal.
- The risk of prostate cancer is reduced.

## 2 Introduction

The Klinefelter syndrome was first described in 1942 [1]. It affects approximately 1 / 600 men and thus belongs to the most frequently occurring genetic syndromes. Its cause is at least one extra X chromosome [2, 3]. The common clinical symptom consists in a distinctly reduced volume of the testes, which occurs in association with azoospermia. The manifestation of other symptoms is variable. Testosterone levels are either low or in the low normal range, whereas gonadotropin levels (LH, FSH) are increased.

Numerous publications reported about a correlation between Klinefelter syndrome and malignant diseases, which caused anxiety among the people affected. This article summarizes the current knowledge about cancer risk, the symptoms, and the therapy of malignant diseases in cases of Klinefelter syndrome.

## 3 General Cancer Risk

There are numerous case reports dealing with the cancer risk of men with Klinefelter syndrome, but there are only few epidemiological studies [4- 8]. None of the studies revealed an increased overall risk for cancer diseases in men with Klinefelter syndrome. However, there is an increased incidence of two otherwise seldom occurring malignomas:

- Male breast cancer
- Extragonadal germ-cell tumor

In addition, there are reports about findings concerning the incidences and / or mortalities of the entities below:

- Lymphomas and leukemia
- Lung cancer
- Prostate cancer

As regards mortality, recent evaluations of register data are available from Denmark and Great Britain. The total mortality rate of men with Klinefelter syndrome has been found to be significantly increased (hazard ratio in Denmark = 1.4, HR in Great Britain = 1.5). Cancer-related mortality was slightly (HR 1.2) increased in Great Britain, however, the increase was not statistically significant [9].

## **4 Male Breast Cancer**

### **4.1 Incidence**

Breast cancer is a seldom occurring disease among men [10]. In Germany, the number of newly diagnosed male patients is estimated to be at about 1% of all cases of breast cancer. The age-standardized rate is at about 0.9/100,000 inhabitants. The median age lies between 65 and 70 years.

The association between Klinefelter syndrome and breast cancer is based on both cytogenetic analyses in men who had acquired breast cancer [11] and epidemiological studies. It has been calculated that men with Klinefelter syndrome have a 15- to 20-fold higher risk to acquire breast cancer [7, 12].

### **4.2 Clinical Presentation**

All the information given below relates to the whole group of men with breast cancer. Specific studies focused on the course of the disease, diagnostics and therapy of men with Klinefelter syndrome do not exist.

The dominant symptom is the painless formation of a nodule in the chest. It seems that breast cancer will occur more often whenever there has been a preexisting condition of gynecomastia [13]. Prospective studies dealing with this subject are not available. Gynecomastia belongs to the clinical symptoms in up to 40 percent of all men with Klinefelter syndrome [14].

Other local symptoms consist of skin alterations above the tumor and alterations of the mamilla, including retraction, ulceration, or secretion. General symptoms are absent in the early stages of the disease. Weight loss and reduced stamina might occur in advanced stages. One symptom of advanced disease, for example, consists in the swelling of an arm as a result of lymphatic edema due to lymph-node metastases of the axilla [15].

### **4.3 Prevention and Early Diagnosis**

An early breast cancer detection program applicable to men does not exist. Any persisting gynecomastia among men with Klinefelter syndrome should lead to further diagnostics, see Chapter 3.4..

### **4.4 Diagnosis**

The diagnostic and therapeutic recommendations are based on the guidelines for diagnostics and therapy in breast cancer [15- 17]. Most concepts were developed for women. The differences to males concern diagnostics, the extent of surgery, and endocrine therapy [15].

The first step consists in corroborating the clinical and/or image-based tentative diagnosis. Standard procedure of diagnostics is mammography, followed by a targeted biopsy (puncture biopsy, vacuum biopsy, or open biopsy), sonography of both mammary glands and the axillae, as well as bilateral magnetic resonance imaging.

## 4.5 Therapy

As to operations, the radical surgical removal of the tumor is invariably recommended to men, along with an analysis of the lymph-node status using to the sentinel node method.

The indications for an adjuvant radiation of the chest wall and the regional lymph nodes are based on on the same criteria that are applicable to mastectomized women. The recommended doses are also the same.

Ninety percent of the male breast carcinomas express estrogen receptors. Tamoxifen has gained acceptance as endocrine standard therapy, although there is no prospective randomized study comparing it with placebo or alternative hormonal ablation strategies (orchiectomy, LHRH analogues) [15].

The only prospective study on adjuvant chemotherapy had still been conducted with CMF and revealed a five-year survival rate of 80 %, significantly better than the historical control group [15]. In a retrospective analysis using anthracyclines the five-year survival rate was at 86%. As concluded by analogy, the same criteria that apply to breast cancer in women are applied for an indication of adjuvant chemotherapy.

## 4.6 Prognosis

The age- and stage-adapted prognosis of men with breast cancer is similar to that of afflicted women [15]. Upon comparing the overall survival rates, it must also be taken into consideration that the median age of males with breast cancer is higher than in women.

# 5 Extragonadal Germ-Cell Tumor

## 5.1 Incidence

Germ-cell tumors belong to the rather rare types of cancer. In Germany, 4,500 – 5,000 new cases are diagnosed each year. The rate of new diseases amounts to 12 / 100,000 males [2]. The great majority of germ-cell tumors develop in the testes. Extragonadal manifestations only account for approx. 2-5% of all male germ-cell tumors.

Altogether, the incidence of germ-cell tumors in men with Klinefelter syndrome is not increased. However, the incidence of mediastinal tumors is increased [8]. By now over 80 case reports of extragonadal germ-cell tumors in men with Klinefelter syndrome have been published worldwide. About 75 % are located in the anterior mediastinum, supporting the mediastinal germ-cell tumor as an unusual but distinct disease entity in men with Klinefelter Syndrome [18, 19]. The age lies between 4 and 30 years.

## 5.2 Presentation

Pubertas praecox is characteristic among boys [18, 19]. Other symptoms originate from the preferential localization in the anterior mediastinum: coughing, respiratory distress, and chest pain. Other seldom occurring extragonadal manifestations are located retroperitoneal and intracerebral.

## 5.3 Diagnosis

Recommendations are based on the guidelines for diagnostics and therapy in germ-cell tumors [20, 21]. Initial diagnostics is based on imaging procedures. If an extragonadal germ-cell tumor is suspected a primary testicular carcinoma will have to be excluded.  $\alpha$ -fetoprotein and / or  $\beta$ -

HCG will be increased in most patients. A biopsy to secure the diagnosis will be necessary if tumor markers are negative. Histology discerns all subgroups of seminomas and non-seminomatous germ-cell tumors (chorion carcinoma, yolk-sac tumor, embryonal carcinoma, mature and immature teratoma).

## **5.4 Therapy**

The intensity of therapy in germ-cell tumors is risk-adapted [20, 21]. In this regard extragonadal germ-cell tumors are classified as prognostically unfavorable. Treatment is based on poly-chemotherapy with platinum-containing combinations.

## **5.5 Prognosis**

Patients with extragonadal germ-cell tumors have a high chance of cure by the intensive, multi-modal therapy.

# **6 Hematological Neoplasias**

## **6.1 Leukemias**

There are numerous reports about the occurrence of hematological neoplasias in men with Klinefelter syndrome. Leukemias dominate in the case reports [22]. A review article published in 2002 reported of 31 cases [23]. Ever since, more reports about leukemia patients have been published. Among them are all subtypes and all age groups: acute myeloid leukemia (AML) with various morphologies and various genetic aberrations, acute lymphocytic leukemia (ALL) with various morphologies and various genetic aberrations, chronic myeloid leukemia (CML), myelodysplastic syndromes (MDS) of various risk groups, myeloproliferative syndrome (MPN) and chronic lymphocytic leukemia.

Epidemiological studies failed to calculate an increased leukemia risk for patients with Klinefelter syndrome [4- 8]. A possible explanation for this discrepancy may be provided by the special features of modern leukemia diagnostics: a cytogenetic analysis from bone marrow or peripheral blood is standard procedure for these malignant diseases only. Accordingly, the likelihood of the 'incidental' diagnosis of a Klinefelter syndrome is high.

## **6.2 Non-Hodgkin Lymphomas**

There are only isolated case reports on Non-Hodgkin lymphomas. However, the largest epidemiological study on cancer diseases calculated an increased mortality related to Non-Hodgkin lymphomas in cases of Klinefelter syndrome [7]. The incidence of Non-Hodgkin Lymphomas was not increased in this study nor in other studies.

At present, the question whether there is a special risk for men with Klinefelter syndrome to acquire Non-Hodgkin lymphomas remains unanswered. It is urgently recommended to treat patients in the scope of multicenter studies. The standardized protocols enable high cure rates among patients with aggressive lymphomas and long, progression-free survival periods in patients with indolent lymphomas.



## 7 Lung Cancer

### 7.1 Incidence

Two epidemiological studies revealed that the risk of contracting lung cancer was increased 1.5 to 1.7 fold in men with Klinefelter syndrome [6, 7]. In particular, the percentage of patients with small-cell lung cancer was relatively high [7].

The reason for the increased risk is not known. Particularly in case of lung cancer external risk factors are of great relevance. Studies attempting to distinguish exogenous noxae from genetic predisposition do not exist yet.

### 7.2 Prevention and Early Diagnosis

An early detection program for lung cancer does not exist. Considering the potentially higher risk among men with Klinefelter syndrome the general guidelines for the prevention of lung cancer are especially important [24]:

- No smoking
- Avoidance of passive smoking
- Avoidance of occupational exposure
- Avoidance of radiation exposure
- Physical activity
- A diet which is rich in fruits and fresh vegetables

Drug-based primary or secondary prevention is not recommended outside of clinical trials.

### 7.3 Diagnosis and Therapy

Recommendations are based on the guidelines for diagnostics and therapy in lung cancer [24].

## 8 Prostate Cancer

### 8.1 Incidence

The largest epidemiological study on the cancer risk of men with Klinefelter syndrome revealed that the incidence of prostate cancer and prostate cancer specific mortality were significantly lower than in the control group [7].

A more recent concern arises from the practice that some men with Klinefelter syndrome are nowadays treated with long-term testosterone substitutions. Clinical studies hitherto conducted with a focus on testosterone substitution therapy in men with hypogonadism did not indicate an increased malignization rate of prostate tissue [26]. Observations made with respect to prostate carcinomas in men of Klinefelter syndrome are limited to single case reports [27].

### 8.2 Prevention and Early Diagnosis

Recommendations are based on the guidelines for diagnostics and therapy in prostate cancer [27]. They also include recommendations as to how to proceed in case of hypogonadal men [28]. There are no distinct studies on men with Klinefelter syndrome.

Testosterone can be substituted in hypogonadal patients not displaying any clinically evident prostate carcinoma. Prior to testosterone substitution a digitorectal examination, a determination of the PSA value, and an optional transrectal sonography of the prostate should be carried out.

Follow-up examinations should take place semiannually in the first year under testosterone substitution, thereafter in annual intervals. They should include digitorectal examination, laboratory analysis of the PSA, testosterone, and differential blood cell counts [28, 29].

## 9 Impact of Other Chromosomal Aberrations on Cancer Risk

The characteristic chromosome constellation 47,XXY is found in 80% of men with Klinefelter syndrome. In addition, further numeric deviations of sex chromosomes have been described (e.g. 48,XXYY, 48,XXXXY, 49,XXXXY), also occurring in combination with structural alterations. All these karyotypic constellations may also appear in various mosaics. Results showing 4 or 5 sex chromosomes occur predominantly in mosaics [29]. The severity of the disease increases with the number of X-chromosomes. In men with an additional isochromosome X(q) the phenotype occasionally deviates distinctly from the classical Klinefelter syndrome [30]. An association between the mosaic 47,XXY / 46,XY and male breast cancer and between karyotype 48,XXYY and Non-Hodgkin lymphomas [4] have been observed in single studies. Confirmatory studies are pending.

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according to the rules of the German Association of Hematology and Medical Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.

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