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Adolescents and Young Adults (AYA)

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

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Adolescents and Young Adults (AYA)

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Compliance rules:

- Guideline
- Conflict of interests

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1 Definition and Basic Information

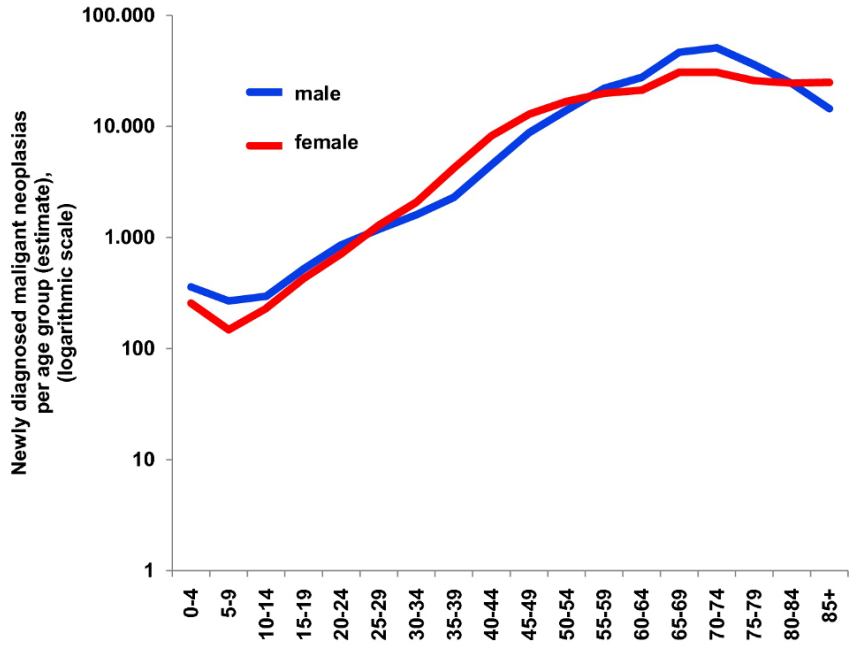
Attending to adolescents and young adults (AYA) with cancer poses a special challenge to the competence of physicians and the entire medical team [15]. The medical and psychosocial requirements of this age group differ essentially from those of children on the one hand, and from those of elderly people on the other. The prognosis of adolescents and young adults who suffer from cancer is better than average, more than 80 percent are cured in the long term. Apart from new therapeutic strategies, an optimization of healthcare provisions is needed in order to achieve a further increase of the number of patients sustainably cured [8, 36, 37].

The age definition as published in medical journals is rather inconsistent. A span from 15 to 18 years is considered as the lower boundary, whereas the upper age boundary ranges from 28 to 39 years. The group of adolescents and young adults is in itself very heterogeneous. The characteristics they share are a high chance of being cured from the disease, the necessity of having to deal with cancer in an age-dependent, complex psychosocial situation, and the fear of late biological effects and contracting secondary diseases.

2 Epidemiology

Cancer is a disease that generally affects elderly people. Malignant diseases occur only relatively seldom in adolescents and young adults. In Germany, approximately 4,500 patients aged between 15 and 39 years are newly diagnosed each year, with a total of 450,000 new diseases registered altogether [13]. Men are somewhat more often affected in this age group, whereas women are more affected in the age interval of 30 to 40 years, see Figure 1.

Figure 1: Total of New Diseases Depending on Age (estimated by GEKID, logarithmic scale)



Epidemiological data reveal that the distribution of diagnoses of all age cohorts is gradually changing [13, 16], see Table 1 and 2. The malignant melanoma is the relatively most frequent cancer disease in women between 20 and 30 years. In the next decade the mammary carcinoma is already on first place, the cervical carcinoma on third. Testicular carcinomas account for almost one half of all malignant diseases in men aged between 20 and 35 years.

Table 1: Relative Incidence Rate of New Diseases Among Females in Germany, 2009 [GEKID]

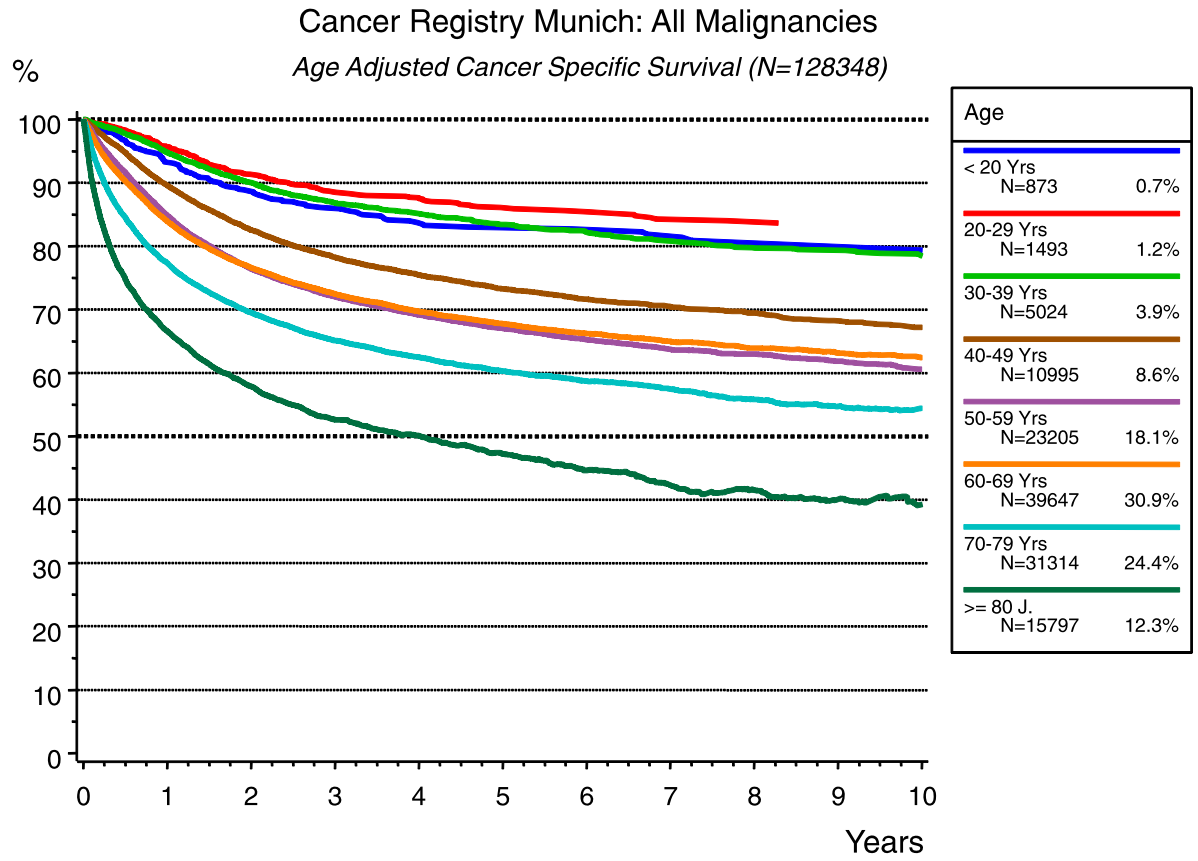
15 – 19 Years		20 – 24 Years		25 – 29 Years		30 – 34 Years		35 – 39 Years	
Diagnosis	**%**	**Diagnosis**	**%**	**Diagnosis**	**%**	**Diagnosis**	**%**	**Diagnosis**	**%**
Hodgkin's Lymphoma	23	Melanoma	22	Melanoma	23	Breast Cancer	30	Breast Cancer	40
Leukemia	15	Thyroid Cancer	17	Breast Cancer	18	Melanoma	15	Melanoma	13
Thyroid Cancer	11	Hodgkin's Lymphoma	13	Thyroid Cancer	12	Cervical Cancer	13	Cervical Cancer	11
Melanoma	10	Non-Hodgkin Lymphoma	7	Cervical Cancer	11	Thyroid Cancer	12	Thyroid Cancer	9
CNS	8	Leukemia	6	Hodgkin's Lymphom	7	Colorectal Cancer	3	Colorectal Cancer	4
Others	33	Others	36	Others	30	Others	26	Others	25

Table 2: Relative Incidence Rate of New Diseases Among Males in Germany, 2009 [GEKID]

15 - 19 Years		20 - 24 Years		25 - 29 Years		30 - 34 Years		35 - 39 Years	
Diagnosis	**%**	**Diagnosis**	**%**	**Diagnosis**	**%**	**Diagnosis**	**%**	**Diagnosis**	**%**
Germ-Cell Tumor	20	Germ-Cell Tumor	40	Germ-Cell Tumor	43	Germ-Cell Tumor	37	Germ-Cell Tumor	28
Leukemia	14	Hodgkin's Lymphoma	11	Melanoma	11	Melanoma	10	Melanoma	12
Hodgkin's Lymphoma	12	Non-Hodgkin Lymphoma	10	Hodgkin's Lymphoma	8	CNS	7	Colorectal Cancer	9
CNS	9	Melanoma	9	CNS	6	Non-Hodgkin Lymphoma	6	Renal Cancer	5
Non-Hodgkin Lymphoma	7	Leukemia	7	Non-Hodgkin Lymphoma	6	Thyroid Cancer	5	CNS	5
Others	38	Others	24	Others	27	Others	34	Others	42

The data of the Tumor Register in Munich reveals a prognosis which is better than average for young patients, see Figure 2.

Figure 2: Relative Survival Rate according to Age (Data of the Tumor Register, Munich)



Legend:
(D. Hölzel and J. Engel, 2011)

3 Primary Prevention and Early Recognition

3.1 Primary Prevention

The recommendations on primary prevention are related to previously identified, acquired risk factors:

- No smoking
- Avoidance of obesity
- Balanced diet rich in vegetables, fruits, and fiber
- Avoidance of high UV skin exposure
- HPV vaccine in case of female adolescents and young women before first sexual intercourse; the HPV vaccine is also effective in males to prevent HPV infection and reduce the precursors of malignant diseases [14]. Formal evidence for an influence on the incidence of malignomas is pending.

3.2 Early Detection (Screening)

There is no reasonable early detection program which is applicable to adolescents and young adults who do not have a familial predisposition. Instructions how to conduct self-examinations of the skin, breast, and the testes are being advocated, however, they are not part of the quality-controlled health programs and perhaps are even the cause of negative impacts (high percentage of false-positive results, excitation of anxiety and stress). Genetic counseling is recommended to members of families with hereditary disposition. Screening should commence at the latest ten years earlier than the age at which the affected relative had been initially diagnosed.

An individualized plan for early-detection measures is recommended in adolescents and young adults with acquired predisposition, e.g. chronic inflammatory bowel disease.

4 Patient Information

The topics of patient informations for adolescents and young adults are summarized in Table 3 in the form of a checklist.

Table 3: Subjects of Patient Informations for Adolescents and Young Adults

Subjects	Checklist
Type and stage of the malignant disease	
Therapy	-----
Standard	
Alternatives	
Clinical Trials	
Treatment Recommendation	
Prognosis	
Side effects	-----
Acute side effects	
Medium- and long-term side effects	
Fertility	
Strategies to prevent side effects	
Psycho-oncologic support	
Social support	
Information material, additional information sources	
Naming of contact persons	

5 Therapy Concepts

The therapy of adolescents and young adults does not differ in principle from that applied to elderly patients. It depends on the histological and cytological diagnosis, the stage of the disease, the cell biological risk factors, and existing comorbidity. The distribution of biological subtypes might differ from that of elderly patients [1, 18, 29]. Information about the current recommendations are listed in Table 4 and 5 with respect to the more frequently occurring diseases.

Table 4: Guidelines to Malignant Neoplasias in Adults

Tumor Entity	Association / Organization	Sources
ALL - Acute Lymphoblastic Leukemia	DGHO Leukemia Competence Network	onkopedia ALL
AML - Acute Myeloid Leukemia	DGHO Leukemia Competence Network	onkopedia AML
Germ-Cell Tumor	European Consensus Conference	Keimzelltumor
Hodgkin's Lymphoma	DGHO Malignant Lymphoma Network	onkopedia HD
Breast Cancer	AWMF S3 Guideline DGHO	Mamma 032-045OL onkopedia
Melanoma	AWMF S2 Guideline	MaM 032-024OL
Non-Hodgkin Lymphoma, aggressive	Malignant Lymphoma Competence Network	NHL
Soft-Tissue Sarcoma	DGHO	onkopedia
Cervical Cancer	AWMF S2 Guideline	Zervix 032-033

Table 5: Guidelines to Malignant Neoplasias in Children and Adolescents

Tumor Entity	Association / Organization	Sources
ALL - Acute Lymphoblastic Leukemia	AWMF S1 Guideline GPOH	ALL AWMF 025-014 ALL GPOH
AML - Acute Myeloid Leukemia	AWMF S1 Guideline GPOH	AML AWMF 025-014 AML GPOH
Ewing – Sarcoma and PNET	AWMF S1 Guideline GPOH	Ewing AWMF 025-006 Ewing GPOH
CNS malignancies	AWMF S1 Guideline GPOH	ZNS AWMF 025-022 ZNS GPOH
Hodgkin's Lymphoma	AWMF S1 Guideline GPOH	HDp AWMF 025-012 HD GPOH
Osteosarcoma	AWMF S1 Guideline GPOH	OS AWMF 025-005 OS GPOH
Non-Hodgkin Lymphoma	AWMF S1 Guideline GPOH	NHLp AWMF 025-013 NHL GPOH
Soft Tissue Sarcomas	AWMF S1 Guideline GPOH	WTSp AWMF 025-007 WTS GPOH

Therapy protocols for some malignant diseases may be different in pediatric and medical oncology. This applies to the Hodgkin's lymphomas, the acute leukemias, the aggressive non-Hodgkin lymphomas, sarcomas, and certain brain tumors. Therapy concepts rely on identical modalities (surgery, radiation, chemotherapy, targeted therapy, etc.), however, they differ in dosages, the length of therapy and the therapy intervals, or in the indication for stem-cell transplantation.

In contrast to the international literature, it makes no prognostic difference in German-speaking countries whether adolescents are treated according to the protocols of pediatric or medical oncology, see AYA Knowledge Database, ALL Knowledge Database or Hodgkin Lymphoma Knowledge Database.

Current pediatric or adult therapy optimization studies define an age limit at 18 years. The available knowledge predominantly relates to cohorts with this age limit. Adolescents and young adults should be treated in the scope of clinical trials (therapy optimization studies) of either medical and/or pediatric hematology and oncology, see Tables 4 and 5.

6 Psychosocial Situation

The diagnosis of cancer belongs to the most intensive experiences of life anyone involved can make. As to adolescents and young adults, it comes at a time in which thoughts of one's own disease and death are remote. Other topics are of importance, depending on the stage of personality development: independence, being accepted by friends and partners, sexual orientation and experience, mobility, use of alcohol and drugs, detachment from parental care, job qualification, employment, and professional career, founding a family of one's own, etc. [25, 27].

When confronted with an existentially threatening disease, the processes of detachment, identity finding, and orientation is about to stagnate. Heteronomy and dependence increase again both objectively and subjectively. Compared with older patients, adolescents and young adults have greater psychosocial deficits [2, 3, 24] and are additionally encumbered to a greater extent by financial problems. On the other hand, they are less prone to deny the diagnosis of cancer [35].

High-quality therapy of adolescents and young adults includes an early and long-term offer for psycho-oncological guidance and professional support teaching how to cope with the social, occupational, and financial problems.

7 Therapy Adherence

Therapy adherence is a special subject that has to be dealt with when treating adolescents and young adults [10, 28]. A labile mental situation and stressful social factors can impair therapy adherence and worsen the prognosis [10]. This includes a greater readiness to assume a risk with delayed response to critical side effects and a more generous interpretation of predetermined therapy intervals [28].

Strategies to support therapy adherence are

- Precise information
- Learning how to access additional information sources [19]
- Mediation of contacts with others likewise afflicted and of similar age
- The same level of language
- Shared decision-making starting with the first contact between physician and patient
- Establishment of mutual trust
- Clear assignment of contact persons
- Active, responsible role of the patient
- Promotion of the patient's development according to his/her age

Not conducive are overly proactive, overly controlling behavior and a schematic treatment as "children" or "immature adults" [25].

8 Long-Term Effects of Therapy and Secondary Diseases

The first objective is cure, the second objective consists of avoiding side effects, including long-term complications, as much as possible. The cancer therapy of young patients does not differ from that of elderly patients in this regard. Particularly stressful to adolescents and young adults are disruptions of physical integrity, the impairment of fertility, and the risk of secondary neoplasias [29].

8.1 Fertility

Frequently occurring adverse effects of systemic cancer therapy are impairment of ovarian function up to premature ovarian failure in women, and azoospermia in men. Radiation therapy applied to small pelvis in women, the testes in men, and the skull also impair fertility. Risk factors for permanent infertility are [5, 23]:

- Age at the time of therapy
- Type of therapy: radiation, chemotherapy
- Intensity of therapy and cumulative dose

Information about the infertility risk must be a part of the patient information for adolescents and young adults.

8.1.1 Females

Due to the administered medication, and/or in connection with an exposure of the pelvis to radiation, an acute failure of ovarian function (acute ovarian failure), or a premature onset of menopause (premature ovarian failure), might occur subsequent to an interval of apparently undisturbed ovarian function, either immediately under therapy or shortly thereafter [12]. The previous menstruation history is an unreliable parameter. Most promising is the analysis of the anti-Müllerian hormone (AMH) in the serum which is applied in order to determine the ovarian follicle pool [31]. However, based on the AMH value or other serum hormone values alone, it is not possible to draw unequivocal conclusions with respect to fertility.

Various fertility-preserving methods are available by now [32, 33]. The choice of the appropriate method depends on

- the type of oncological therapy applied
- the time between diagnosis and start of oncological therapy
- the likelihood of ovarian metastases
- the partner status
- age
- the patient's preferences
- costs.

A network for fertility-preserving measures under chemotherapy and radiation therapy has been established in Germany, Austria, and Switzerland since 2006 [20]. Female patients who desire to have children should be referred to a fertility center that has experience in this field before oncological therapy is initiated.

8.1.1.1 Ovariopexy

The follicles are highly sensitive to radiation. If radiation of the small pelvis including the ovaries is planned, the function of the latter may be protected by means of their surgical craniolateral displacement, i.e. removal out of the field of radiation exposure. If possible, ovariopexy should be conducted by a minimally invasive technique such as laparoscopy or in the scope of open tumor surgery. Due to scattered radiation a combination of this measure with the removal of ovarian tissue for the purpose of cryopreservation may be considered.

In case of a combined radiochemotherapy an additional risk of damage caused by the planned cytostatic agents must be taken into account when making decisions.

8.1.1.2 Cryopreservation of Oocytes

Oocytes are removed by means of vaginal follicle puncture subsequent to hormonal stimulation. In female patients who are living in committed relationship there is the option of an intracytoplasmic sperm injection (ICSI) coupled with cryopreservation of fertilized oocytes. However, the fertilized oocytes can only be implanted with the consent of both partners. An alternative consists in the cryopreservation of unfertilized oocytes. The pregnancy rates are lower than with cryopreserved fertilized oocytes. The time needed for hormonal stimulation amounts to approx. 14 days; the stimulation may be initiated by means of new stimulation protocols which are independent of the cycle [21, 34]. The occurrence of an ovarian hyperstimulation syndrome (= OHSS), which might delay the start of systemic therapy is a rare event.

8.1.1.3 Cryopreservation of Ovarian Tissue

Cryopreservation of ovarian tissue previously removed by laparoscopy represents a new experimental approach. Due to the age-dependent decrease of follicle density in the ovaries this fertility-preserving technique is recommended to women up to an age of 35 years only. The measure is independent of a current firm partnership and would also improve the endocrinological situation of the patient in case of a later successful implantation. Cryopreservation of ovarian tissue requires up to two days. As yet, only few data pertaining to a successful retransplantation of the tissue are available. Reports of nine pregnancies have been published worldwide so far.

8.1.1.4 GnRH Analogues

The rationale for the application of GnRH analogues to delay or prevent premature ovarian failure is based on trials conducted with laboratory animals. Most studies with humans are retrospective. They agree in that no protective effect could be observed when radiation therapy was applied. Prospective studies with female chemotherapy patients were conducted with small case numbers and/or a short follow-up periods and thus produced inconsistent data [4, 6, 7, 9, 17, 30]. Side effects of the GnRH analogues might consist of climacteric complications, and in case of a treatment over six months consisted in the reduction of bone mass.

The application of GnRH analogues to protect ovarian function under chemotherapy is not recommended as standard therapy. GnRH analogues do not protect against the effects of radiation therapy.

8.1.2 Males

Transient infertility is a common side effect of oncological therapy in males. It might persist up to two years after termination of therapy, depending on the type of therapy applied, it also may irreversible. Analytic parameters in the ejaculate are sperm concentration, motility, and morphology.

8.1.2.1 Cryopreservation of Sperm

Cryopreservation of sperm obtained by masturbation is a safe and established method [22, 23]. It is applied prior to the onset of chemotherapy or radiation therapy. An optimum yield is obtained subsequent to a sexual abstinence period of at least 48 hours. After cryopreservation of the sperm cells, successful fertilizations are possible over more than 10 years later.

If neither masturbation nor ejaculation are possible, there still remains the option of obtaining sperm cells by means of a testicular biopsy.

8.2 Secondary Neoplasms

Patients who receive the initial cancer diagnosis at an age between 18 and 39 years have a 2–3-fold increased risk for acquiring a secondary neoplasm [11]. The pattern of secondary neoplasms depends particularly on the nature of the primary disease. A dominant cause are common predisposing factors, e.g. genetic or toxic. The relatively highest risk for patients with breast cancer or testicular germ-cell tumors consists in a contralateral secondary neoplasm.

Elements of oncological therapy, like radiation or certain substances applied in chemotherapy have a mutagenic potential. The highest risk exists in case of a combined or sequential radiochemotherapy and/or high-dose therapies. Distinct secondary neoplasms are breast cancer in female patients with a status post mediastinal radiation prior to their thirtieth year of life [11] or thyroid carcinomas with status post cervical radiation prior to the patient's twentieth year of life [11]. The absolute number of iatrogenic secondary neoplasms is low [11].

Increased risks for certain secondary neoplasms are set against significantly lowered risks for other neoplasms [11]. It has not yet been clarified whether this is explained with factors of predisposition or the result of a healthier life style subsequent to the initial diagnosis.

Generally valid concepts in the sense of follow-up = prophylaxis do not exist for adolescents and young adults yet. Currently, individual prevention and early detection concepts are recommended based on the respective initial diagnoses.

8.3 Other Late Biological Effects

Particularly drug therapy and radiation, but also surgery, are capable of causing impairments to endocrine (e.g. hypothyroidism), cardiovascular (e.g. cardiomyopathy, coronary heart disease), pulmonary (e.g. lung fibrosis) and other somatic function in the long term. These adverse effects are not limited to adolescents and young adults, but may pose a lifelong burden. As controlled studies are lacking, medical counseling, diagnostics and therapy must proceed individually.

9 Rehabilitation

Oncological therapy can result in secondary disorders exhibiting various degrees of severity. The most essential objectives of rehabilitation measures consist of overcoming physical impair-

ments, supporting the patient's mental coping with the disease, his reintegration into social life and occupational reintegration [26].

Patients should be informed at an early stage about existing options of ambulatory and hospital rehabilitation measures as well as legal claims which ensue from social legislation. As far as the choice of the rehabilitation hospital is concerned, the preferences of the patients should also be taken into consideration (Art. 9 of German Social Security Code IX). The rehabilitation of adolescents and young adults is recommended to proceed at facilities which are specialized in observing the needs of this particular patient group.

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11 Links

Network supporting fertility-protective measures

http://www.fertiprotekt.de/index.php?lang=uk

Rehabilitation Centers with specialty in the treatment of adolescents and young adults

Rehabilitation Clinic Katharinenhöhe
Oberer Katzensteig 11
D-78141 Schönwald/Black Forest
Phone: +49 / 7723 / 6503-0
www.katharinenhoehe.de

Klinik Bad Oexen
Oexen 27
D-32549 Bad Oeynhausen
Phone: +49 / 5731 / 537-0
www.jer-reha.de

Luise von Marillac Clinic
Elly-Heuss-Knapp.Weg 7
73337 Bad Überkingen

Phone: +49 / 7331 / 4422-0
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13 Disclosure

according to the rules of the German Association of Hematology and 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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