International
Melanoma Conference

From Prevention to Treatment

November 7 - 8, 2008
Ljubljana, Slovenia

Organisers

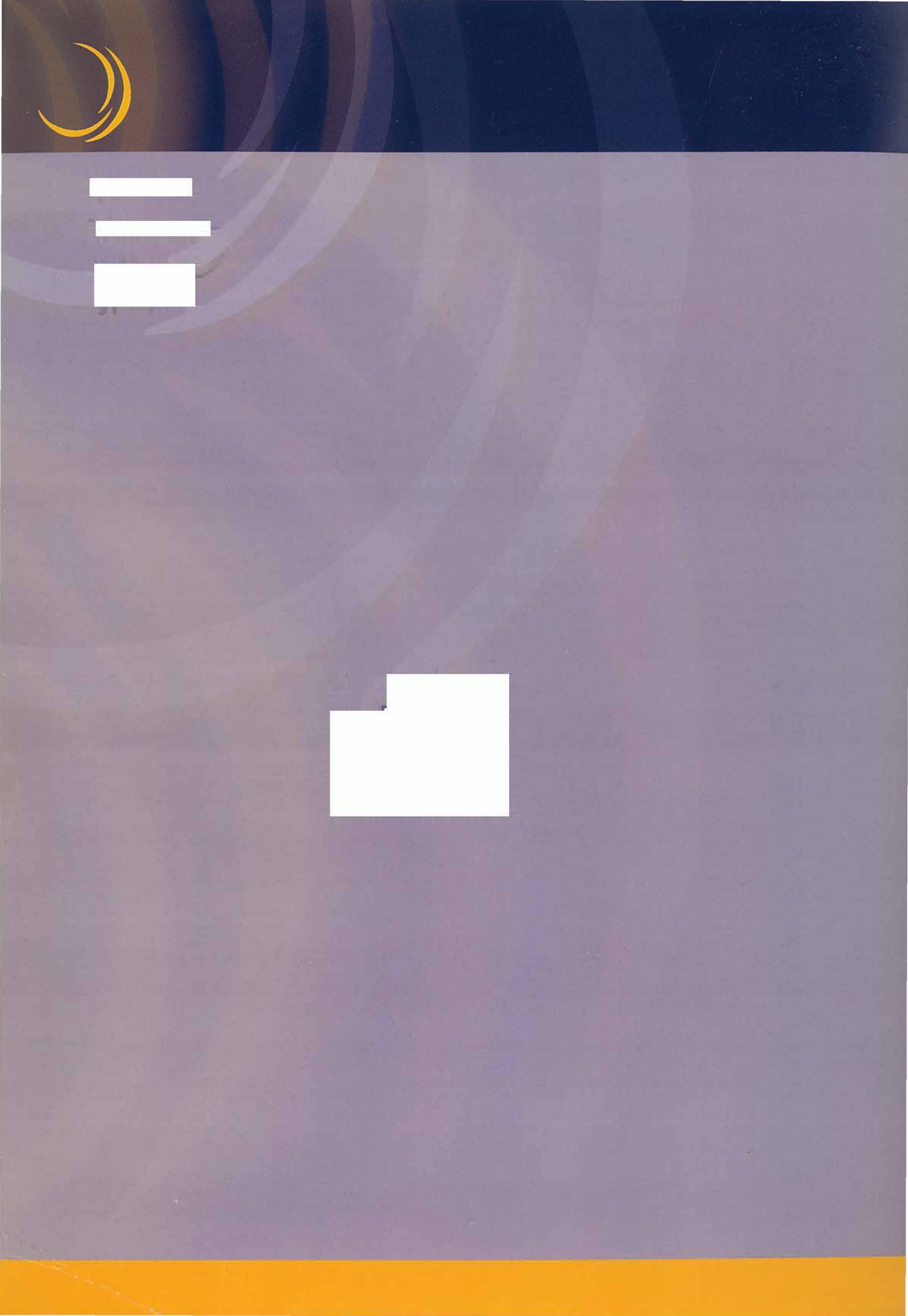
Onkološki Inštitut Ljubljana
Institute of Oncology Ljubljana

Endorsed by

ESSO

Sponsor

Schering-Plough



International Melanoma Conference

From Prevention to Treatment

Melanoma is a skin cancer with its incidence dramatically on the rise. Physicians are therefore more frequently than ever challenged with the disease, not merely with its diagnosis, but also with the follow-up, as the survival of melanoma patients has fairly improved recently. At the present time, at which the spread of information is incredibly rapid, the patients and their relatives have access to various data about the disease, of which some may be founded on a firm scientific basis while, on the other hand, they are also overwhelmed with ill sources of information without any scientific value. In case of so serious disease as melanoma, the patients' naivety and their longing for health may thus be open to manipulations.

Therefore, the aim of the International Melanoma Conference is to provide comprehensive and scientifically verified information on the development, detection and treatment of melanoma to the medical doctors of different specialties who often come across this cancer in the patients that they treat in their every day practice. A special emphasis will be laid to the prevention and early detection of melanoma given that the results of Australian research studies confirm that this approach to treatment considerably increases the survival and reduces the incidence of melanoma. The participants will also be informed of the basic treatment modalities of melanoma, i.e. surgery, irradiation and systemic treatment. The presentation of surgical treatment will focus particularly on the sentinel node biopsy which has been proved to be effective in prolonging the survival of certain groups of melanoma patients. The latest irradiation techniques have also markedly improved the effectiveness of this treatment method, whereas in the field of systemic treatment of melanoma, the major benefit has been found to be adjuvant treatment with high doses of Interferon alpha.

The topics presented by the lecturers will be further extended at the workshops on surgery, dermatoscopy, radiotherapy and systemic treatment of melanoma and on the management of toxic treatment effects. The participants will thus have the opportunity to learn more about melanoma by taking part in discussions and also to expand their knowledge about the disease by acquiring more facts that could be useful in finding answers to most interesting and sometimes essentially controversial questions.

Janja Ocvirk
President of the Scientific committee

International Melanoma Conference

From Prevention to Treatment

Organising Committee

Janja Ocvirk, MD, PhD
President of the Scientific committee
Institute of Oncology Ljubljana, Division of Medical Oncology

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Institute of Oncology Ljubljana, Division of Surgical Oncology

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Marko Snoj, MD, PhD
Institute of Oncology Ljubljana, Division of Surgical Oncology

Igor Bartenjev, MD, PhD
Outpatient Clinic Dermatologija Bartenjev-Rogl, University of Ljubljana, Faculty of Medicine

Organiser
Institute of Oncology Ljubljana

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Scientific Agenda

DAY 1 - November 7

10.00-12.00 **Workshops**
Location: Institute of Oncology Ljubljana. Transfer to the location Institute of Oncology will be organized free of charge. Departure will be from City hotel at 9:15.

Dermoscopy in early diagnosis of melanoma
Igor Bartenjev (MD, PhD, Outpatient Clinic Dermatologija Bartenjev-Rogl, University of Ljubljana, Faculty of Medicine)
Mirjam Butina Rogl (MD, Outpatient Clinic Dermatologija Bartenjev-Rogl)

Presentation of typical surgical procedures use in melanoma management (Sentinel lymph node biopsy, lymphadenectomy)
Marko Hočevar (MD, PhD, Institute of Oncology Ljubljana)

Management of adverse event of high-dose interferon α2b adjuvant therapy - Patient Management
Janja Ocvirk (MD, PhD, Institute of Oncology Ljubljana)

Radiotherapy indications and techniques in melanoma management
Primož Strojan (MD, PhD, Institute of Oncology Ljubljana)

12.30-14.00 **Lunch**
Location: City Hotel Ljubljana

14.00-14.15 **Welcome and Introduction**
Location: City Hotel Ljubljana

Session I: Chair: Marko Hočevar MD, PhD; **Janja Ocvirk** MD, PhD

14.15-14.45 **Epidemiology of melanoma and primary prevention**
Borut Žgavec (MD, University Medical Centre Ljubljana, Department of Dermatovenereology)

14.45- 15.15 **Etiology and risk factors**
- **Genetics of familial melanoma**
- **Genetic testing and patient counseling in melanoma**
  Marko Hočevar (MD, PhD, Institute of Oncology Ljubljana)

15.15-16.00 **Q&A**

16.00-16.15 **Coffee Break**

Diagnosis

Session II: Chair: Marko Snoj MD, PhD; **Igor Bartenjev** MD, PhD

16.15-16.45 **Clinical presentation and early diagnosis of melanoma**
Igor Bartenjev (MD, PhD, Outpatient Clinic Dermatologija Bartenjev-Rogl, University of Ljubljana, Faculty of Medicine)

16.45-17.15 **Pathology**
Matej Bračko (MD, PhD, Institute of Oncology Ljubljana)

17.15-17.45 **Specifics in functional diagnostic imaging in melanoma**
Maja Marolt Mušič (MD, Institute of Oncology Ljubljana)

17.45-18.15 **Staging and prognosis of melanoma**
Marko Snoj (MD, PhD, Institute of Oncology Ljubljana)

18.15-18.45 **Q&A**

DAY 2 - November 8
Location: City Hotel Ljubljana

Management

Session III: **Chair: Marko Hočevar** MD, PhD; **Janja Ocvirk** MD, PhD

9.00-10.00 **Melanoma surgery**
- **Surgical margins**
- **SLNB**
- **Surgical management of melanoma in difficult sites**
- **Surgery for stage IV disease**
- **Management of recurrent or in-transit disease - Isolated Limb perfusion**
  Alexander M.M. Eggermont (MD, PhD, Erasmus University Medical Center, Rotterdam, The Netherlands)

10.00-12.30 **Interferon in adjuvant therapy for melanoma**
- **Adjuvant treatment with HDI**
  Peter Mohr (MD, Elbeklinikum, Buxtehude, Germany)
- **Long term treatment with PEG-IFN alfa 2b**
  Alexander M.M. Eggermont (MD, PhD, Erasmus University Medical Center, Rotterdam, The Netherlands)

12.30-12.45 **Q&A**

12.45-13.00 **Coffee Break**

Session IV: **Chair: Primož Strojan** MD, PhD; **Janja Ocvirk** MD, PhD

13.00-13.30 **Role of radiotherapy in melanoma management**
Primož Strojan (MD, PhD, Institute of Oncology Ljubljana)

13.30-14.00 **Treatment options for metastatic melanoma**
Janja Ocvirk (MD, PhD, Institute of Oncology Ljubljana)

14.00-14.15 **Practice guidelines in melanoma**
Marko Snoj (MD, PhD, Institute of Oncology Ljubljana)

14.15-14.30 **Q&A**

14.30-15.30 **Lunch**

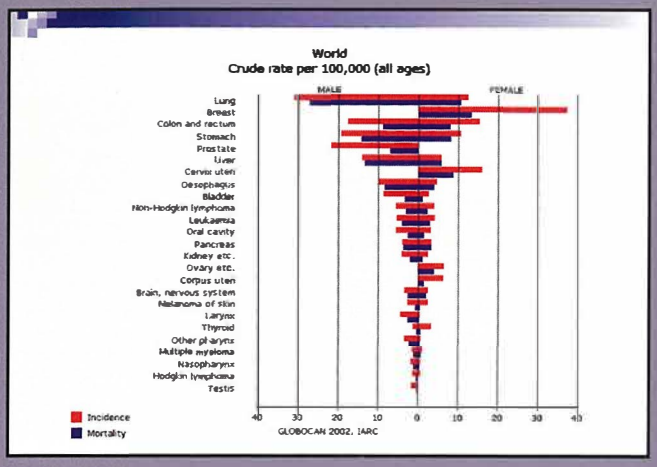
Epidemiology of melanoma and primary prevention

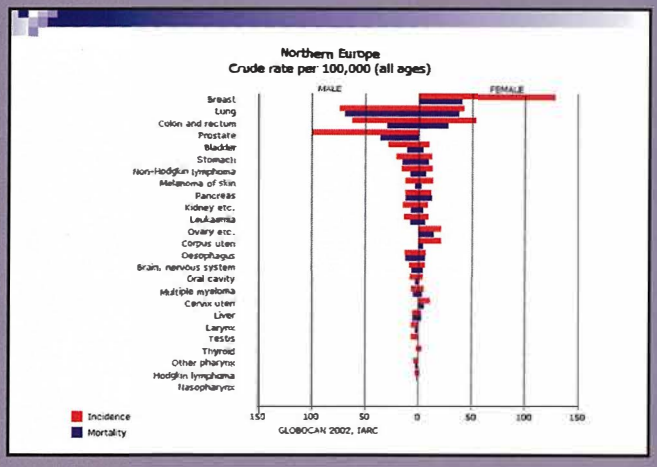
Borut Žgavec
Dept. Of Dermatology
University Clinical Center of Ljubljana

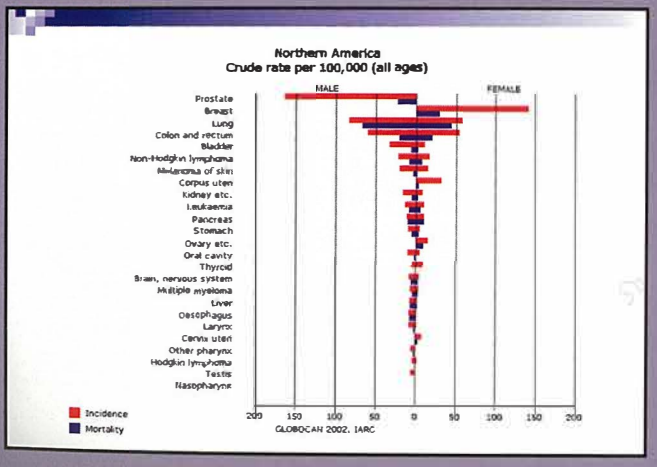
Introduction

- Melanoma is a malignant tumor with the most inclined curve of growing incidence in the last few decades all over the world.

How frequent is melanoma ?


World
Crude rate per 100,000 (all ages)
MALE
FEMALE
Lung
Breast
Colon and rectum
Stomach
Prostate
Liver
Cervix uteri
Oesophagus
Bladder
Non-Hodgkin lymphoma
Leukaemia
Oral cavity
Pancreas
Kidney etc.
Ovary etc.
Corpus uteri
Brain, nervous system
Melanoma of skin
Larynx
Thyroid
Other pharynx
Multiple myeloma
Nasopharynx
Hodgkin lymphoma
Testis
40 30 20 10 0 10 20 30 40
Incidence
Mortality
GLOBOCAN 2002, IARC


Northern Europe
Crude rate per 100,000 (all ages)
MALE
FEMALE
Breast
Lung
Colon and rectum
Prostate
Bladder
Stomach
Non-Hodgkin lymphoma
Melanoma of skin
Pancreas
Kidney etc.
Leukaemia
Ovary etc.
Corpus uteri
Oesophagus
Brain, nervous system
Oral cavity
Multiple myeloma
Cervix uteri
Liver
Larynx
Testis
Thyroid
Other pharynx
Hodgkin lymphoma
Nasopharynx
150 100 50 0 50 100 150
Incidence
Mortality
GLOBOCAN 2002, IARC


Northern America
Crude rate per 100,000 (all ages)
MALE
FEMALE
Prostate
Breast
Lung
Colon and rectum
Bladder
Non-Hodgkin lymphoma
Melanoma of skin
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Kidney etc.
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Pancreas
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Oral cavity
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Brain, nervous system
Multiple myeloma
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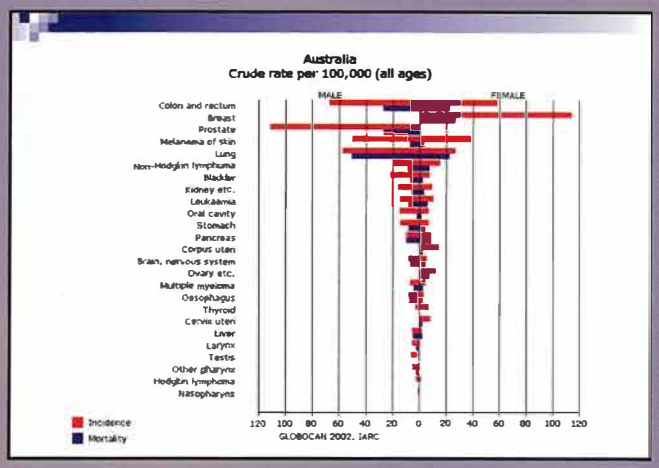
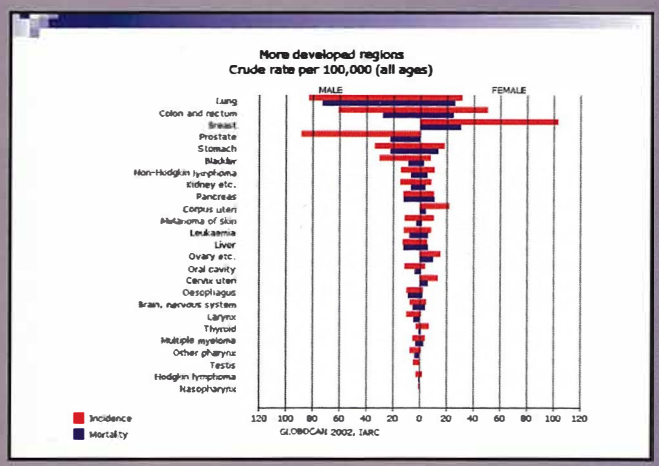
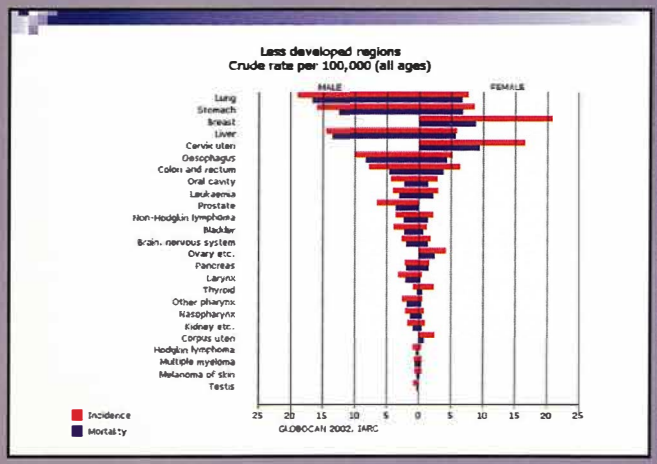
Other pharynx
Hodgkin lymphoma
Testis
Nasopharynx
200 150 100 50 0 50 100 150 200
Incidence
Mortality
GLOBOCAN 2002, IARC

Borut Žgavec

Epidemiology of melanoma and primary prevention





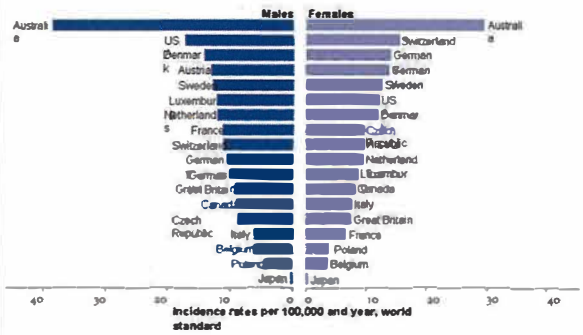


Incidence

- ↑↑↑ Australia / New Zeland
  - M=37,7 F=29,4
- ↑↑ Nord America
  - M=16,4 F=11,7
- ↑ Nord Europe
  - M=8,3 F=10,0
- Asia - the lowest
  - M=0,3 - 0,5 F=0,2 - 0,4
- World
  - M=2,8 F=2,6

Ferlay J, Bray F, Pisani P, Parkin DM.
GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence
Worldwide. IARC CancerBase No. 5. version 2.0.
IARCPress, Lyon 2004. (http://www-dep.iarc.fr/)

Melanoma incidence worldwide 2002



Globocan estimation 2002,

Slovenija

- *Incidence rate per 100,000*
  - 1963-1967 → male 1,7/100 000
    → female 2,6/100 000
  - *1996–2000* → male 11,0/100 000
    → female 11,8/100 000
  - *2001–2005* → male 14,5/100 000
    → female 16,3/100 000
- *Incidence rate per 100,000* (95% prediction interval)
  - *2008* → male 18,0/100 000
    → female 20,0/100 000

CANCER REGISTRY OF SLOVENIA
The Cancer Incidence in Slovenia 2005
Report No. 47 | Ljubljana 2008

Borut Žgavec

Epidemiology of melanoma and primary prevention

Sex

- United States: a slight male predilection
  - 1 in 52 males,
  - 1 in 77 females (Jemal, 2006).
- Worldwide: in 2002 estimated 160,000 new cases
  - women were affected slightly more than men
  - male-to-female ratio, 0.97:1.

  Conversely in 2002 estimated 41,000 worldwide deaths,
  - more occurred in men than in women
  - male-to-female ratio 1.2:1
- *V Slovenija (incidence rate):*
  - 1970-1979 M= 2,1 F=3,5
  - 1985-2004 M: from 4,1 to 17,1 (4x ↑)
    F : from 5,4 to 17,7 (3,2x ↑)

Race

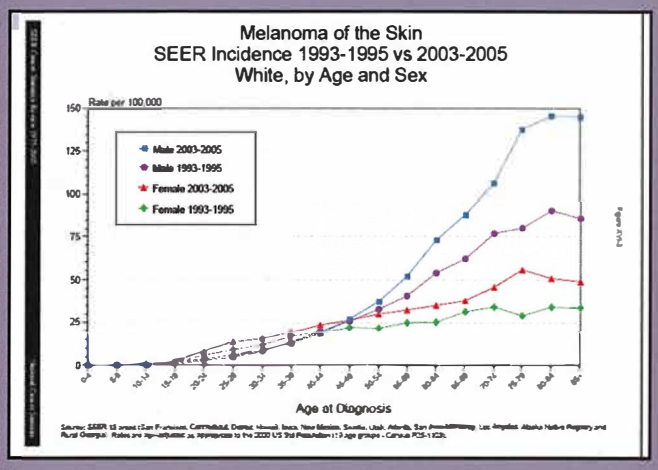
- Melanoma is primarily a malignancy of white individuals.
- African American persons develop melanoma approximately one twentieth as frequently as white persons
- Incidence in Hispanic persons is approximately one sixth of that in white persons.
- Mortality rates are higher in African Americans and Hispanics,
  - more likely to have acral melanoma
  - advanced disease at presentation.

Age

USA

- The median age at melanoma diagnosis ≈ 53 years
- The most common cancer in women aged 25-29 years
- Second to breast cancer in women aged 30-34 years
- The most striking differences in melanoma incidence and mortality occur in individuals older than 65 years
- modest differences in age-specific incidence and mortality are notable in persons older than 50 years (Geller, 2002).
- Older individuals more likely
  - to acquire
  - to die from melanoma

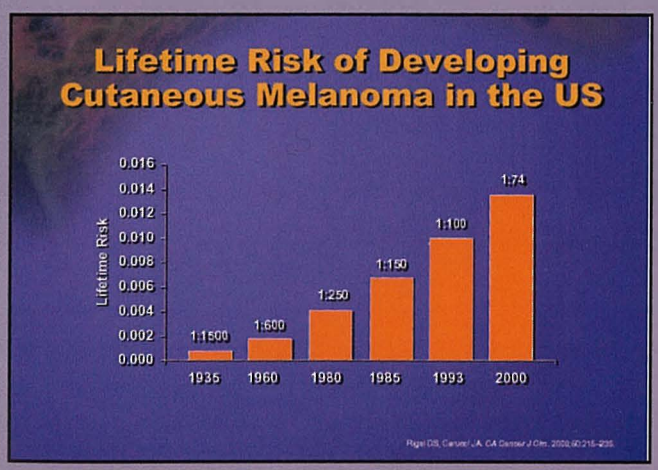
Elderly persons should be a primary target for secondary melanoma prevention (early detection and screening)



Lifetime Probability of Developing Cancer, by Site, Men, US, 1997-1999

	Risk
All sites	1 in 2
Prostate	1 in 6
Lung & bronchus	1 in 13
Colon & rectum	1 in 17
Urinary bladder	1 in 29
Non-Hodgkin lymphoma	1 in 47
Melanoma	1 in 57
Leukemia	1 in 69
Oral cavity	1 in 71
Kidney	1 in 72
Stomach	1 in 79

SEER Program, National Cancer Institute, 2002



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Epidemiology of melanoma and primary prevention

5-year relative survival rate

- USA:
  - 1996-2004 = 91.2%
  - by race and sex:
  - 88.8% for white men
  - 93.5% for white women
  - 71.2% for black men
  - 81.0% for black women.
- Europe ≈ 81%
- Developing countries ≈ 40%

5-year relative survival rate

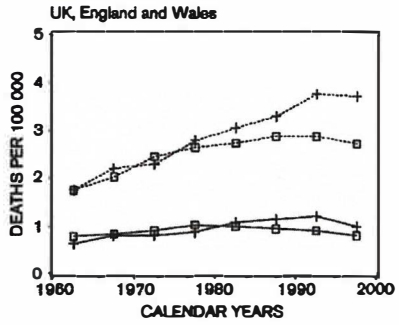
- *Slovenija*
- *1973 - 1977*
  - *Males* *33,3 %*
  - *Females* *58,3 %*
- *1998-2002*
  - *Males* *76,4 %*
  - *Females* *83,7 %*

Mortality

- melanoma:
  - ≈ 4% of all skin cancers,
  - > 77% of skin cancer deaths
- increased after the 1970's *(especially in white males)*
- stabilized after 1990's

Mortality

- EU 1960 -2000

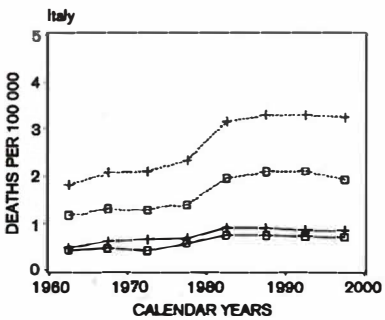


← 35-65 years

← all ages

Mortality

- EU 1960 -2000



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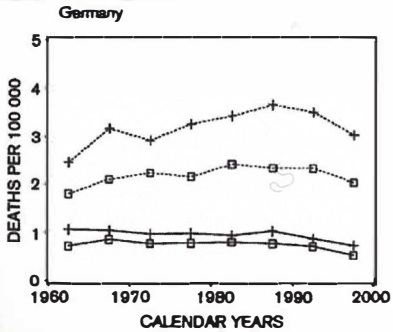
Mortality

- EU 1960 -2000



← 35-65 years

← all ages

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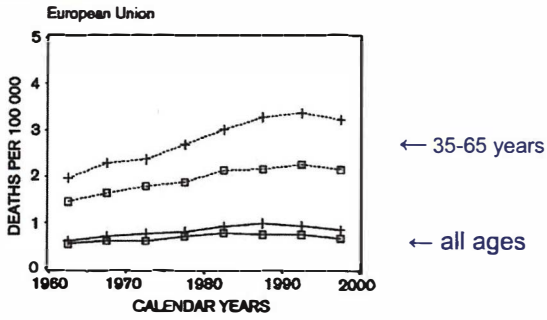
Epidemiology of melanoma and primary prevention

Mortality

- EU: 1960 -2000



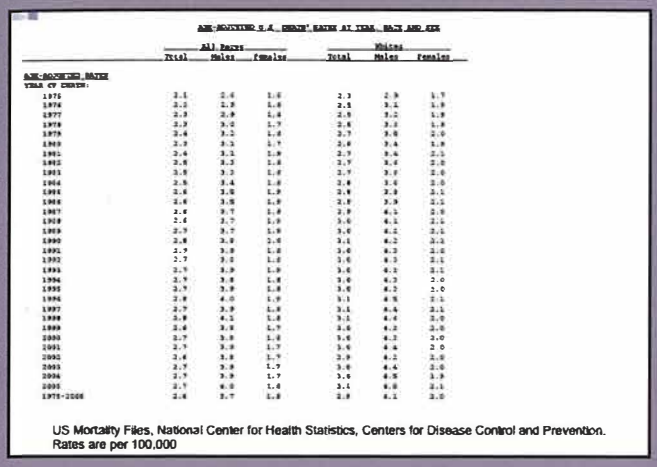
Melanoma Research 2004, 14:301–309

Incidence and Mortality USA

- 1973 -1995 Incidence increased 126 %
  rate ≈ 6 % per year
- Mortality rate:
  - 1973 = 2,1 (non-Hispanic whites)
  - 1992 = 2,9
  - 1973 – 2002 females 20-54 years ↓ for 23%
    males 20-54 years ↓ for 11%
    females 55-64 years ↑ for 15%
    males 55-64 years ↑ for 11%

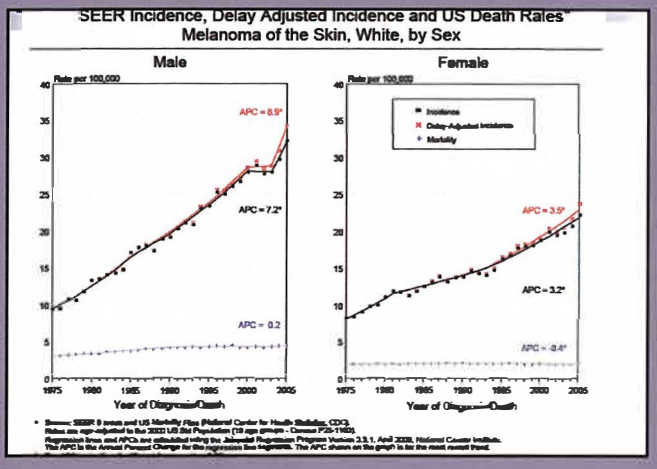
AGE-ADJUSTED SEER [INCIDENCE* RATES BY YEAR, RACE AND SEX

	All Races			Whites		
	Total	Males	Females	Total	Males	Females
AGE-ADJUSTED RATES YEAR OF DIAGNOSIS						
1975	7.9	8.5	7.4	8.7	9.4	8.2
1976	8.1	8.7	7.7	9.0	9.6	8.5
1977	8.8	9.6	8.2	9.9	10.8	9.1
1978	9.2	9.8	8.7	10.1	10.7	9.9
1979	9.6	10.4	8.9	10.6	11.3	10.1
1980	10.5	11.9	9.6	12.0	13.4	11.1
1981	11.1	12.3	10.4	12.6	13.6	12.0
1982	11.3	12.5	10.3	12.7	14.1	11.8
1983	11.1	12.7	10.0	12.6	14.4	11.4
1984	11.4	12.9	10.2	13.0	14.9	11.9
1985	12.8	15.1	11.1	14.4	17.1	12.6
1986	13.3	15.7	11.6	15.1	17.9	13.2
1987	13.7	16.9	12.2	15.4	18.1	14.0
1988	12.9	15.0	11.4	14.9	17.4	13.2
1989	13.7	16.4	11.9	15.9	18.9	13.8
1990	13.8	16.6	11.8	16.1	19.2	13.9
1991	14.4	17.6	12.5	17.0	20.4	14.7
1992	14.8	18.2	12.2	17.3	21.3	14.3
1993	14.6	18.1	12.1	17.0	20.9	14.3
1994	15.6	19.0	12.6	18.3	23.1	14.9
1995	16.4	20.2	13.7	19.2	23.4	16.3
1996	17.2	21.6	14.1	20.4	25.3	16.8
1997	17.7	21.6	14.8	20.8	25.1	17.8
1998	17.8	22.1	14.9	21.3	26.1	18.0
1999	18.2	22.8	15.0	21.7	26.9	18.2
2000	18.8	23.7	15.2	22.6	28.1	18.8
2001	19.5	24.3	16.2	23.7	28.9	20.0
2002	18.9	23.5	15.8	22.9	27.9	19.5
2003	19.3	23.6	16.1	23.3	28.0	19.9
2004	20.1	24.9	16.9	24.5	29.8	20.9
2005	21.8	26.8	17.9	26.4	32.3	22.3
1975-2005	14.9	18.1	12.7	17.3	20.9	15.0



	All Races			Whites		
	Total	Males	Females	Total	Males	Females
AGE-ADJUSTED RATES						
YEAR OF DEATH:						
1975	2.1	2.6	1.6	2.1	2.9	1.7
1976	2.2	2.9	1.6	2.5	3.1	1.9
1977	2.3	2.9	1.6	2.5	3.2	1.9
1978	2.3	3.0	1.7	2.6	3.3	1.9
1979	2.4	3.2	1.6	2.7	3.5	2.0
1980	2.3	3.1	1.7	2.6	3.4	1.9
1981	2.4	3.1	1.8	2.7	3.4	2.1
1982	2.5	3.3	1.8	2.7	3.6	2.0
1983	2.5	3.3	1.8	2.7	3.6	2.0
1984	2.5	3.4	1.8	2.8	3.6	2.0
1985	2.6	3.5	1.8	2.8	3.8	2.1
1986	2.6	3.5	1.9	2.9	3.9	2.1
1987	2.6	3.7	1.8	2.9	4.1	2.0
1988	2.6	3.7	1.9	3.0	4.1	2.1
1989	2.7	3.7	1.9	3.0	4.2	2.1
1990	2.8	3.9	1.8	3.1	4.2	2.1
1991	2.7	3.8	1.8	3.0	4.3	2.0
1992	2.7	3.8	1.8	3.0	4.3	2.1
1993	2.7	3.9	1.8	3.0	4.3	2.1
1994	2.7	3.8	1.8	3.0	4.3	2.0
1995	2.7	3.9	1.8	3.0	4.3	2.0
1996	2.8	4.0	1.9	3.1	4.5	2.1
1997	2.7	3.9	1.8	3.1	4.4	2.1
1998	2.8	4.1	1.8	3.1	4.4	2.0
1999	2.6	3.8	1.7	3.0	4.2	2.0
2000	2.7	3.9	1.8	3.0	4.3	2.0
2001	2.7	3.9	1.7	3.0	4.4	2.0
2002	2.6	3.8	1.7	2.9	4.2	2.0
2003	2.7	3.9	1.7	3.0	4.4	2.0
2004	2.7	3.9	1.7	3.0	4.3	1.9
2005	2.7	4.0	1.8	3.1	4.6	2.1
1975-2005	2.6	3.7	1.8	2.9	4.1	2.0

US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention.
Rates are per 100,000



Most striking features

1. The incidence has been substantialy increasing over past few decades
2. The mortality has been increasing only slightly (even decreasing in certain age groups)
3. The proportion of early diagnosed melanomas (thin melanomas) has been increased

Borut Žgavec

Epidemiology of melanoma and primary prevention

Two higlight points

1. Fast increasing incidence
2. Slow increasing or levelling off mortality

The questions ?

- Is incidence realy increasing so much?
- Are we getting so much better now ?
- Were we so bad in the past ?
- Are we erronieus now ?

The possible reasons of discrepancy between incidence and mortality

1. Overdiagnosed now
2. Misdiagnosed in the past
3. "Non-diagnosed" in the past
4. Not notificated in the past
5. Concept of "benign melanoma"
6. True increasing incidence

True increasing incidence

- The question: WHY?
- Etiology of melanoma: still unknown

Risk factors:

- Genotypic
- Phenotypic
- Environmental

Primary prevention

- Prevent sun or other UV sources exposure
- Focus on population at high risk
- Promote self examination
- Inform, educate, teach....
  - Individuals
  - The whole society

Melanoma - etiology and risk factors

Marko Hocevar, MD, PhD
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Cancer

- stepwise accumulation of somatic mutations
- growth advantage
- eventually the ability to invade and metastasize

Genetic mutations

Acquired	Inherited
Enviornmental factors	Genetic factors

Melanoma

- Enviornmental factors
  - UV irradiation
    - UV-B
    - UV-A
- Genetic factors
  - Genetic (in)stability
  - Fenotype
    - Anatomical site
    - Skin type

UV irradiation - sun exposure

- Chronic or intermittent pattern
- H&N melanomas
  - Higher levels of chronic sun exposure (↑ 2,43)
  - Hihger levels of occupational sun exposure (↑ 3,25)
- Trunk melanomas
  - Higher levels of intermittent/recreational sun exposure

Whiteman DC. J Clin Oncol 2006.

Fenotype – anatomical site

- Different type and number of melanocytes
- H&N melanoma over represented
  - 9% body surface → 14,8% of all melanomas (↑1,6)
  - Face surface 3,5% → 8,9% (↑ 2,6)
- Trunk melanomas under represented

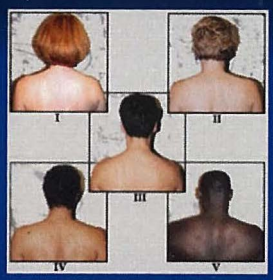
Hoersch B. Brit J Dermatol 2006.

Marko Hočevar

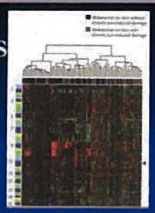
Etiology and risk factors

Fenotype - skin type

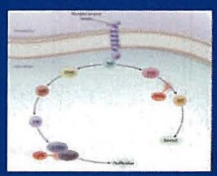
- **Type I**
  Often burns, rarely tans. Tends to have freckles, red or fair hair, blue or green eyes.
- **Type II**
  Usually burns, sometimes tans. Tends to have light hair, blue or brown eyes.
- **Type III**
  Sometimes burns, usually tans. Tends to have brown hair and eyes.
- **Type IV**
  Rarely burns, often tans. Tends to have dark brown eyes and hair.
- **Type V**
  Naturally black-brown skin. Often has dark brown eyes and hair.
- **Type VI**
  Naturally black-brown skin. Usually has black-brown eyes and hair.



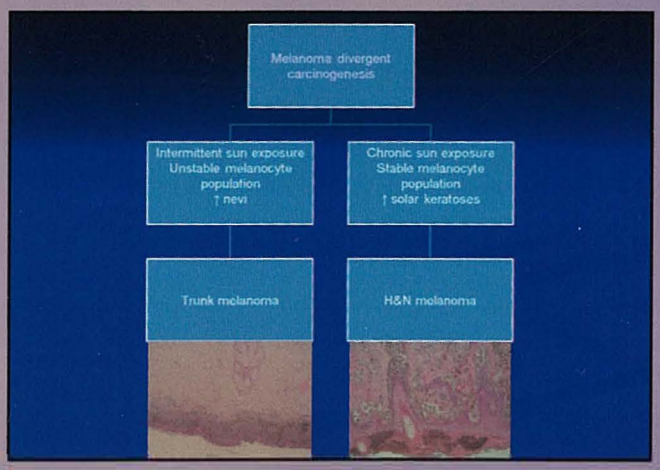
Etiology - genetics



- Trunck melanomas
  - BRAF and N-RAS mutations
- H&N melanomas
  - KIT mutation and CDK4 CCND1 amplification



Curtin JA. N Engl J Med 2005.
Curtin JA. J Clin Oncol 2006.



Lifetime risk of Developing or Dying of Cancer

Melanoma of the Skin

- Whites 2.11 (2.09, 2.14)
- Blacks 0.08 (0.07, 0.10)

http://seer.cancer.gov/csr/1975_2005/results_merged/topic_lifetime_risk.pdf

Risk factor

Anything that increases the chance of developing a disease is called a risk factor

Risk factors in melanoma

- Sunlight (UV irradiation)
- Light complexion (skin type I and/or II)
- Number of pigmented lesions
  - Freckles and common/atypical moles
- Prior cutaneous melanoma
  - 10xRR, greatest risk in first two years
- Positive family history
- Immunosupression

Tsao H. NEJM 2004.

Melanoma risk calculator

http://www.cancer.gov/melanomarisktool/index.aspx

Hereditary cancer

- 5 % of all cancers
- autosomal dominant trait
- variable penetrance (50-90% melanoma, 60-85% breast cancer, 95% medullary thyroid cancer)
  - genetic factors
  - environment (UV irradiation)

Cancer predisposition genes

- tumor suppresor genes
- proto-onkogenes
- mismatch-repair genes

Hereditary cancer

Familial history

Hereditary cancer

- familial clustering (first/second degree relatives)
- early age at onset (10-20 years earlier as sporadic cancers)
- multiple tumors (breast and ovary, colon and endometrium, melanoma and pancreas…)

Genetic counseling (cancer familiy clinic)

- probability of hereditary cancer
- genetic testing
- familial (non-hereditary) cancer
- prevention and control programs

Probability of hereditary cancer

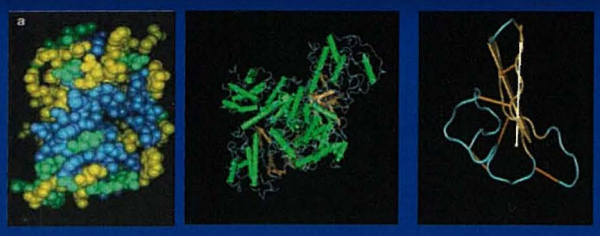
- family tree (three generations)
- statistical models (MELApro, BRCApro)

Genetic testing (ASCO recomendations)

- interpretation of test result
- influence on preventive/treatment decisions
- mutation probability ≥ 10%

Hereditary melanoma

CDKN2A CDK4 MC1R



CDKN2A

- cyclin dependent kinase 2A
- Chromosome 9p21
- tumor suppresor gene
- Four exons (1α, 1β, 2 and 3)
- two different proteins
  - INK4A (p16)→CDK4/6 →RB → G1 to the S-phase
  - ARF (p14) → p53

Kamb A, Nat Genet 1994.

CDKN2A

- Germline mutation in 10-25% melanoma families (Australia, North America, Europe)
- Population prevalence 0,01% (1/10000)
- P16 mutated in majority of pts
- Exon 1β mutations very rare (additional CNS tumors)

CDKN2A

- Penetrance (latitude dependent)
  - Europe 56%
  - USA 76%
  - Australia 91%

Bishop DT. J Natl Cancer Inst 2002.

CDK4

- Only 8 families worldwide
- ↑ penetrance (≈100%)
- Exon 2 – codon 24 (p16 biding site)

Helsing P, Gene Chromosomes Cancer 2008.

MC1R

- Low-penetrance gene
- Melanocortin receptor – MSH
- Skin fototype
  - eumelanin – fotoprotective
  - feumelanin – mutagenic

Rees JL, Pigment Cell Res 2000.

MC1R

- RHC variants (R151C, R160W in D294H)
  - ↑ melanoma risk
  - Modify CDKN2A penetrance
- MC1R variants→somatic BRAF mutations in non chronic solar damaged melanomas

Fargnoli MC. J Invest Dermatol 2008.

Hereditary melanoma in Slovenian population

- Genetic test in 67
  - 26 families
  - 26 multiple primaries
  - 3 children
- Positive in 8 (31%) families, 15 (37%) individuals
- CDK4 - 0

Peric B, BMC Med Genet 2008.

GenoMel (The Melanoma Genetics Consortium)

- Since 1997
- http://www.genomel.org/
- Mission to develop and support collaboration between member groups to:
  - Identify melanoma susceptibility genes
  - Evaluate genes-environment interactions
  - Asses the risk of melanoma and other cancers related tio variations in these genes

CLINICAL PRESENTATION AND EARLY DIAGNOSIS OF MELANOMA

MIRJAM ROGL BUTINA
prof. dr. IGOR BARTENJEV

CLINICAL PRESENTATION AND EARLY DIAGNOSIS OF MELANOMA

- Skin cancers constitute the most common malignancies in the white population
- Melanoma incidence all over the world has in the last 25 years increased more rapidly than any other cancer
- 5 years survival in melanoma
  - 95 % in thinner than 1 mm, nonulcerated
  - 24 % in thicker than 4mm, ulcerated and with lymph node metastasis

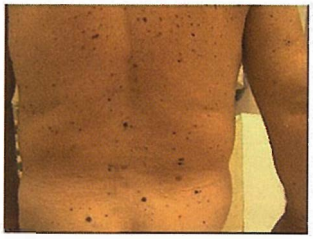
CLINICAL PRESENTATION AND EARLY DIAGNOSIS OF MELANOMA

- The incidence of MM is high
- Early diagnosis is crucial
- Clinical detection based on ABCDE criteria is weak with
  - small MM
  - MM regular in shape and colour

CLINICAL PRESENTATION AND EARLY DIAGNOSIS OF MELANOMA

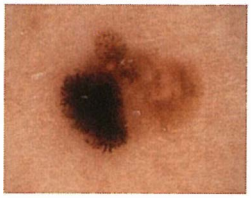
- Epiluminencent dermatoscopy
  - estimate changes from the surface down to the D-E junction
  - many pros but also some contras
- EL is an important support but not a substitute in the clinical diagnosis of melanoma

MELANOMA DEVELOPEMENT RISK FACTORS



- genetics
- numerous melanocytic nevi
- dysplastic melanocytic nevi
- congenital nevi (> 1,5 cm)
- phototype 1 and 2
- excessive UV insulation exposure

MELANOMA DEVELOPMENT

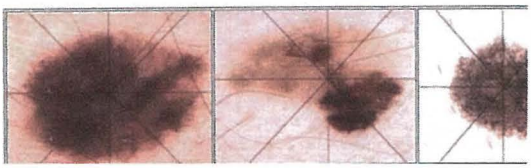


- DE NOVO – 50%
- MELANOCYTIC NEVUS – 25%
- LENTIGO MALIGNA - 10-15%
- KONGENITAL MELAN. NEVUS – 5 – 10%

CLINICAL PRESENTATIONS OF MELANOMA

- SSM – superficial spreading m. (70%)
- nodular m. (10 -15%)
- LMM – lentigo maligna m. (10 -15%)
- ALM – acral lentiginous m. (5%)

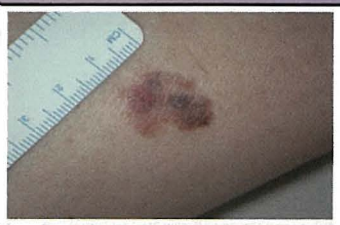
SUPERFICIALLY SPREADING MELANOMA

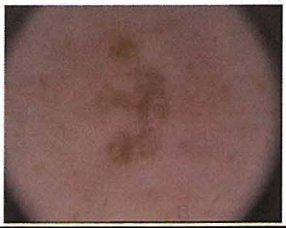


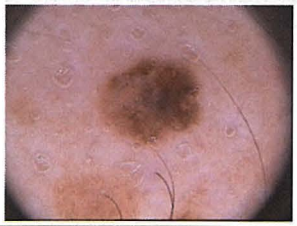
- most common, 70% in white population
- 30 – 50 years, M>F, upper back, legs
- episodic sunbathing
- developing over years (horizontal, than vertical growth)
- cardinal features are ABCDE criteria

Early diagnosis is based on
- history
- dermatoscopy

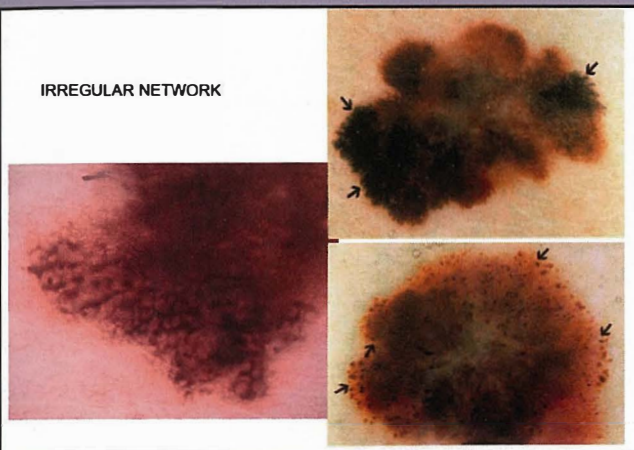
ASIMMETRY



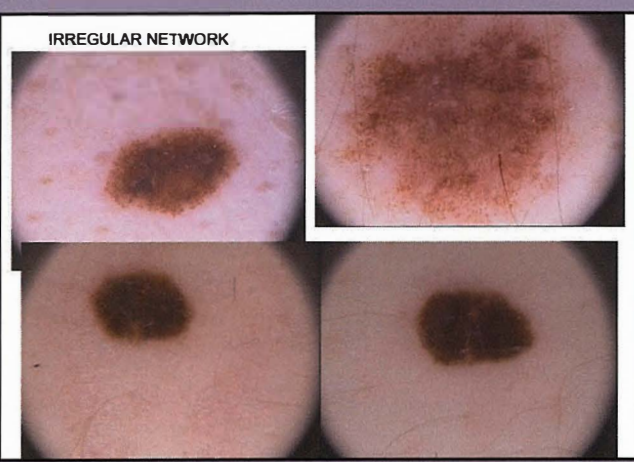




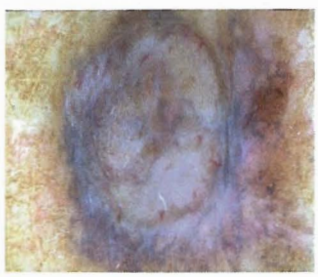
IRREGULAR NETWORK

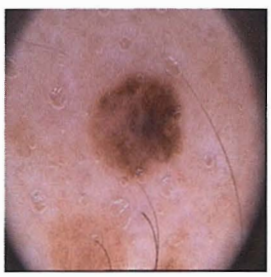


IRREGULAR NETWORK



SCARLIKE AREAS, BLUE WHITISH WEIL





WEIL:

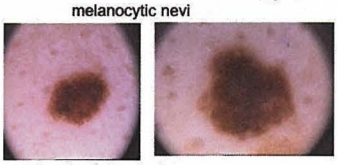
-H: acanthotic epidermis with focal hypergranulosis above sheets of hevily pigmented melanocytes in the dermis

REGRESION

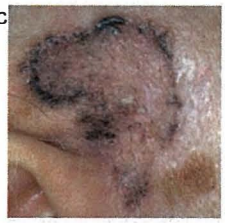
- H: thickened papillary dermis with fibrosis +/- melanophages

Ddg of SSM:

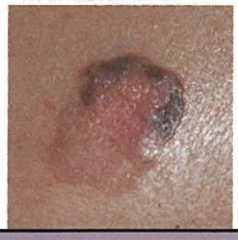
melanocytic nevi



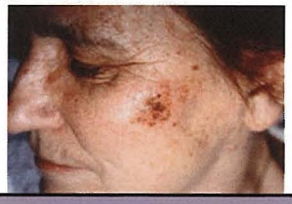
pigmented BCC



seborrhoeic keratosis

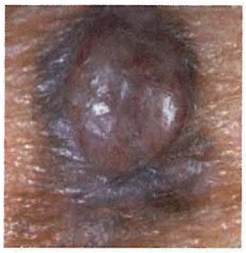


lentigines



NODULAR MELANOMA

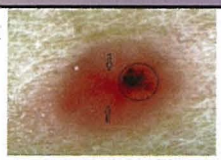
- 10 – 15 %
- Median age 50 years, M=F, all races
- episodic sunbathing
- grows quickly, 6 -18 months, strongly influences mortality of MM
- Vertical phase of growth from the beginning

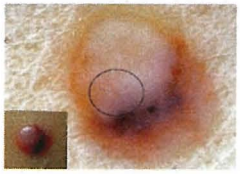


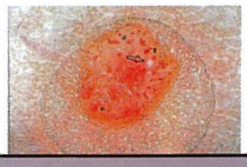
Early diagnosis of nodular melanoma

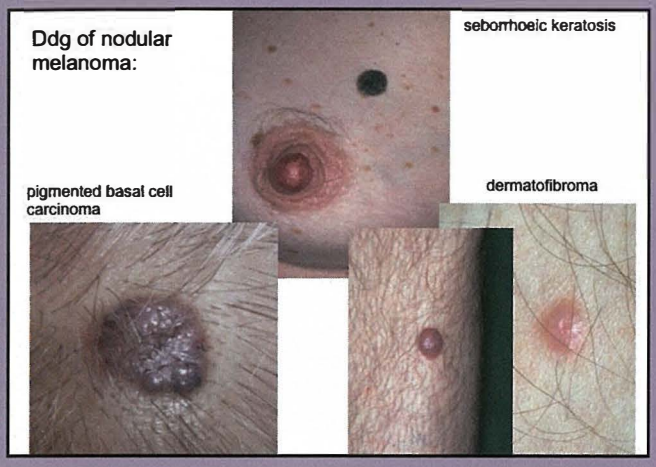
-THINK OF IT

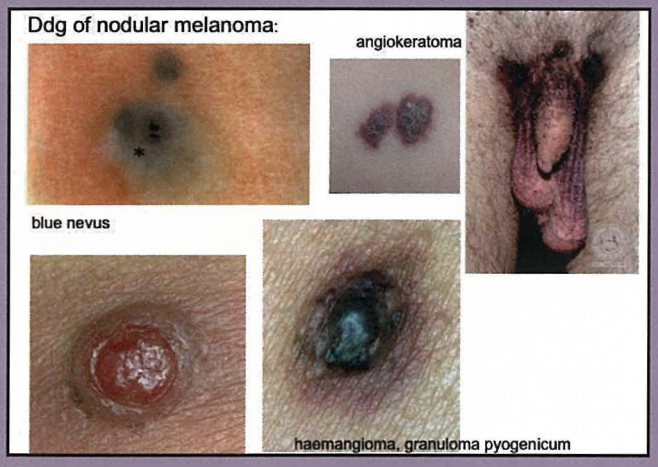
- network
  - asymmetrical, irregular structures
  - absent: structurless areas / amelanotic
- yascular appearances
  - dilated vessels running over the surface
  - red globules / red dots





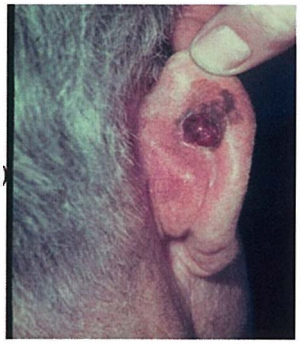






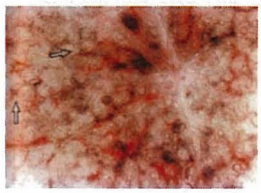
LENTIGO MALIGNA MELANOMA

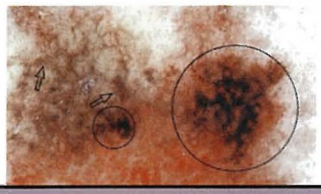
- 10 - 15%
- median age 65 years, face, forearm
- phototype I, II, III; heavily sun damaged skin
- slowly developing (decades)
- LENTIGO MALIGNA – intraepidermal lesion, invasive MELANOMA with focal papular, nodular lesions



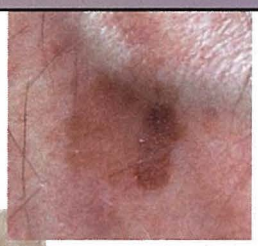
Early diagnosis of LMM:

- gray teint
- -obliteration of follicular openings (asymmetrically pigmented)
- annular-granular structures (rhomboid structures)
- homogenous parts



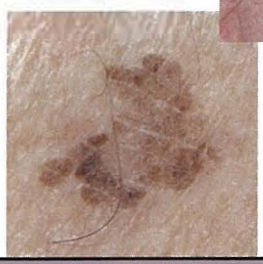


Ddg of LMM:

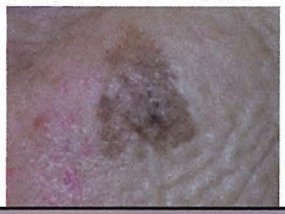


solar lentigo

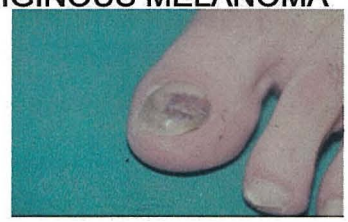
seborrhoeic keratosis



pigmented actinic keratosis



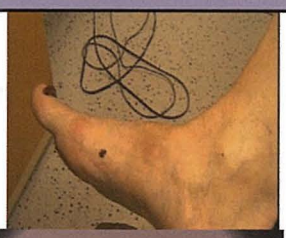
ACRAL LENTIGINOUS MELANOMA

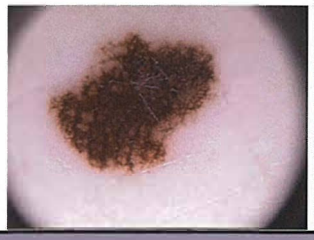


- Rare – 5%
- Median age 65 years, all races – for phototypes V, VI the most common MM
- Relatively slowly developing
- Soles, palms, nail bed, ears, genitalia, mouth
- Subungual:
  - plaques and nodules may be amelanotic
  - Hutchinson's sign

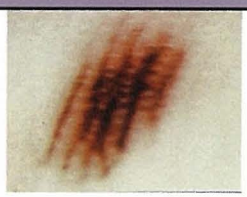
Early diagnosis of ALM:

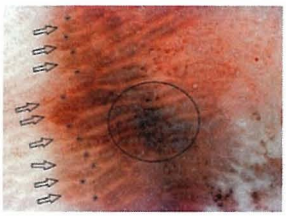
- lentiginous appearance with pigmented network at the border
- centre with
  - black/blue homogenous zones
  - whitish structureless areas





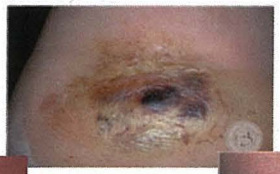
Early diagnosis of ALM:
- parallel wide brown lines on the ridges

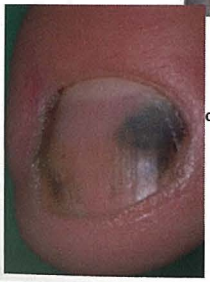




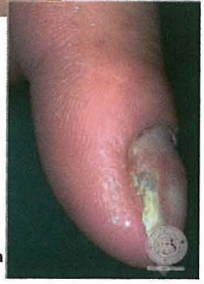
Ddg of ALM:

- haematoma (subungual, black heel)





onychomycosis



subungual verruca

Pathology of malignant melanoma

Matej Bračko

Department of Pathology
Institute of Oncology Ljubljana

melanocytes

- origin: neural crest, from which they migrate at the 13th week of embryonic life and come to lie at the dermo-epidermal junction
- function: production of melanin (in melanosomes), which is transferred to basal keratinocytes; melanin protects the nuclei of keratinocytes from solar irradiation

benign pigmented lesions

- ephelides (freckles): increased pigmentation, no increase in number of melanocytes
- lentigo: increased number of individual melanocytes at dermo-epidermal junction
- nevus: proliferation of melanocytes, forming nests
  - junctional nevus
  - compound nevus
  - intradermal nevus
  - blue nevus

Malignant melanoma

- malignant tumor of melanocytes

Progression of malignant melanoma

- radial growth phase (non-tumorigenic melanoma)
  - radial expansion through epidermis (melanoma in situ)
  - migration of melanoma cells into dermis, but showing no proliferation (microinvasive melanoma)
- vertical growth phase (tumorigenic melanoma)
  - new clone of melanoma cells in the dermis, which have the ability to survive and proliferatie
    - dermal nodule larger than any epidermal nest
    - mitoses in the dermal component

MM – histologic types

- superficial spreading melanoma
- lentigo maligna / lentigo maligna melanoma
- acral-lentiginous melanoma
- nodular melanoma

- other rare types

Lentigo maligna

- a form of melanoma in situ occuring on the sun-exposed skin of elderly people
- lentiginous growth of atypical, hyperchromatic, often markedly pleomorphic melanocytes in the epidermis
- atrophic epidermis
- dermal solar elastosis

Lentigo maligna melanoma

- lentigo maligna (in situ) + invasive melanoma
- invasive component often composed of spindle cells

Acral-lentiginous melanoma

- occurs on the palms, soles and subungual sites
- rare in Caucasians (2%); most common form in dark-skinned people (80%)
- radial growth: lentiginous proliferation of atypical, often heavily pigmented melanocytes; accompanied by acanthosis and hyperkeratosis of the epidermis
- vertical growth: usually spindle cells

Nodular melanoma

- second most common type of melanoma (10-15%)
- invasive by definition!
- no melanoma cells in the epidermis beyond the margins of the dermal component (= no radial growth phase!)

Rare types of melanoma

- nevoid melanoma
- desmoplastic melanoma
- desmoplastic neurotropic melanoma
- melanoma arising from blue nevus (malignant blue nevus)
- malignant melanoma with prominent pigment synthesis (equine/animal-type melanoma)

Prognostic factors

- the extent of invasion:
- Breslow's thickness (quantitative):
  - measured in mm from the epidermal surface or base of the ulcer
- Clark's levels (qualitative):
  - levels I to V

Levels of invasion (Clark)

I	tumor cells confined to the epidermis (melanoma in situ)
II	partial infiltration of the papillary dermis
III	tumor fills and expands the papillary dermis
IV	infiltration of the reticular dermis
V	infiltration of the subcutaneous tissue

Prognostic factors

- Breslow's thickness is a more powerful prognosticator than Clark's level
- Clark's level remains a powerful prognostic variable in thin (≤ 1 mm) melanomas
- Ulceration (not attributable to trauma) is a strong independent adverse prognostic factor

Tis	melanoma in situ (Clark I)
T1	tumor thickness 1 mm or less
	T1a: Clark II or III, no ulceration
	T1b: Clark IV or V, or ulceration
T2	tumor thickness > 1mm and ≤ 2 mm
	T2a: no ulceration
	T2b: ulceration
T3	tumor thickness > 2 mm and ≤ 4 mm
	T3a: no ulceration
	T3b: ulceration
T4	Tumor thickness > 4 mm

AJCC 2002 revised melanoma staging

Stage	Histological [illegible]/TNM classification	Overall survival		
		1 year (%)	5 years (%)	10 years (%)
0	[illegible] (Tis[illegible])		100	100
IA	≤ 1 mm without ulceration and Clark level II/III (T1aN0M0)		95	88
IB	≤ 1 mm with ulceration or level IV/V (T1bN0M0) 1.01–2 mm without ulceration (T2aN0M0)		91 88	83 79
IIA	1.01–2 mm with ulceration (T2bN0M0) 2.01–4 mm without ulceration (T3aN0M0)		77 79	64 51
IIB	2.01–4 mm with ulceration (T3bN0M0) > 4 mm without ulceration (T4aN0M0)		63 67	51 54
IIC	> 4 mm with ulceration (T4bN0M0)		45	32

Other possible prognostic factors

- mitotic activity
- tumor-infiltrating lymphocytes
- regression
- blood vessel and lymphatic invasion
- microscopic satellites

N categories in malignant melanoma	
N0	no lymph node metastasis
N1	metastasis in one node
	N1a: microscopic (clinically occult)
	N1b: macroscopic (clinically apparent)
N2	metastases in 2 or 3 nodes *or* intralymphatic regional metastases
	N2a: microscopic (clinically occult)
	N2b: macroscopic (clinically apparent)
	N2c: satellite or in-transit *without* lymph node metastasis
N3	metastasis in 4 or more lymph nodes *or* matted lymph nodes *or* satellite / in-transit metastasis *with* lymph node metastasis

Diagnostic imaging in melanoma

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Institute of Oncology
Ljubljana

MM - prognosis

- Thickness of primary tumor
  - +/- ulceration
- Regional status of lymph nodes
  - number
  - micro /macrometastases

Balch,JCO 2001

Clinical procedures in suspected MM

1/ diagnostic excision with safe margin 2-5 mm

In histopathologically confirmed MM :

2/ radical excision and sentinel lymph node biopsy (SNB)

3/ lymph node basin dissection

Role of Imaging in MM

- **Primary staging of the disease**
  - **US of the primary lesion**
  - US of regional lymph nodes(LN)
- Follow - up
- Relaps

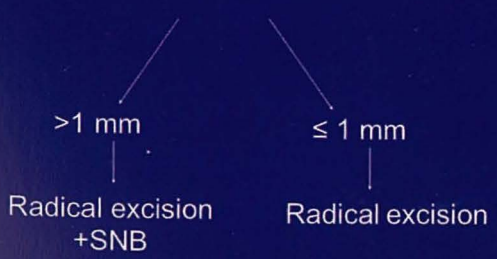
US of primary MM

- Dermatology - special US with 20 MHz probe
- US with linear probe 12-15 MHz ??

L. Serrone, Mel.Res 2002

US – primary MM

- Before surgery
- US of primary MM (12 – 15 MHz)



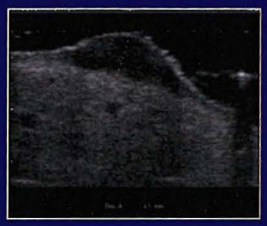
Maja Marolt Mušič

Specifics in functional diagnostic imaging in melanoma

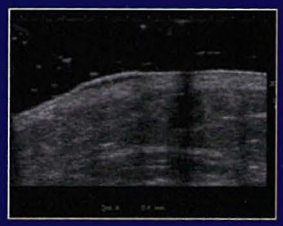
12-15MHz – our results

- 73 PSL, clinicaly suspected of being MM
- US before surgical excision
- Linear probe 12-15 MHz
- Thickness of primary tu was measured
- Comparison to patohistological exam
- PPV,NPV,sensitivity, scpecificity

Primary MM - thickness

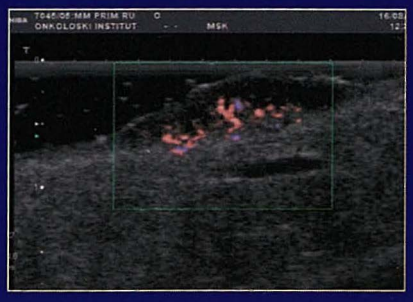


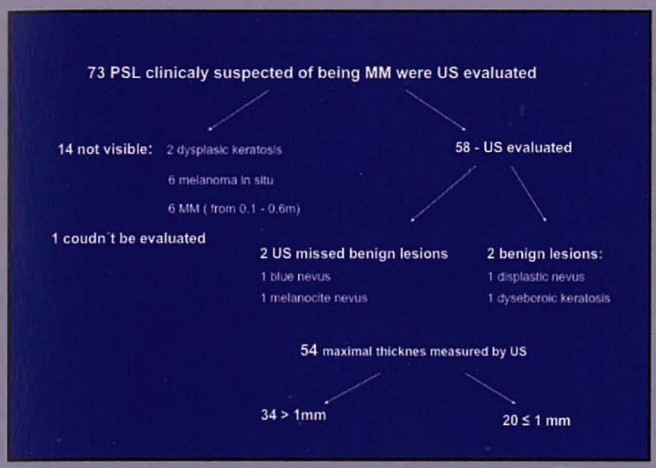
4 mm



0.4 mm

Primary MM - Vascularization





US of primary MM

- Sensitivity 90 %,
- Specificity 87.5%
- PPV 84%
- NPV 83%

US of primary MM- Conclusions

- US with 12-15 MHz linear transducer can reliably differentiate between primary MM thicker than 1 mm and those thinner than 1 mm, it can be most helpful in planning optimal surgical procedure
- It cannot diferentiate between MM and benign PL

Role of Imaging in MM

- Staging of the disease at diagnosis
  - US of primary lesion
  - **US of lymph nodes (LN)**
- Follow - up
- Relaps

MM - prognosis

Lymph node metastases

Most important prognostic factor

- ⇓ 10-year survival for 20 -50%
  - Clinically palpable
  - Non- palpable

Balch et al J Clin Oncol 2001

Sentinel lymph node biopsy (SNB)

Advantages:

- reliably assesses the status of regional lymph node basin
- identifies patients who need lymph node dissection

Morton et all. Arch Surg. 1992

Sentinel lymph node biopsy (SNB)

Indicated in patients with primary MM

- > 1mm
- thinner < 1 mm:
  - Clark IV/V
  - uceration

Preoperative evaluation of regional lymph nodes

- US
- CT
- MRI
- PET-CT

Wagner JD. Cancer 2003

SNB - US

- Metastases < 2 - 4 mm not visible by US
- 10% of patients can be spared one surgical procedure

Rossi et all Jorn Surg Oncol 2003

Sttani E. An Surg Oncol. 2005

Maja Marolt Mušič

Specifics in functional diagnostic imaging in melanoma

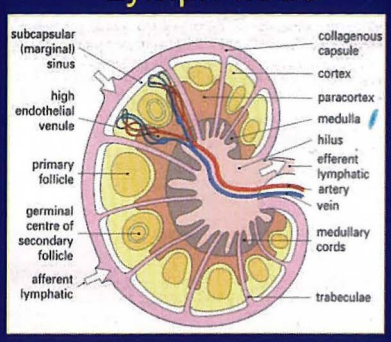
US of LN

- US + FNAB is a valuable method of preoperative regional lymph nodes staging
- PPV 100%
- Low sensitivity

US of regional LN

- Non-invasive
- Cheap
- Quick
- Dynamic procedure, largest diameter of LN can be measured
- Operator dependent

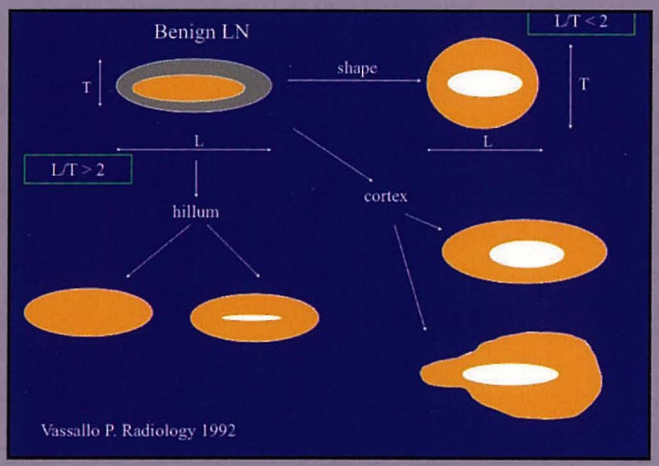
Lymph node



Lymph node (LN) - US

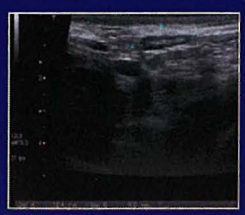
- Size of LN is not important
- Longitudinal - transversal ratio **L/T**
- Hilum / cortex

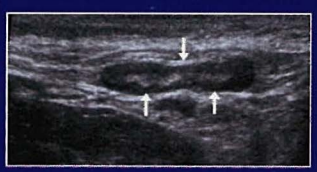
Vassallo P. Radiology 1992



Benign LN - US

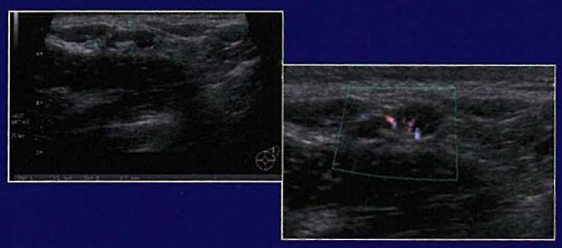
- L/T ratio > 2
- Hyperechoic hilum
- Hilar type of vascularization



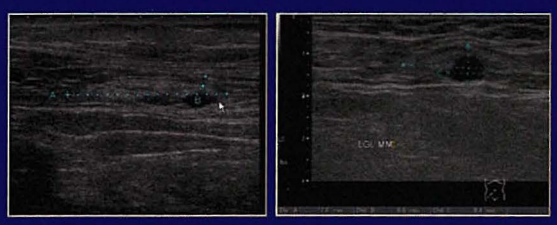


Benign LN - US

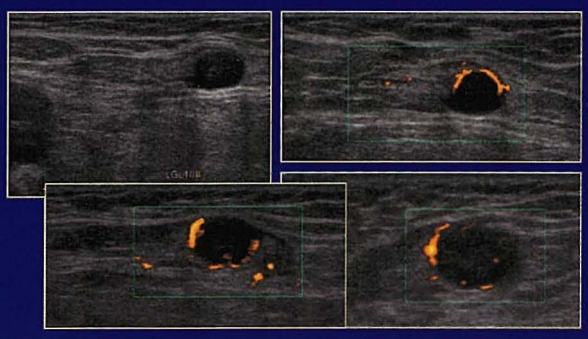
Hilar type of vascularization



Malignant LN

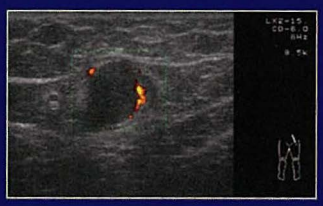


Malignant LN



Malignant LN

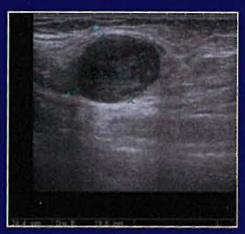
- L/T ratio changes, LN – roundish
- Asimmetric hilum
- Neoangiogenesis: periferal vascularization



Vassallo P. Radiology 1992

US of LN bassin- follow up

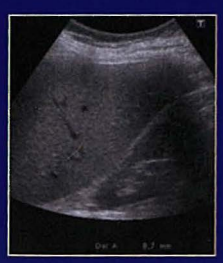
- US examination of regional LN basins is highly sensitive
- Superior to physical examination
- + FNAB : definitive dg
- Survival benefit
- Sensitivity, specificity vary

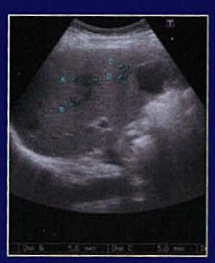


Blum A.et al.Cancer 2000

Voit: Sem in Onc 2002

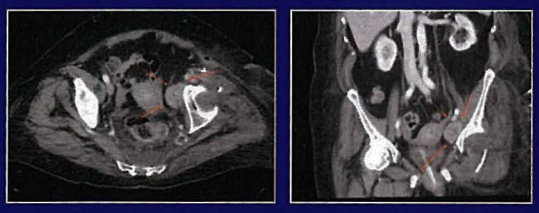
Relaps of MM - imaging





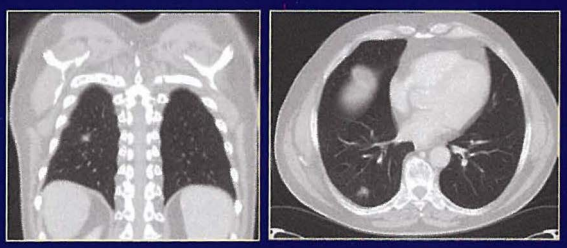
US – liver metastases

Relaps of MM - imaging



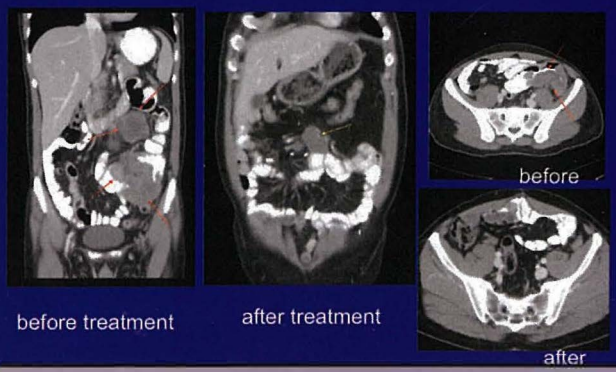
Iliacal LN metastases

Relaps of MM - imaging



CT- lung metastases

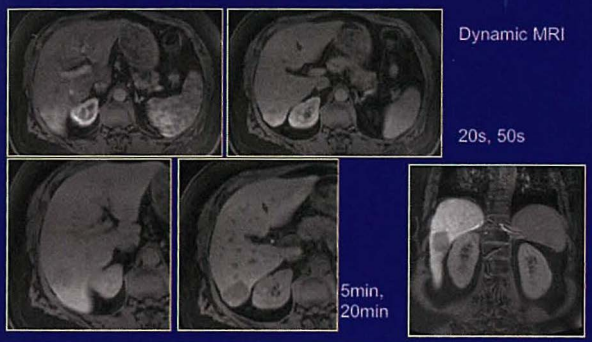
Relaps of MM



before treatment

after treatment

Relaps of MM - imaging



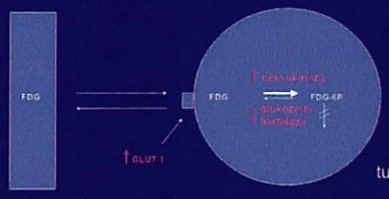
Dynamic MRI

20s, 50s

5min,
20min

PET/CT

- 18- FDG (increased uptake of flour deoxi glucose in malignant tumors)



Courtesy of dr. B. Vidergar

PET/CT

False positive uptake:

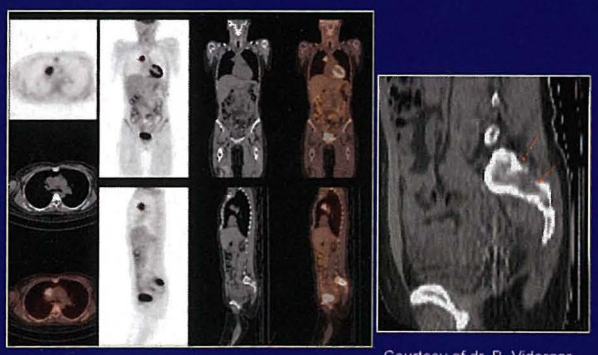
- after biopsy or operation (healling)
- after irradiation and/or chemotherapy
- growth factors (bone marrow and spleen uptake).
- benign lesions (goiter, parath-, tyroid adenoma, gynecomastia, polyps, leiomyoma)
- physiological conditions
- artefacts

Courtesy of dr. B. Vidergar

PET/CT

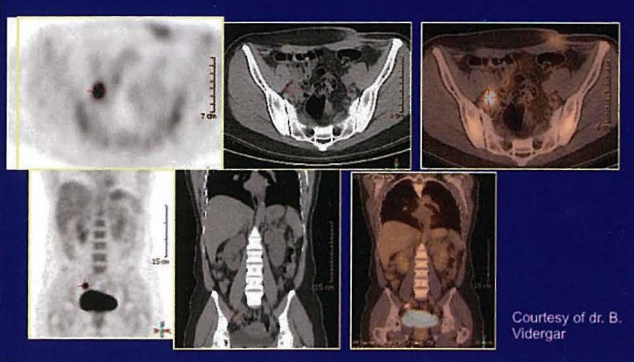
- False negative:
  - No accumulations in tu lesions due to temporary blockade
  - Malignant lesion < 5-7 mm
  - Slowly growing and well differentiated tu (neuroend. tu., bronchoalveolar ca, lobullar ca of the breast, mucinous ca, low grade sarcoma)

PET/CT



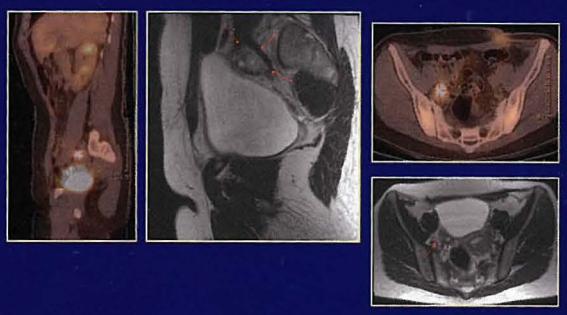
Courtesy of dr. B. Vidergar

PET/CT



Courtesy of dr. B. Vidergar

PET/CT - MR



Staging and prognosis of melanoma

Marko Snoj, Institute of Oncology Ljubljana

Mr.D. aged 59 years, of light hair and fair complexion, presented on February 6, 1817 with a tumor of his abdominal wall midway between umbilicus and pubis. There had always been the mole on this position, but nine months previously , it began to grow and tumor developed. It was half size of hen's egg, of a deep brown colour, of a firm and fleshy feel, ulcerated, and discharging s highly foetid ichtiourous fluid.

William Norris, *Edinb Med Surg J, 1820*

1840 – "no remedy is known".. "the only chance for benefit depends upon early removal"(S.Cooper)
1851 – excison of metastatic inguinal node(Mr Ferguson)
1885 –extensive excision of melanoma(J. Coates)
1892- radical dissection of regional nodes(H.Snow)
1907- circular excision of the tumor including margin of noninvolved skin, subcutis and muscular fascia
(W.S. Handley)

Source	No. of cases	Cutaneous (%)	Ocular(%)
Pemberton 1853	23	61	39
Coley and Hoguet 1916	79	86	12
Broders and McCarty 1916	70	94	6
Coke 1928	43	77	23
Gleave 1929	40	55	45
US National Cancer Data Base(1985-94)	77 370	94	6

Till 1980 rare disease in Western world (~ 1% all cancers).

Incidence in Slovenia is growing, doubling time 6 to 10 years.

Incidence in Slovenia is growing more in females than in males.

In 1988 incidence for men was 5 3, and for women 4.7 (per 100.000) with peak in middle ages. in 1999 incidence for men was 11 and in women 13. In 1988 there were 50 new cases in men and 47 in women; in 1999 was 106 new cases in men and 134 in women.

27 12:50

Prognostic Factors Analysis of 17,600 Melanoma P
Validation of the American Joint Committee on
Melanoma Staging System

Charles M. Balch, Seng-Jaw Soong, Jeffrey E. Gershenwald, John F. Thompson, Douglas S. Reintgen, Marshall Urist, Kelly M. McMasters, Morrick I. Ross, John M. Kirkwood, Michael B. Atkins, John A Daniel G. Coit, David Byrd, Renee Desmond, Yuting Zhong, Ping-Yu Liu, Gary H. Lyman, and Abe

urpose: The American Joint Committee on Cancer CC) recently proposed major revisions of the tumor-de-metastases (TNM) categories and stage groupings cutaneous melanoma. Thirteen cancer centers and ner cooperative groups contributed staging and sur-al data from a total of 30,450 melanoma patients from ir databases in order to validate this staging proposal. *Patients and Methods:* There were 17,600 mela-

following three independent factors the number of metastatic nodes, whet tases were clinically occult or clinical the presence or absence of primary and (3) in the M category, nonviscera associated with a better survival co ceral metastases. A marked diversi history of pathologic stage III melan strated by five-fold differences in 5-y

2002 AJCC* Melanoma Staging System

- Evidence-based system compiled from survival data in well-followed populations
- Classification validated by prognostic factors analysis in 17,600 melanoma patients
- Tumor thickness & ulceration: best survival predictors in localized melanoma (stages I-II)
- Lymph node number, nodal tumor burden,† & ulceration: best survival predictors in melanoma with regional metastasis (stage III)

*AJCC—American Joint Committee on Cancer
†Defined as microscopic vs macroscopic nodal involvement

Balch CM, et al. J Clin Oncol. 2001;19:3622-3634.

New Criteria: Rationale

- Tumor ulceration adds prognostic value and should be part of staging criteria
- Number of positive nodes is a more powerful prognostic indicator than size of the nodal metastases
- Nodal, in-transit, and local satellite recurrences are all related and have similar prognoses
- New system separates pathologic staging from clinical staging; pathological staging preferred

Buzaid AC, et al. J Clin Oncol. 1997;15:1039-1051.
Balch CM, et al. J Clin Oncol. 2001;19:3622-3634.

Changes in the AJCC Staging Criteria for Cutaneous Melanoma

Factor	*Old System*	*New System*
Level of invasion T1	↑ determinant	Used only for of T staging melanomas
Thickness	Thresholds of 0.75, 1.5, 4.0 mm	Thresholds of 1.0, 2.0, 4.0 mm
Ulceration	Not included	Used for T and N staging
Thickness >4.0 mm	In stage IIIA	In stage IIB and IIC
Nodal size	↑ factor for N staging	Not used
No. of nodal metastases	Not used	↑ determinant for N staging
Metastatic tumor burden	Not included	Included in N staging
Clinical vs pathologic stage	SLN results not incorporated	SLN results incorporated

Balch CM, et al. J Clin Oncol. 2001;19:3635-3648.

Prognostic Factors for Primary Melanoma

Patients Staged after Node Dissection

Variable	*P*	*Risk Ratio*	*95% CI*
Nodal status	<0.00001	2.239	1.913-2.621
Ulceration	<0.00001	1.938	1.674-2.242
Thickness	<0.00001	1.583	1.433-1.749
Site	<0.00001	1.483	1.281-1.716
Age	0.0002	1.095	1.044-1.147
Level of invasion	0.9082	1.007	0.896-1.131
Sex	0.1705	0.900	0.774-1.046

Balch CM, et al. J Clin Oncol. 2001;19:3622-3634.

AJCC Staging Criteria: T Stage (Node Negative)

Variable	χ^2
Thickness*	
Ulceration*	
Age	
Site	
Level	
Gender	

Balch CM, et al. J Clin Oncol. 2001;19:3622-3634.
American Joint Committee on Cancer. Melanoma. In: Greene FL, et al, eds. AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer; 2002:209-217.

AJCC Staging Criteria: T Stage

	Ulceration	
Depth	**–**	**+**
<1.0 mm	95%	91%
1.01-2.0 mm	89%	77%
2.01-4.0 mm	78%	63%
>4.0 mm	67%	45%

*10-year survival rate 10-15% less in each category

Balch CM, et al. J Clin Oncol. 2001;19:3635-3648.

2002 AJCC Melanoma Staging System:T Classification

Depth	Ulceration*	Stage
≤1.0 mm	a†	IA
	b‡	IB
1.01-2.0 mm	a	IB
	b	IIA
2.01-4.0 mm	a	IIA
	b	IIB
>4.0 mm	a	IIB
	b	IIC

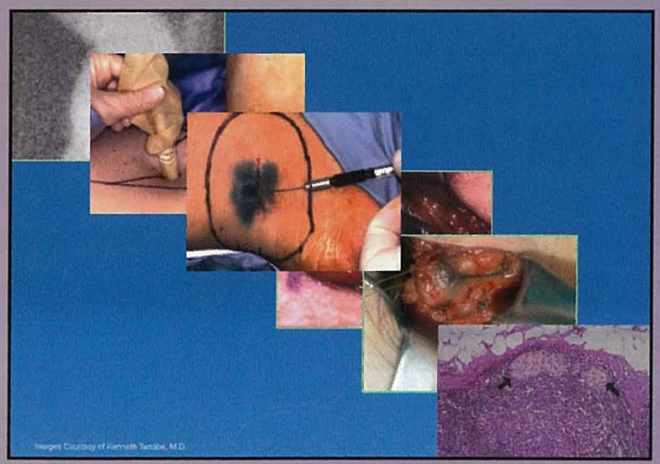
†Ts, no ulceration; b, ulceration (Clark's level IV/V)
‡Ulceration or Clark's level IV/V

Balch CM, et al. J Clin Oncol. 2001;19:3635-3648.

AJCC Staging Criteria: N Stage (Node Positive)

Variable	χ^2
Number	57.6
Micro vs Macro*	40.3
Ulceration	23.2
Thickness	1.9

Balch CM, et al. J Clin Oncol. 2001;19:3622-3634.



Images Courtesy of Kenneth Tyrone, M.D.

Prognostic Value of the Number of Positive Nodes

- Significant predictor of outcome in patients with regional metastases
- Risk groups are best divided into
  - 1 positive node
  - 2 to 3 positive nodes
  - 4+ positive nodes

Balch CM, et al. J Clin Oncol. 2001;19:3622-3634.

5-Year Survival by Node Class

+ Nodes	Microscopic	Macroscopic
1	61%	46%
2	56%	37%
3	56%	27%
4	36%	24%
>4	35%	24%

Balch CM, et al. J Clin Oncol. 2001;19:3622-3634.

2002 AJCC Melanoma Staging System: N Classification

	Number	Type	Stage*
N1	1	a micro	IIIA/B
		b macro	IIIB/C
N2	2-3	a micro	IIIA/B
		b macro	IIIB/C
		c in-transit or satellite, no + nodes	IIIB
N3	4+ and/or matted, in-transit, satellite or ulceration		IIIC

*Reflects effects of ulceration

Balch CM, et al. J Clin Oncol. 2001;19:3635-3648.

5-Year Survival in Stage III Melanoma

Microscopic

Ulceration	1+ Node	2-3 Nodes	>3 Nodes
Absent	69%	63%	27%
Present	52%	50%	37%

Macroscopic

Ulceration	1+ Node	2-3 Nodes	>3 Nodes
Absent	59%	46%	27%
Present	29%	25%	13%

2002 AJCC Melanoma Staging System: M Classification

	Location	*Stage*
Mx	Unassessable	
M0	No distant metastases	
M1	Distant metastases	IV

a: Skin, subcutaneous tissues, distant lymph nodes
b: Lung
c: All other distant sites or at any site with ↑ LDH*

2002 AJCC Pathologic Stage Groupings for

Stage	*T*	*N*	*M*
0	Tis	0	0
I A	T1a	0	0
B	T1b	0	0
	T2a	0	0
II A	T2b	0	0
	T3a	0	0
B	T3b	0	0
	T4a	0	0
C	T4b	0	0

2002 AJCC Pathologic Stage Groupings for

Stage	T	N	M
IIIA	T1-4a	N1a	0
	T1-4a	N2a	0
B	T1-4b	N1a	0
	T1-4b	N2a	0
	T1-4a	N1b	0
	T1-4a	N2b	0
	T1-4a/b	N2c	0
C	T1-4b	N1b	0
	T1-4b	N2b	0
	Any	N3	0
IV	Any	Any	M1

2002 AJCC Melanoma Stage Groupings

Stage	TNM Classification	Description	5-Year Survival Rates
IA	T1a N0M0	T ≤1.0 mm, no ulceration (Clark level II/III)	95%
IB	T1b N0M0	T ≤1.0 mm, ulceration or Clark level IV/V	91%
	T2a N0M0	T 1.01-2.0 mm, no ulceration	89%
IIA	T2b N0M0	T 1.01-2.0 mm, ulceration	77%
	T3a N0M0	T 2.01-4.0 mm, no ulceration	78%
IIB	T3b N0M0	T 2.01-4.0 mm, ulceration	63%
	T4a N0M0	T >4.0 mm, no ulceration	67%
IIC	T4b N0M0	T >4.0 mm, ulceration	45%

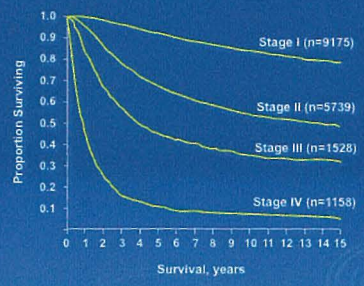
2002 AJCC Melanoma Stage Groupings

Stage	TNM Classification	Description	5-Year Survival Rates
IIIA	AnyTN1a M0	1 micro node, no ulceration	69%
	AnyTN2a M0	2-3 micro nodes, no ulceration	63%
IIIB	AnyTN1a M0	1 micro node, ulceration	53%
	AnyTN2a M0	2-3 micro nodes, ulceration	50%
	AnyTN1b M0	1 macro node, no ulceration	59%
	AnyTN2b M0	2-3 macro nodes, no ulceration	46%
IIIC	AnyTN1b M0	1 macro node, ulceration	29%
	AnyTN2b M0	2-3 macro nodes, ulceration	24%
	AnyTN3 M0	≥4 nodes, matted nodes or nodes + in-transit metastasis	27%
IV	AnyTAnyN M1a	Distant skin, subcutaneous, or node metastasis	19%
	AnyTAnyN M1b	Lung metastasis	7%
	AnyTAnyN M1c	Any visceral metastasis or elevated LDH* with metastasis	10%

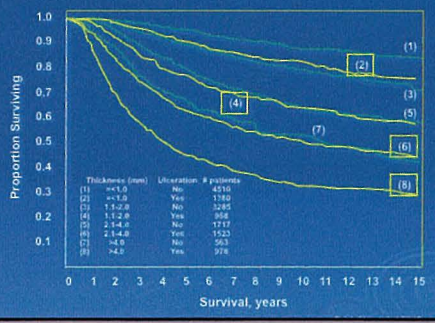
Marko Snoj

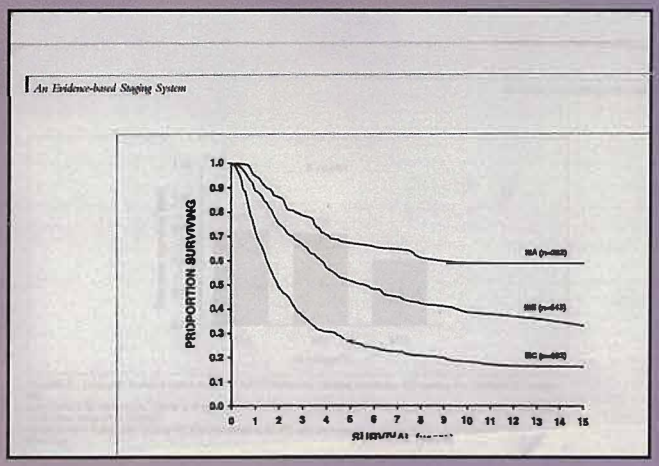
Staging and prognosis of melanoma

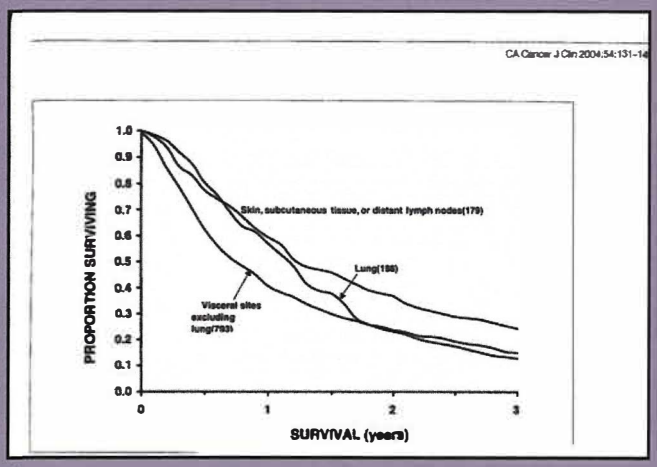
Cutaneous Melanoma: 15-Year Survival by Stage



15-Year Survival Stratified by Tumor Thickness and Ulceration*






CA Cancer J Clin 2004;54:131-14
PROPORTION SURVIVING
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
SURVIVAL (years)
Skin, subcutaneous tissue, or distant lymph nodes(179)
Lung(186)
Visceral sites
excluding
lung(793)

Adjuvant High-Dose- Interferon Treatment in Melanoma

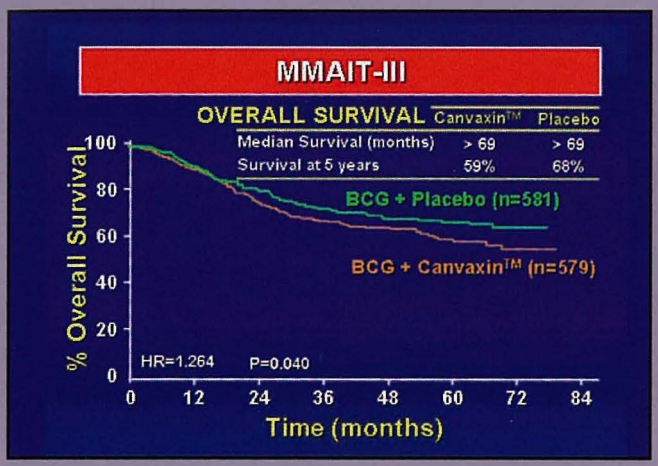
Peter Mohr
Elbekliniken Buxtehude, Germany

AJCC-Classification 2002

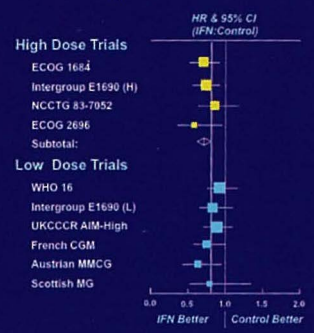
Stage	TNM	Thick-ness	Ulcer.	Number LN-Met	5-Year-Survival
I A	TIaN/M0	< 1,0mm	No	-	95 %
I B	TIbN/M0 T2aN/Mo	< 1,0mm 1-2 mm	yes No	-	ca. 91 %
II A	T2bN/M0 T3aN/M0	1-2 mm 2-4 mm	yes No	-	ca. 78 %
II B	T3bN/Mo T4aN/M0	2-4 mm > 4 mm	yes No	-	63 % 67 %
II C	T4bN/M0	> 4 mm	Ja	-	45 %
III A III B III C	all T	-	No yes / No yes / No	1-3 sent. LN sent./ clinical LN 1-3 small/ in transit	65 % 51 % 25 %
IV	all T	-	-	all N	2-6 %

Adjuvant Therapy in Malignant Melanom

- Chemotherapy
- Vaccination
- Immunotherapy



Rates of recurrent melanoma: High-dose and low-dose IFN



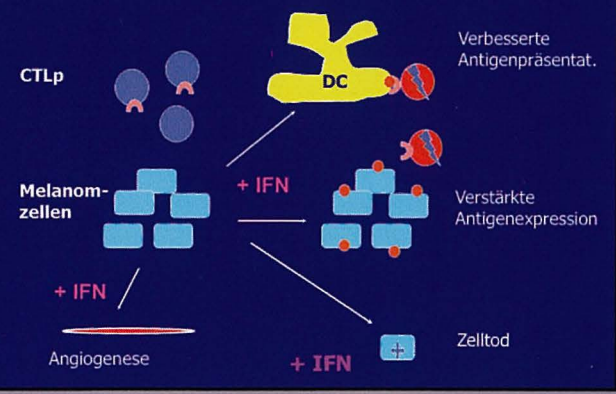
- HDI reduced risk of disease recurrence by 26%, P_2 = 0.00009
- Trend for increased benefit with high dose, P = 0.02

Questions and perspectives regarding adjuvanten interferon therapy

- How does interferon work in melanoma patients
- Is there a diference in stage II and III melanoma regarding activity of IFN
- Dosage, route of application, duration of therapy
- Value of pegylated Interferons
- Can we reduce the toxicity in interferon high-dose therapy (grad III toxicity 60 % to 70%; grad IV toxicity 10 %)
- Guidelines for the management of interferon side effects
- Identification of surrogat parameters

How does Interferon work?

Wirkmechanismus adjuvanter IFNα Therapien



Adjuvant therapy in stage II and III melanoma

- **„no-dose“**
- **„low-dose“**
- **„intermediate-dose“**
- **„high-dose“**
- **„PEG-dose“**

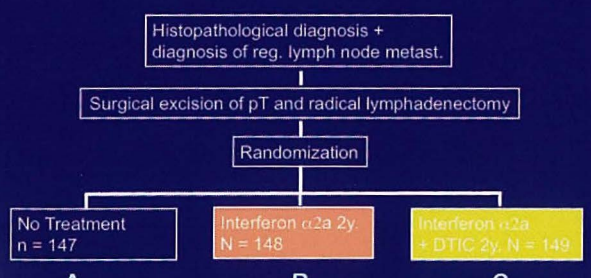
„Low dose“ interferon trials in stage II melanoma

	AJCC stage	Pat. (n)	Therapy schedule	DFS	OS	Follow up
Grob	IIA,B	499	IFN-a2a 3x3 Mill IE s.c. 18 months vs. observation	.035	.059	5 years
Pehamberger	IIA.B	311	IFN-a2a 3x3 Mill IE s.c. 18 months vs. observation	0.02	+	3 years

Low-dose interferon studies stage III malignant melanoma

Collaborating group	AJCC stage	Patients (n)	Therapy and dose	DFS	OS	median follow up
EORTC 18871	IIA,B; III	800	IFN-a2a 1MIU s.c. daily over 2 years vs. g-IFN 0.2 mg daily vs. observation	–	–	7 years
Cascinelli	III	444	IFN-a2a 3MIU s.c. over 2 years vs. observation	–	–	3 years
Scotisch	II, III	95	IFN-a2a 3MIU s.c. over 2 years vs. observation	–	–	2 years
ECOG 1690	IIB, III	642	HDI vs. IFN-a2b 3 MIU s.c. over 2 years vs. observation	–	–	3 years
DeCOG	III	470	-IFN-α2a 3 MIU s.c 2 years + DTIC: 850 mg/m² i.v. 2 years -IFN-α2a 3 MIU s.c 2 years vs. -observation	– +	– +	4 years
UK-MCG	III	654	IFN 3 MIU s.c. 2 years vs. observation	–	–	3 years

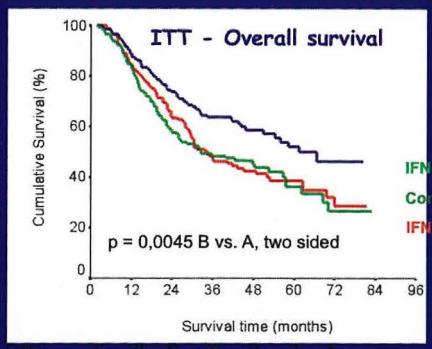
ADO-ADJ1



Interferon alpha 2a 3 MIU SC 3x/wk x 24 mo vs.
Interferon alpha 2a 3 MIU SC 3x/wk + DTIC 850 mg/m² x 24 mo

Peter Mohr

Adjuvant High-Dose Interferon treatment in melanoma



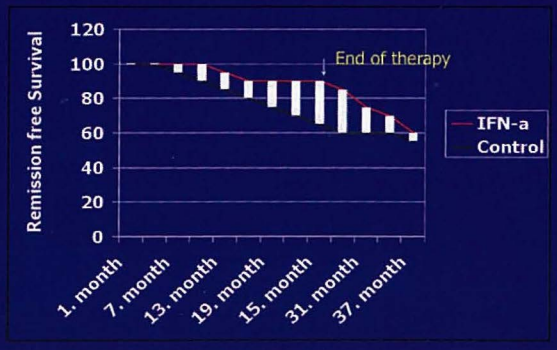
AIM HIGH Study

674 pat. stage III melanoma: IFNα 3 MU 3 x week s.c. , 2 years vs. Observation

	odds ratio	95% CI	p-Value
RFS IFNα	0.91	0.75 – 1.1	0.3
OS IFNα	0.94	0.75 – 1.18	0.6

J Clin Oncol. 2004 1;vol 22 :53-61

Survival curves of adjuvant „low-dose" interferon therapy

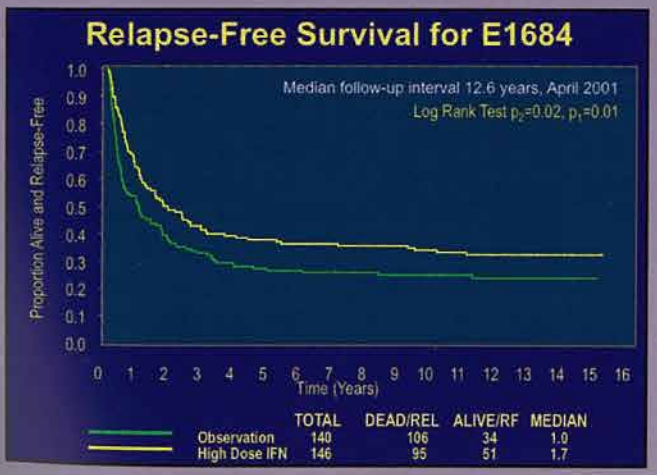


Interferon "high dose" in stage III melanoma

	Rezidivfreies Überleben	gesamt Überleben
ECOG 1684	P = 0.004	P=0.04
ECOG 1690	P=0.054	P=0.995
ECOG 1694	P=0.0007	P=0.035

Overall Survival for E1684

Relapse-Free Survival for E1684



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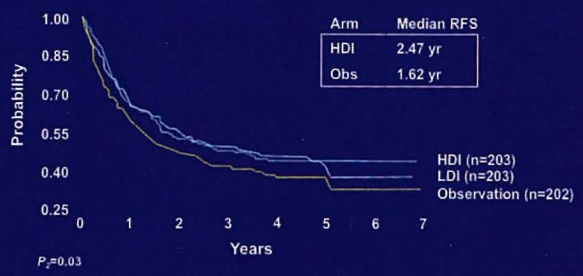
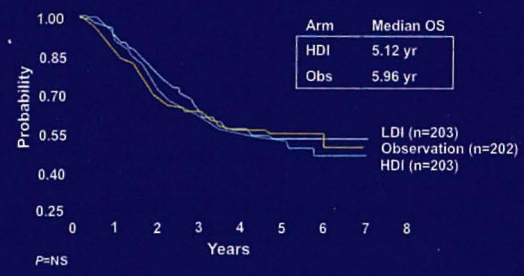
Adjuvant High-Dose Interferon treatment in melanoma

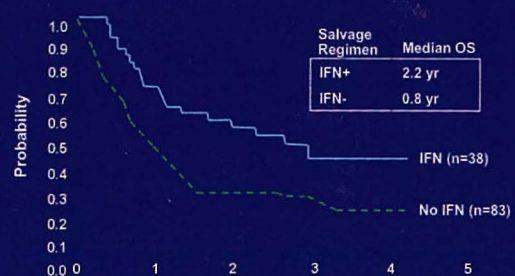
E1690: Relapse-Free Survival by Treatment Group



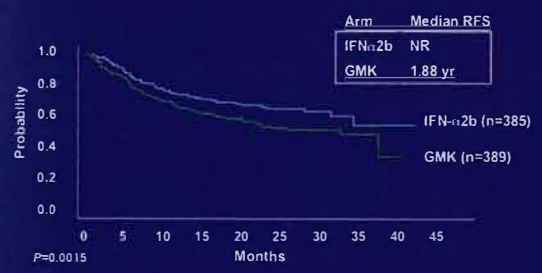
E1690: Overall Survival by Treatment Group



E1690: Post-Relapse Survival Observation Group

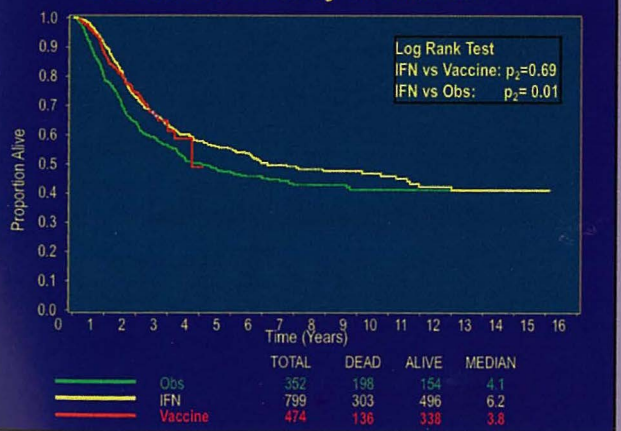


E1694: Relapse-Free Survival by Treatment Group



E1694: Overall Survival by Treatment Group

Overall Survival by Treatment



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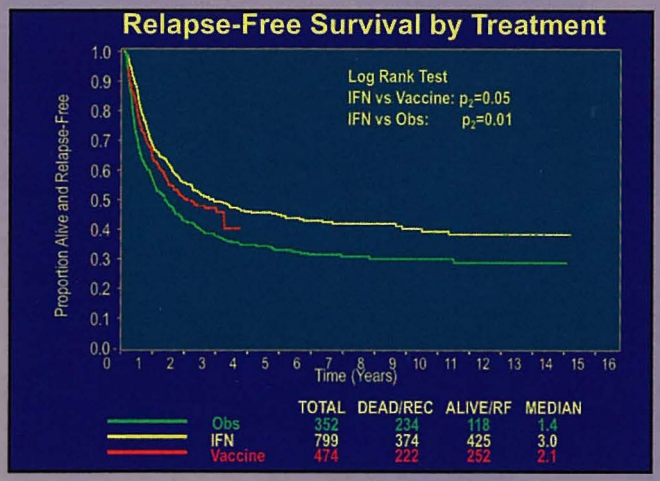
Adjuvant High-Dose Interferon treatment in melanoma

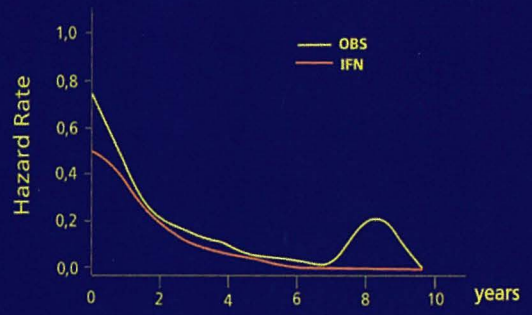


Risk of death: High-dose IFN

- HDI reduced risk of death by 15%, $P_2 = 0.06$

Does the route of application play a role in interferon high-dose therapy? (s.c. versus i.v.)

The hazard analysis of the high dose therapy shows a positive effect within the first 3 months



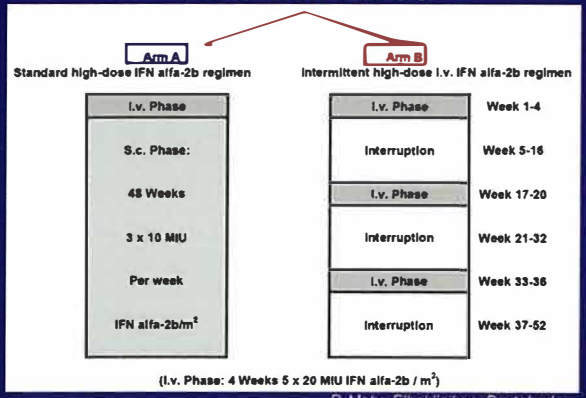
ECOG 1697 in stage IIb, IIc, IIIa melanoma

- IFN-α2α: (Induktion ECOG 1684) 20 Mill I.E./m² 5x/w i.v. 4w versus
- Observation

coordinator: ECOG / USA

pat. (n): 1420

ADO MM-ADJ5



P. Mohr, Elbekliniken, Buxtehude

Phase II Study: Intermittent high-dose interferon of RFS and OS after 2 years

RFS / OS at 2 years	ECOG 1684 (142)	ECOG 1690 (212)	ECOG 1694 (394)	IFN i.v. phase II (46) median follow up 25 months
RFS	46 %	52 %	63 %	66 %
OS	65 %	72 %	77 %	77 %

Interim Analysis of Randomized High-Dose Interferon Trial; DeCOG MM-ADJ-5, Endpoints

- Primary endpoint: distant metastasis free survival (DMFI)
- Secondary endpoints:
  overall survival (OS)
  relapse free survival (RFS)
  toxicity
  qu
- Correlation of Mx-protein expression with efficacy, and side effects

Interim Analysis High-Dose Interferon DeCOG MM-ADJ-5

377 evaluable patients

	Arm A (standard HDI)	Arm B (pulsed HDI)	fe
male	107	108	
Age (mean) [years]	57.8	54.2	
All stages	**185**	**192**	
stage IIIA	**50 (27.0 %)**	**56 (29.2 %)**	
stage IIIB	**80 (43.4 %)**	**87 (45.3 %)**	
stage IIIC	**55 (29.7 %)**	**49 (25.5 %)**	

Interim-Analysis High-Dose Interferon DeCOG MM-ADJ-5

Early Termination

	Arm A (standard HDI)	Arm B (pulsed HDI)
Neutropenia	1 (0.5%)	0
Liver function	3 (1.6%)	3 (1.6%)
CK-elevation	0	2 (1.0%)
Fatigue/ Depression	17 (9.2%)	5 (2.6%)**
Other	27 (14.6%)	14 (7.3%)*

Interim Analysis High-Dose Interferon DeCOG MM-ADJ-5

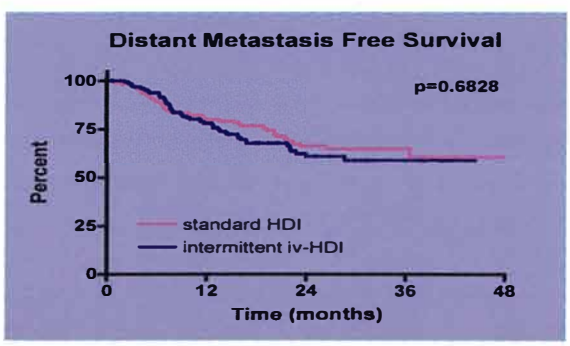
Relapse free survival

Arm A: 67 patients	Arm B: 66 patients	
68.1 %	67.7 %	(p=0.75)

Median follow up:

72 weeks	67 weeks

Interim Analysis High-Dose Interferon DeCOG MM-ADJ-5



Peter Mohr

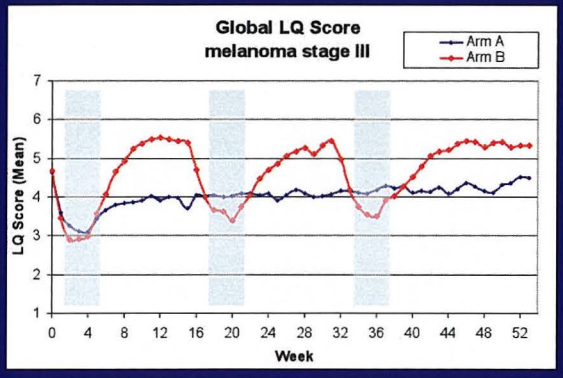
Adjuvant High-Dose Interferon treatment in melanoma

Interim Analysis High-Dose Interferon DeCOG MM-ADJ-5

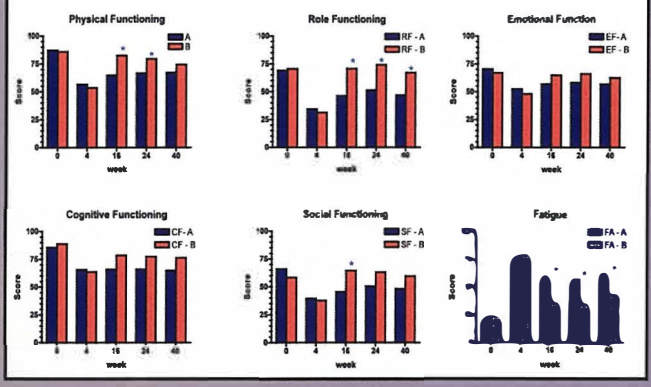
Treatment discontinuation

Treatment discontinuation due to adverse events or impact on quality of life:

Arm A (standard)	Arm B (pulsed)	
48 (20.5 %)	24 (12.5 %)	(p = 0.01)



EORTC QLQ-C30 dimensions



Conclusion, Interim Analysis High-Dose Interferon, DeCOG MM-ADJ-5

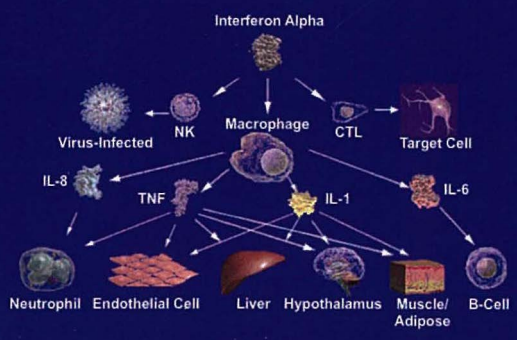
- Toxicity: Less depression / fatigue in the pulsed i.v. arm
- No cumulative toxicity in the pulsed i.v. arm
- Less treatment discontinuation in the pulsed i.v. arm
  12.5 % vs. 20.5 % (p = 0.01)
- No significant difference in DMFS, OS and RFS in 377 pat. after 101 events and follow up of 1.4 years
- A statement in regards of equivalence of both regimens can not be made yet

Interferon: Adverse Events

Profile of Toxicities

www.thebody.com/ pw/images/interferon.gif

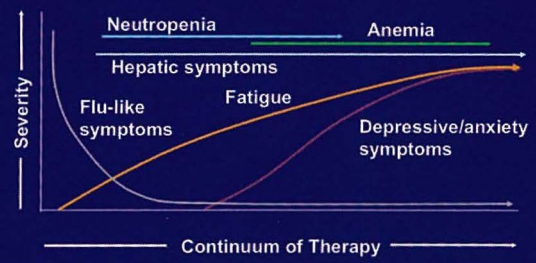
The Interferon Cascade



General Requirements of Side Effects and Adverse Events

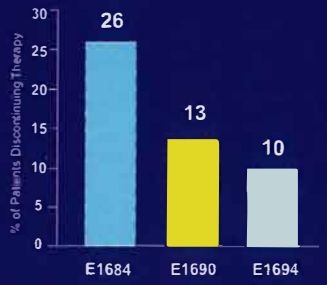
- Dose dependent of the single dose
- Dependent on rout of aplication
- Dependent on cumulative dose
- Dependent on duration of therapy
- Side effects can occur independent of dose- and application

Suggested Course of Selected Interferon alfa for Injection Side Effects*

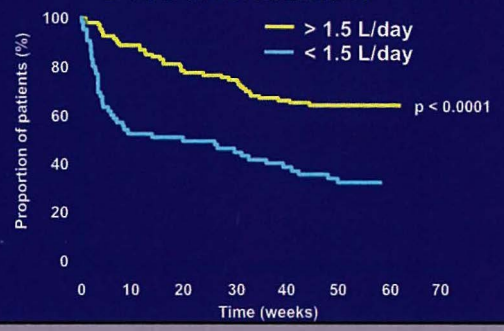


Discontinuation due to Adverse Events in High-dose IFN α-2b Clinical Trials

- With appropriate management, including dose modifications, the majority of patients tolerated a full course of therapy (ie, 52 weeks or until



Fluid Intake > 1.5 L/day Prevents Early and Late Discontinuation



Neuro-Psychiatric Symptoms

- Irritability
- Cognitive disorders
- Disturbed sleep
- Depression
- Fear disorders
- Fatique-syndrome

Psychiatric Side Effects

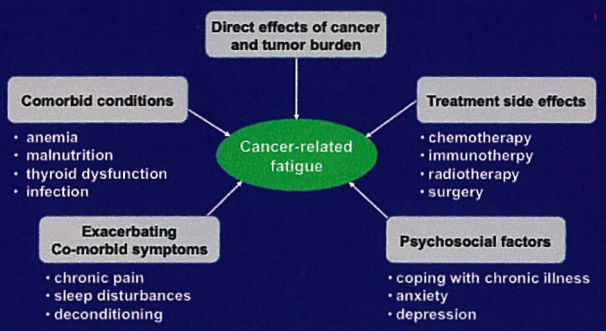
- 13 - 23% of all IFNα-treated patients
- Depression light : 56%
- medium : 19%
- serious : 25%
- suicidale syndrome 6% of patients
- Cave : „personality disorders“

Schaefer et al, Prog Neuro Psychopharmacol 26: 731 (2002)

Managing Depression

- Prophylactic treatment?
- Dubble-blind-study : 20 + 20 patients
- (high-dose IFN α2b-therapy)
- Paroxetin (Seroxat®, Tagonis®) vs. placebo
- serious depression : 11 % vs. 45%
- Discontinuation of IFN : 5 % vs. 35%

Cancer-Related Fatigue Is Multifactorial



Wagner, Cella. *Br J Cancer.* 2004;91:822–828

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JOURNAL OF CLINICAL ONCOLOGY Vol. 20 No. 17 September 2002

Printed in U.S.A.

REVIEW ARTICLE

Mechanisms and Management of Toxicities Associated With High-Dose Interferon Alfa-2b Therapy

By John M. Kirkwood, Catherine Bender, Sanjiv Agarwala, Ahmad Tarhini, Janice Shipe-Spotloe, Barbara Smelko, Sandra Donnelly, and Lori Slover

With appropriate monitoring, dose modifications, and aggressive supportive care, HDI can be

ROLE OF RADIOTHERAPY IN MELANOMA MANAGEMENT

Primož Strojan

Department of Radiation Oncology
Institute of Oncology Ljubljana

- INTRODUCTION
- RADIOBILOGY
  - FRACTINATION PATTERN
  - XRT DOSE
- INDICATIONS
- TECHNIQUE
- CONCLUSIONS

INTRODUCTION

FIRST EXPERIENCES:

- Primitive irradiation devices
- Lack of knowledge on radiobiological characteristics
- Advanced tumors

XRT = ineffective → palliation

INTRODUCTION

XRT TODAY:

- **Most effective non-surgical mode of therapy**
- **Locoregional treatment**

➡ **ITEGRAL PART OF MULTIDISCIPLINARY MANAGEMENT OF PATIENTS WITH MELANOMA**

INTRODUCTION

70s – INTEREST FOR XRT RENEWED:

- **Modern (MV) radiotherapy devices and computer based systems for radiotherapy treatment planning**
- **Knowledge on radiobiology principles escalated**
- **Accumulation of clinical experiences**

RADIOBIOLOGY

- **Tumor volume – response to XRT** ***(YES)***
- **Variability in intrinsic radiosensitivity to XRT** ***(YES)***
- **XRT dose – response** ***(YES)***

Primož Strojan

Role of radiotherapy in melanoma management

RADIOBIOLOGY
TUMOR VOLUME *vs.* RESPONSE

TABLE V

Relationship between mean tumour diameter and frequency complete response in tumours treated with an ETO dose between 106 and 122 Gy.

Mean diameter (cm)	Complete response/ no. of tumours
< 1.0	6/7 (86%)*
1.0–2.9	32/41(78%)
3.0–4.9	7/15(47%)
5.0–9.9	3/10(30%)
≥ 10.0	0/4 (0%)

* Statistically significant related to tumour size ($p < 0.001$).

Overgaard et al. Radiother Oncol 1986; 5: 183-92

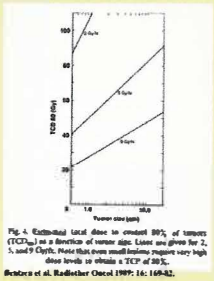
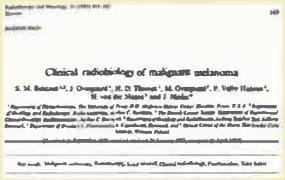


Fig. 4. Estimated total dose to control 80% of tumors (TCP_{80}) as a function of tumor size. Lines are given for 2, 3, and 9 Gy/fr. Note that even small fractions require very high dose levels to obtain a TCP of 80%.

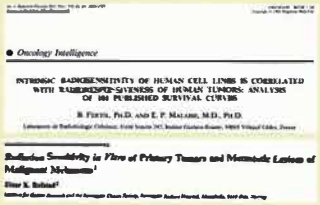
Benčina et al. Radiother Oncol 1989; 16: 169-82.

RADIOBIOLOGY
INTRINSIC RADIOSENSITIVITY

- **Low α/β-ratio (but wide 95% CI → large variations in radiosensitivity)**
- **Role of glutathione, immunological response, issue oxygenation?**



Clinical radiobiology of malignant melanoma

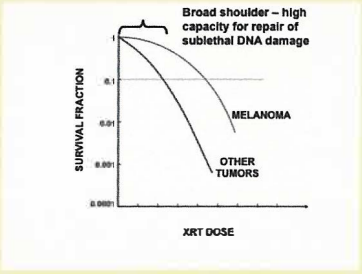


Oncology Intelligence

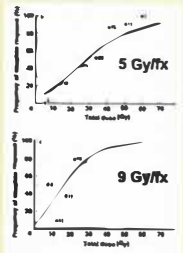
INTRINSIC RADIOSENSITIVITY OF HUMAN CELL LINES IS CORRELATED WITH RADIORESPONSIVENESS OF HUMAN TUMORS: ANALYSIS OF 101 PUBLISHED SURVIVAL CURVES

B. FIETTE, PH.D. AND E. P. MALAISE, M.D., PH.D.

RADIOBIOLOGY
INTRINSIC RADIOSENSITIVITY



RADIOBIOLOGY
TUMOR DOSE *VS.* RESPONSE



Overgaard et al. Radiother Oncol 1986; 5: 183-92.

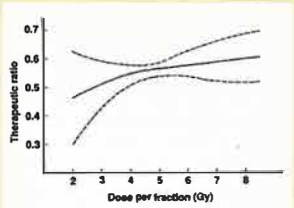


Fig. 8. Estimated therapeutic ratio as a function of fraction size (full line). The therapeutic ratio is the quotient between the (predicted) isoeffect dose for 50% probability of severe subcutaneous fibrosis and for 80% probability of complete tumor response. Stippled lines are the 95% confidence limits calculated by standard propagation of error techniques.

Peters et al. Radiother Oncol 1989; 14: 169-82.

RADIOBIOLOGY
FRACTIONATION PATTERN

	RESPONSE TO XRT	
	<4Gy/odmerek	≥4 Gy/fx
Halbermalz, 1976	21%	92%
Overgaard, 1980	35%	81%
Harwood, 1981	25%	71%
Katz, 1981	27%	72%
Strauss, 1981	46%	81%
Doss, 1982	39%	67%
Overgaard, 1986	42%	86%
TOTAL	64/176 (36%)	254/309 (82%)
Bone metastases	73%	84%
Skin & lymph node metastases	49%	75%
Brain metastases	38%	50%
TOTAL	[illegible]	483/636 (75%)

Modified from Rallo MT, Ang KK. Surg Clin North Am 1995; 75: 333-42.
Trodd A, Peters LJ. Ann Plast Surg 1992; 28: 39-44.

RADIOBIOLOGY
FRACTIONATION PATTERN

Are high doses/fx really advantageous???

- **1 randomized trial only: RTOG Trial 83-05**
  (Sause et al. Int J Radiat Oncol Biol Phys 1991; 20: 429-32)
  - **XRT regimens (126 pts): 50 Gy/25 fx vs. 32 Gy/8 fx**
  - **no difference in response rate (CR+PR = 60%)**
  - **no data on duration of response**
- **Retro/prospective studies (on postoperative XRT):**

STUDY	TU SITE	NO OF PTS	D/FX	RR
Corry, 1999	all	42	2 Gy	10%
Burmeister, 2006	all	234	2.4 Gy	6.8%
Chang, 2006	all	14 41	1.71-2 Gy 6 Gy	12%, no difference between the two groups

INDICATIONS FOR XRT

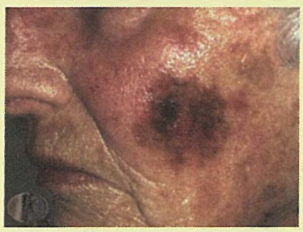
1) XRT AS PRIMARY TREATMENT
2) ADJUVANT/POSTOPERATIVE XRT
3) XRT AS A PART OF PALLIATIVE TREATMENT

INDICATIONS
XRT AS PRIMARY TREATMENT

RARELY:

- extensive facial *lentigo maligna* melanoma
- primary *mucosal* melanoma
- patients in poor general condition
- patients who refused proposed surgery

LENTIGO MALIGNA MELANOMA

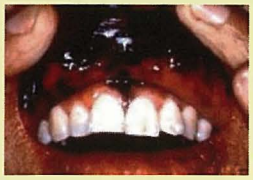


Harwood AR. Int J Radiat Oncol Biol Phys 1983; 9: 1019-21.
Schmid-WendtnerMH et al. J Am Acad Dermatol 2000; 43: 477-82.
Farshad A et al. Br J Dermatol 2002; 146: 1042-6.

XRT OF LMM IS EFFECTIVE MODE OF TREATMENT WITH CURATIVE POTENTIAL

ALTERNATIVE TO SURGERY WHEN IT WOULD CAUSE IMPORTANT FUNCTIONAL AND/OR COSMETIC IMPAIRMENT

MUCOSAL MELANOMA



Treatment of choice: SURGERY
→ LRR ≈50%

XRT:
- **seems to improve LC (particularly after nonradical resection ± - large primaries - perineural invasion - nasal cavity/paranasal sinuses primaries**
- **most effective treatment for unresectable disease**
- **role of elective nodal XRT = ?**
- **no influence on survival**

Ballo M, Ang KK. Surg Clin N Am 2003: 323-42.
Mendenhall WM et al. Am J Clin Oncol 2005; 58: 626-30.
Kreagli M et al. Crit Rev Oncol Hematol 2008; 65: 121-8.

INDICATIONS FOR XRT
ADJUVANT/POSTOPERATIVE XRT

After surgery of primary tumor:
high risk for local recurrence after surgery alone

- **close/positive resection margins**
  (re-operation not possible)
- **early local recurrence**
- **multiple recurrent tumors**
- **H&N *desmoplastic* primaries**
  (when adequate surgical margins could not be achieved)
- **H&N *mucosal* melanoma**

INDICATIONS
ADJUVANT/POSTOPERATIVE XRT

After surgery of regional lymphatic metastases

- **Nonradical surgery**
- **Extracapsular tumor extension**
- **Diameter of involved node ≥3 cm**
- **Multiple nodal involvement**

} **RR ≤50%**

Nodal basin recurrence rate: H&N >> axilla > groins

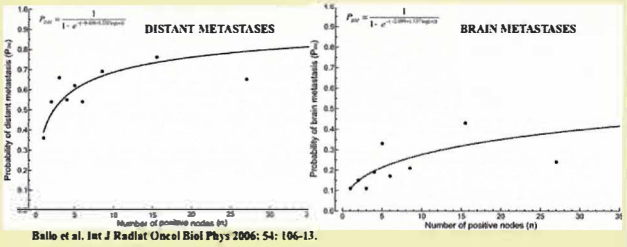
Lee RJ et al. Int J Radiat Oncol Biol Phys 2000; 46: 467-74.

INDICATIONS
ADJUVANT/POSTOPERATIVE XRT

	SURGERY	SURGERY + XRT	
27%	HEAD & NECK mets Browsher (1986), 33% Byers (1986), 50% Singletary (1986), 15% Calabro (1989), 15% O'Brien (1992), 28% O'Brien (1997), 19% Shen (2000), 14%	Ang (1997), 5% O'Brien (1997), 7% Davis (2001), 14% Ballo (2003), 5%	≅10%
19%	AXILLARY mets Browsher (1986), 13% Calabro (1989), 15%	Davis (2001), 8% Ballo (2002), 10%	
19%	INGUINAL mets Browsher (1986), 9% Calabro (1989), 17%	Davis (2001), 6% Ballo (2004), 5%	
	ALL SITES Karakousis (1980), 49% Monsour (1992), 52% Lee (2000), 36%	Corry (1999), 10% Stevens (2000), 11% Ballo (2006), 9% Burmeister (2006), 7%	

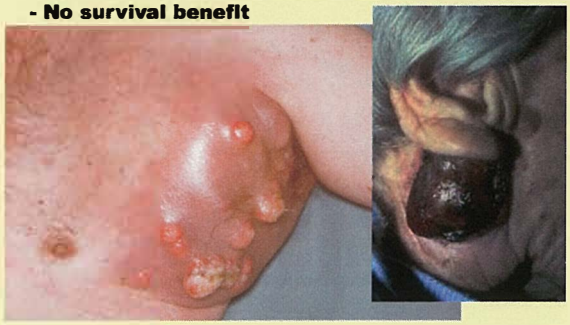
Fife K, Thompson JF.
Lancet Oncol 2001;2: 614-21.

WHEN to irradiate?



Ballo et al. Int J Radiat Oncol Biol Phys 2006; 54: 106-13.

- 50-60% pts will develop distant metastases
- No survival benefit



INDICATIONS
ADJUVANT/POSTOPERATIVE XRT

TREATMENT OF RESIDUAL MICROSCOPIC DISEASE:

- **After SNB_+**
  - **when surgery is not an option because of patient condition**

  (Bonnen et al. Cancer 2004; Ballo et al. Head Neck 2005)
- **After technically unappropriate surgery (excision of clinically apparent nodal disease)**

  → **additional, more extensive surgical procedure is needed which is not feasible or is refused by the patient**

  (Ballo et al. Head Neck 2005)

INDICATIONS
XRT AS A PART OF PALLIATIVE TREATMENT

WHEN?

- **surgery:**
  - **not possible** (inoperable metastases, poor general condition)
  - **ineffective** (multiple mets, multiorgan mets)

WHAT?

- **all sites of mets** (cutaneous, lymphatic, bone, visceral...)

WHY?

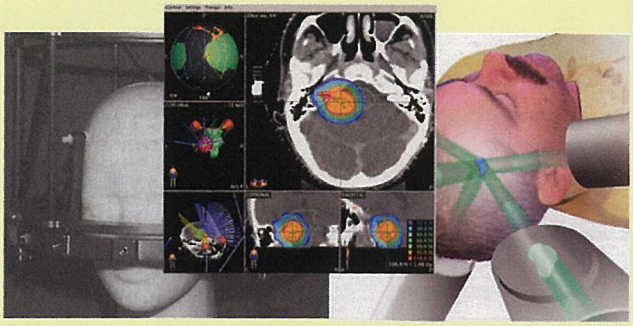
→ **to decrease disease related signs & symptoms**

INDICATIONS FOR XRT
ADJUVANT/POSTOPERATIVE XRT

- **CUTANEOUS – LYMPHATIC METASTASES**
  - **≤1 cm → >85% CR** Overgaard J et al. R&O 1986;5:183-92. Bentzen SM et al. R&O 1989;16:169-82.
  - **>5 cm → <30% CR**
- **BRAIN METASTASES**
  - **multiple: whole brain XRT + corticosteroids** Urist M et al. Cancer 1993;51:2151-6.
    - → **prolongation of median survival for 1-2 mos**
    - → **measurable ↑ of performance status in 60-70% pts**
  - **1-3 mets, 2r <3 cm: stereotactic RS + whole brain XRT**
    - → **local control - 90%**
    - → **prevailing cause of death: mets outside of CNS**
    - → **sporadic long lasting survival**

    Gaudy-Marqueste C et al. IJROBP 2006;65:809-16.

STEREOTACTIC RADIOSURGERY



INDICATIONS
ADJUVANT/POSTOPERATIVE XRT

- **BONE METASTASES**
  - pain relief in 60% Chow E et al. J Clin Oncol 2007;25:1423-36.
  - postoperative XRT (after surgical fixation of fractured bone)
- **METASTASES CAUSING CORD COMPRESSION**
  - solely XRT + corticosteroids
  - postoperative XRT (after laminectomy)
    - → delay local tumor regrowth
    - → prolongation of symptoms free interval

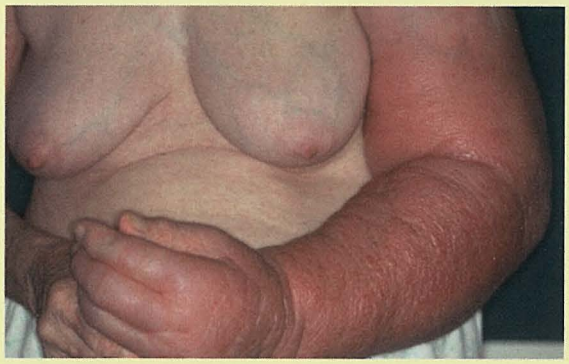
XRT TECHNIQUE

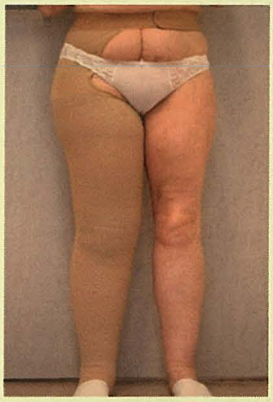
- telecobalt / linear accelerator / RTG photons / electrons
- XRT regimens:

A/ CURATIVE INTENT
- 6 Gy/fx → TD=30-36 Gy
- ↑ risk for development of edema, 2.5 Gy/fx → → TD=45-50 Gy

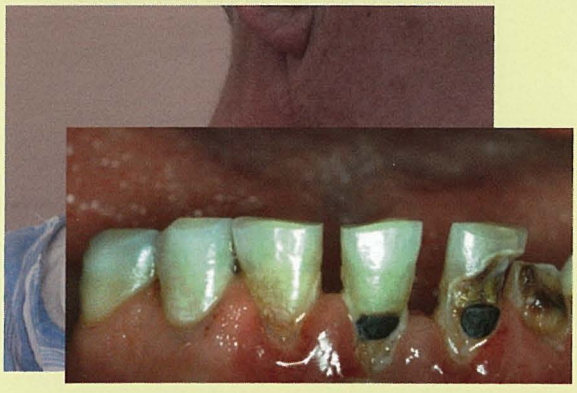
B/ PALLIATIVE INTENT
- higher daily fx, 4-10 Gy
- lower overall TD (10x3 Gy, 5x4 Gy, 2x6Gy)

→ **XRT REGIMEN ADAPTED TO:**
- PATIENT
- CLINICAL SITUATION





Author	Site/fx	Symptomatic lymphedema
Stevens, 2000	Axilla, 6 Gy/fx	58%
Ballo, 2002	Axilla, 6 Gy/fx	16%
Ballo, 2004	Groin, 6 Gy/fx	25%
Brumeister, 2006 (prospective)	Axilla & groin, 2.4 Gy/fx	9% 19%



CONCLUSIONS

1) **SURGERY**
2) **Nonradical surgery and/or adverse prognostic factors → ADJUVANT therapy**
3) **XRT = effective (curative, palliative) & safe**

INDISPENSABLE PART OF
MULTIDISCIPLINARY MANAGEMENT
OF MELANOMA PATIENTS

Treatment Options for Metastatic Melanoma

Janja Ocvirk

Sites of Metastatic Disease

- Skin, subcutaneous tissue, lymph nodes account for 50% of metastatic disease
- Lung 18-36%
- Liver, brain, bone

Distant Metastases at Autopsy

Lung	70-87%
Liver	54-77%
Bowel	26-58%
Brain	36-54%
Heart	40-45%
Adrenals	36-54%
Kidney	35-48%
Bone	23-49%

Janja Ocvirk

Treatment options of metastatic melanoma

TNM Criteria

- Sites and elevated status of serum LDH define 3 categories of M
  - M1a metastasis to skin, subcutaneous tissue or distant lymph nodes
  - M1b metastasis to lung
  - M1c all other visceral organs, elevated LDH regardless of the site of disease
- 1 year survival rates range from 40-60%

Predictors of Survival

- Most important predictors of poor survival in patients with distant metastases:
  - site of metastatic disease
  - elevated LDH
- Sites:
  - skin, subcutaneous tissue, or distant lymph nodes have relatively better prognosis;
  - lung has better prognosis than other visceral sites.

LDH

- Elevated LDH was an independent predictive factor for survival.
- Predictive value is independent of the site of disease.
- If LDH is elevated, the test should be repeated after more than 24 hours as hemolysis or other factors may contribute to false positive values.

Available Therapy

- Stage IV disease continues to comprise an ominous prognosis
- Approaches to treatment have included
  - chemotherapy
  - biotherapy
  - immune adjuvants
  - cancer-specific vaccines
  - cytokines
  - monoclonal antibodies
  - isolated limb perfusion

Single Agent Therapy

Drug	RR
O^6- alkilators	9 – 16 %
Platinum	0 – 15 %
Vinca alkaloids	12 – 26 %
Taxanes	13 – 16%

Single Agent Therapy

Dacarbazine

- is the only FDA and EMEA approved therapy for metastatic melanoma
- RR 8-16%
- TTP 4-6 months
- No statistical survival benefit vs. BSC

Temozolomide

- two randomized phase III studies of Temozolomide vs. Dacarbazine in advanced metastatic melanoma
  - 305 patients - patients with brain metastases excluded
  - oral TMZ 200mg/m^2/day for 5 days every 28 days or IV DTIC 250mg/m^2/day for 5 days every 21 days
  - median PFS 1.9 months in TMZ group vs. 1.5 months in DTIC
  - TMZ demonstrated efficacy equal to DTIC
  - median survival 7.7 months in TMZ group, 6.4 months in DTIC p

Middleton. JCO 18(1), 2000.158-166

- 895 pts
- oral TMZ 150mg/m^2/day for 7 days every 14 days or IV DTIC 1000mg/m^2/day for 1 day every 21 days
- median PFS 2.3 months in TMZ group vs. 1.7 months in DTIC
- CR/PR 14% in TMZ group vs. 10% in DTIC

Patel. Ann Oncol 2008, Abs LBA8

IL-2

- High-dose IL-2 indicated in metastatic melanoma
- 600,00-720,000 units/kg every 8 hours for 14 doses
- Overall response rate 18%, complete response 5% with some durable responses
- Extremely toxic

Polychemotherapy

- BHD: BCNU, hidroxyurea, DTIC
- CVD: Cisplatin, Vinblastine, DTIC
- BOLD: Bleomycin, Vineristine, CCNU, DTIC
- DBCT: DTIC, BCNU, Cisplatin, Tamoxifen

Costanzi 1982, Buzaid 1993, Middelton1988, Chapman 2000

Therapy	N	RR	OS
BHD/DTIC	386	29/18	6.2/6.7
CVD/DTIC	104	24/11	6.0/4.7
DBCT/DTIC+Ifn	103	26/17	6.6/6.5
DBCT/DTIC	240	19/10	
7.7/6.3			

Costanzi 1982, Buzaid 1993, Middelton1988, Chapman 2000

Therapeutic Targets in Metastatic Melanoma

- Signaling pathways
- Gene regulation
- Apoptosis
- Angiogenesis
- Immunomodulation

Oblimersen (Bcl2 antisense)

Oblimersen + DTIC vs. DTIC (phase III- 771 pts)

	Oblimersen+DTIC	DTIC	
Med. Survival	9.0 mo	7.8 mo	p=.077
Med. PFS	2.6 mo	1.6 mo	p<.001
OR	13.5%	7.5%	p=.007
CR	2.8%	0.8%	
Durable res.	7.3 mo	3.6 mo	p=.03

Sig. Increase survival in pts with normal baseline serum LDH (med.OS 11.4 vs. 9.7mo, p=.02)

Bedikian, JCO 2008

Sorafenib

Phase III study sorafenib+carboplatin+paclitaxel vs. carboplatin+paclitaxel+placebo

Med PFS 17.4 weeks vs. 17.9 (HR 0.906, p=.492)

Phase II: sorafenib+DTIC vs. DTIC

Med PFS	21.1 w	11.7 w	HR 0.66
TTP	21.1w	11.7 w	HR 0.619
Mes OS	51.3 w	45.6 w	HR 1.022

Tremelimumab (CTLA4 Mob)

Phase III: tremelimumab vs. DTIC or TMZ (655 pts)

No	328	324	
Med OS	11.8 mo	10.7 mo	HR=1.04

Ribas, JCO 2008 Abs LBA9011

Ipilimumab (CTLA4 Mob)

Phase II: ipilimumab vs. ipilimumab+ DTIC

CR	0%	6%
PR	9%	17%
SD	11%	11%
OS	11.2 mo	14.8 mo
PFS	2.7 mo	3.3 mo

Fischkoff. ASCO 2005. ABS 7525

Phase III study: DTIC vs. DTIC + ipilimumab – ongoing EORTC 18071

Elescomol (HS protein)

STA-4783 + paclitaxel vs. paclitaxel

Med PFS	3.68 mo	1.84 mo	p=.035
RR	15.1%	3.6%	

O'Day 2007

Axitinib (VEGFR inhibitor)

Phase II study, 32 pts (1 with prior treatment for metastatic melanoma)

ORR	15.6 mo
Med PFS	2.3 mo
Med OS	6.8 mo
Med OS subgr.	13.0 mo dBP>90
	6.2 mo dBP<90

Fruehauf. JCO 2008. Abs 9006

Summary

- Therapy for Stage IV melanoma, while undergoing evaluation, remains sub-optimal and palliative in nature.
- For advanced melanoma, the best therapeutic option remains a clinical trial.

Cutaneous Melanoma – Guidelines

Marko Snoj

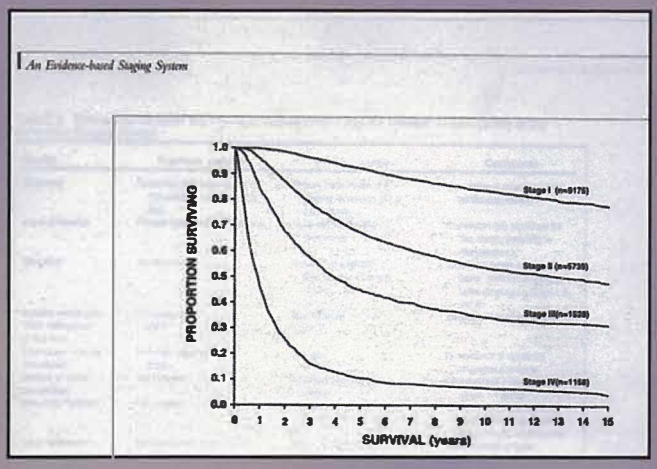
Stage I,II

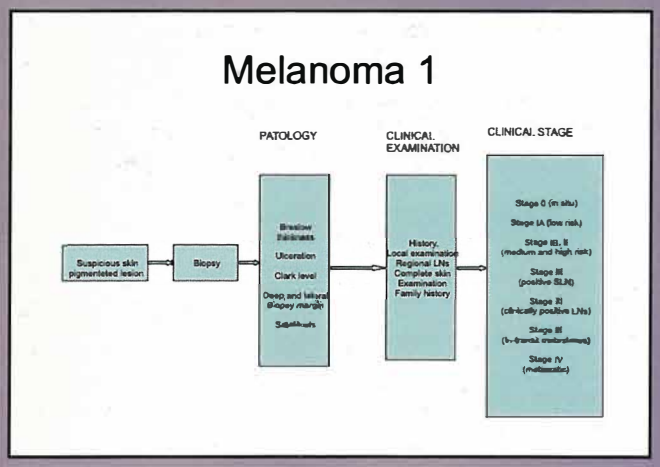
Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0

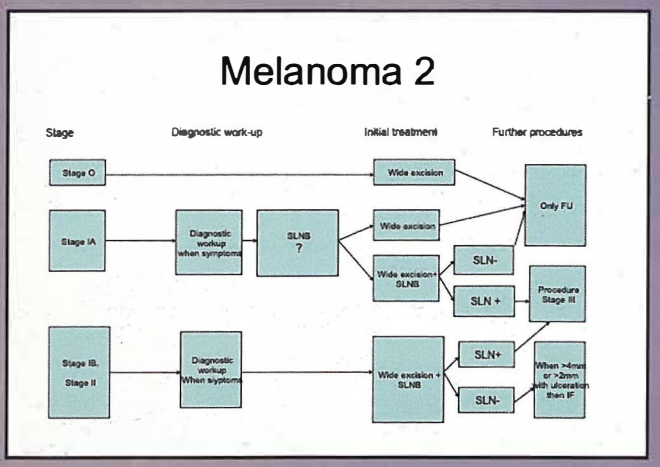
Stage	T	N	M
IIIA	T1-4a	N1a	M0
	T1-4a	N2a	M0
IIIB	T1-4b	N1a	M0
	T1-4b	N2a	M0
	T1-4a	N2b	M0
	T1-4a/b	N2c	M0
IIIC	T1-4b	N1b	M0
	T1-4b	N2b	M0
	T1-4	N3	M0
IV	T1-4	N1-3	M1a-c

Marko Snoj

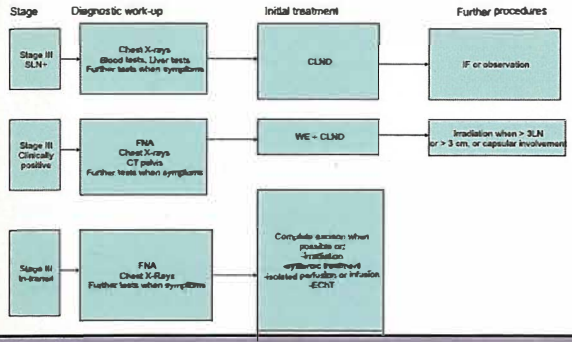
Practice guidelines in melanoma



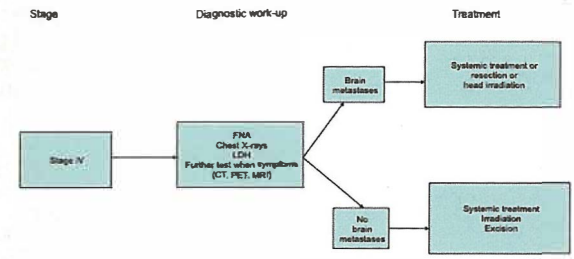




Melanoma 3



Melanoma 4



INTRON® A IMA PREDNOST PRI ZDRAVLJENJU MELANOMA

Intron A 18 milijonov i.e., raztopina za injiciranje, večodmerni peresnik Intron A 30 milijonov i.e., raztopina za injiciranje, večodmerni peresnik Intron A 60 milijonov i.e., raztopina za injiciranje, večodmerni peresnik Kakovostna in količinska sestava Vsak vložek zdravila Intron A raztopina 18 MIE za injiciranje, večodmerni peresnik, vsebuje 15 milijonov i.e.\ml (6 odmerkov po 3 milijoni i.e. ali 12 odmerkov po 1,5 milijona i.e. za skupno količino 18 milijonov i.e.) rekombinantnega interferona alfa-2b. Vsak vložek zdravila Intron A raztopina 30 MIE za injiciranje, večodmerni peresnik, vsebuje 25 milijonov i.e.\ml (6 odmerkov po 5 milijonov i.e. ali 12 odmerkov po 2,5 milijona i.e. za skupno količino 30 milijonov i.e.) rekombinantnega interferona alfa-2b. Vsak vložek zdravila Intron A raztopina 60 za injiciranje, večodmerni peresnik, vsebuje 50 milijonov i.e.\ml (6 odmerkov po 10 milijonov i.e. ali 12 odmerkov po 5 milijonov i.e. za skupno količino 60 milijonov i.e.) rekombinantnega interferona alfa-2b. Seznam pomožnih snovi natrijev hidrogenfosfat dihidrat, natrijev dihidrogenfosfat, dinatrijev edetat, natrijev klorid, meta-krezol, polisorbat 80, voda za injekcije q.s. Volumen raztopine, ki jo je mogoče injicirati s peresnikom = 1,2 ml (v peresniku je nekaj več raztopine, da zagotovimo, da iz peresnika injicirani volumen natančno ustreza odmerku Terapevtske indikacije Kronični hepatitis B, Kronični hepatitis C, Dlakastocelična levkemija, Kronična mieloična levkemija, Multipli mielom, Folikularni limfom, Karcinoidni tumor, Maligni melanom. Odmerjanje in način uporabe Večodmerna pakiranja so namenjena le za posamezne bolnike. Zdravljenje mora uvesti zdravnik z izkušnjami iz zdravljenja bolnikove bolezni. Maligni melanom• Za uvedbo terapije dajte bolniku interferon alfa-2b intravensko v odmerku 20 milijonov i.e.\m2 na dan 5 dni na teden v času 4 tednov. Izračunani odmerek interferona alfa-2b dodajte 0,9 % raztopini natrijevega klorida in ga dajte bolniku v 20-minutni infuziji. Za vzdrževalno zdravljenje je priporočeni odmerek 10 milijonov i.e.\m2, dan subkutano 3 dni na teden (vsak drugi dan) v času 48 tednov. Če se med zdravljenjem z interferonom alfa-2b pojavijo hudi neželeni dogodki, še posebej če število granulocitov pade na < 500\mm3 ali če vrednost ALT\AST naraste na > 5-kratno zgornjo mejo normale, začasno prekinite zdravljenje, dokler se neželeni dogodek ne ublaži. Zdravljenje z interferonom alfa-2b ponovno uvedite z le 50 % prejšnjega odmerka. Če je intolerance trdovratna tudi po prilagoditvi odmerka ali če število granulocitov upade na < 250\mm3 ali se vrednost ALT\AST zviša na > 10-kratno zgornjo mejo normale, prekinite terapijo z interferonom alfa-2b. Četudi optimalni (minimalni) odmerek za doseganje polnega kliničnega učinka ni znan, morate bolnike zdraviti s priporočenimi odmerki, opisanim zmanjšanjem odmerka v primeru toksičnosti. Kontraindikacije Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Anamneza hude obstoječe srčnebolezni, npr. nekontrolirano kongestivno srčno popuščanje, nedavni miokardni infarkt, hude aritmije, Huda ledvična ali jetrna insuficienca, vključno z insuficienco, ki nastane kot posledica metastaz, epilepsija in/ali moteno delovanje osrednjega živčevja. Kronični hepatitis z dekompenzirano jetrno cirozo. Kronični hepatitis pri bolnikih, ki se zdravijo ali so se nedavno zdravili z imunosupresivi, razen Kratkotrajne ukinitve kortikosteroidov. Avtoimunski hepatitis ali avtoimunska bolezen v pretekli anamnezi, imunosuprimirani bolniki po transplantaciji. Obstoječa bolezen ščitnice, razen če jo je mogoče nadzirati s konvencionalno terapijo. Otroci in mladostniki> Obstoječa huda duševna bolezen ali huda duševna bolezen v pretekli anamnezi,še posebej huda depresija, samomorilne misli ali poskus samomora. Posebna opozorila in previdnostni ukrepi Za vse bolnike> Redko so med terapijo z zdravilom Intron A opažali akutne preobčutljivostne reakcije na interferon alfa-2b (npr. urtikarijo, angioedem, bronhokonstrikcijo, anafilaktične reakcije). Če se takšna reakcija razvije, prekinite zdravljenje in uvedite ustrezno medikamentozno terapijo. Pri prehodnem izpuščaju ni potrebna prekinitev zdravljenja. Pri zmernih do hudih neželenih pojavih je lahko potrebna prilagoditev režima odmerjanja, v nekaterih primerih pa tudi prekinitev terapije z zdravilom IntronA. Vse bolnike, pri katerih se med zdravljenjem z zdarvilom Intron A pojavijo motnje delovanja jeter, morate natančno spremljati in zdravljenje prekiniti, če se znaki in simptomi slabšajo. Med terapijo z zdravilom Intron A ali do dva dni po prenehanju terapije lahko nastopi hipotenzija, zaradi katere je lahko potrebna podporna terapija. Pri bolnikih na terapiji z zdravilom Intron A morate vzdrževati ustrezno hidracijo, saj so pri nekaterih bolnikih opažali hipotenzijo zaradi izgube tekočine. V tem primeru je lahko potrebno nadomeščanje tekočine. Četudi je zvišana telesna temperatura lahko povezana z gripoznim sindromom, ki je pogost med zdravljenjem z interferonom, morate najprej izključiti druge vzroke za trdovratno zvišanje telesne temperature. Zdravilo Intron A morate uporabljati previdno pri bolnikih z izčrpujočimi boleznimi in motnjami, npr. pri tistih s pljučno boleznijo v anamnezi (npr. kronična obstruktivna pljučna bolezen) ali sladkorna bolezen z nagnjenostjo h ketoacidozi. Previdnost je potrebna tudi pri bolnikih z motnjami koagulacije (npr. tromboflebitisom, pljučno embolijo) ali hudo mielosupresijo. Pri bolnikih, zdravljenih z interferonom alfa, vključno s tistimi, ki so zdravljeni z zdravilom IntronA, so redko opažali pljučne infiltrate, pnevmonitis in pljučnico, ki so občasno vodili celi do smrti bolnika. Etiologija teh motenj ni bila ugotovljena. O teh simptomih so poročali pogosteje pri sočasni uporabi citajskega zeliščnega pripravka shosaikoto in interferona alfa. Pri vseh bolnikih, ki dobijo zvišano telesno temperaturo, kašelj, dispnejo ali kakšne druge simptome dihal, morate opraviti rentgensko slikanje prsnega koša. Če rentgenogram pokaže pljučne infiltrate ali znake motenosti pljučne funkcije, morate bolnika skrbno nadzorovati in po potrebi ukiniti interferon alfa. Četudi so o tem pojavu poročali pogosteje pri bolnikih s kroničnim hepatitisom C, zdravljenih z interferonom alfa, so ga opažali tudi pri tistih z malignimi boleznimi, zdravljenimi z interferonom alfa. Videti je, da pljučni neželeni pojavi minejo ob takojšnji ukinitvi interferona alfa in zdravljenju s kortikosteroidi. V redkih primerih so po zdravljenju z alfa interferoni poročali o očesnih neželenih dogodkih, npr. krvavitvah v mrežnico, bombažu podobnih lisah in zamašitvi mrežnične arterije ali vene. Pri vseh bolnikih je potreben oftalmološki pregled na začetku zdravljenja. Vsi bolniki, ki tožijo o spremembah ostrine vida ali vidnega polja ali ki imajo druge oftalmološke simptome med zdravljenjem z zdravilom IntronA, morajo biti takoj poslani na celoten oftalmološki pregled. Med zdravljenjem z zdravilom Intron A priporočamo redne preglede vida, še posebej pri tistih z boleznimi, ki so lahko povezane z retinopatijo, npr. sladkorna bolezen ali hipertenzija. Pri bolnikih, pri katerih se pojavijo nove oftalmološke motnje ali se obstoječe poslabšajo, premislite o prekinitvi zdravljenja z zdravilom IntronA. Medsebojno delovanje z drugimi zdravili in druge oblike interakcij Narkotike, hipnotike ali sedative morate uporabljati previdno pri sočasni uporabi z zdravilom IntronA. Interakcij med zdravilom Intron A in drugimi zdravili še niso v celoti ovrednotili. Pri sočasni uporabi zdravila Intron A in drugih potencialno mielosupresivnih snovi priporočamo previdnost. Interferoni lahko vplivajo na oksidativne presnovne procese, kar morate upoštevati med sočasno terapijo z zdravili, ki se presnovijo po tej poti, npr. s ksantinskima derivatoma teofilinom in aminofilinom. Nosečnost in dojenje Za interferon alfa-2b ni kliničnih podatkov o vplivih na nosečnost. Vpliv na sposobnost vožnje in upravljanja s stroji Bolnike poučite, da bodo lahko med zdravljenjem z zdravilom Intron A utrujeni, zaspani ali zmedeni, zato je priporočljivo, da se izogibajo vožnji ali delu s stroji. Rok uporabnosti 15 mesecev. Med uporabo je zdravilo kemično in fizikalno stabilno 27 dni pri temperaturi med 2 in 8 oC. Z mikrobiološkega stališča lahko zdravilo po odpiranju shranjujete največ 27 dni pri temperaturi med 2 in 8 oC. Za čas shranjevanja in druge pogoje shranjevanja med uporabo je odgovoren uporabnik. Posebna navodila za shranjevanje Shranjujte v hladilniku (2 °C - 8 °C). Ne zamrzujte. Imetnik dovoljenja za promet SP Europe 73, rue de StalleB-1180 Bruxelles Belgija. Način in režim izdaje zdravila Izdaja zdravila je le na recept. Datum priprave informacije oktober 2008. Popolno informacijo o tem zdravilu dobite na predstavništvu Schering-Plough CE AG, Dunajska 22, 1000 Ljubljana, tel: 01 300 10 70, fax: 01 300 10 80

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