PROGNOSTIC FACTORS IN SOFT TISSUE SARCOMA

Bodil Bjerkehagen MD PhD
Senior consultant, Department of Pathology, Oslo University Hospital
Associated professor, University of Oslo
Norway

Turku/Åbo, May 12th, 2016
Introduction

• Soft tissue sarcomas are rare and a heterogeneous group of tumors accounting for about 1% of adult cancers.
• No major change in the prognosis of non-metastatic soft tissue sarcomas for the last decades except for gastrointestinal stromal tumors (GISTs).

• 10-30% of the patients develop local recurrence and 35-40% develop metastases.
• The roles of adjuvant chemotherapy and radiotherapy on survival are under investigation.

• Studies on STS are difficult to conduct due to overall low incidence and a further split in different subtypes.
• Few prospective randomized studies trials have been conducted.
Survival of sarcoma in Norway 1960-2007

Includes bone and soft tissue sarcoma

No significant change from 1990-99 to 2000-07

Ref.: Bjerkehagen, unpubl. data
GIST Overall survival
Imatinib vs. historic controls
Locally advanced and metastatic GIST

Imatinib n= 473+473

Historic controls n=86

OBS: Therapy resistance

Prognostic factor - definition

Definition:

- A variable that estimates the risk of an outcome of interest at a specific time.

- Gives information about the expected prognosis.

- Determine diagnostic procedures, treatment and follow-up regimes

End-points

Outcome in studies of prognostic factors
• Local recurrences
• Metastatic relapse
• Death
  • Overall survival
  • Sarcoma-related survival
  • Misclassification of the cause of death
  (Autopsy rate in Norway is 9%)
Prognostic factors

1. Patient-related
2. Tumor-related (focus for the pathologist)
3. Treatment-related
Methodological development in pathology

- 1800: Morphology
- 1860: Morphology, Histochemistry
- 1931: Morphology, Histochemistry, EM
- 1970-tallet: Morphology, Histochemistry, EM, Immunohistochemistry
- 1990-tallet: Morphology, Histochemistry, EM, Immunohistochemistry, Genetics
Important with integrated diagnostics:
In up to 23% of 384 studied cases molecular test allowed diagnostic refinement.
1. Patient-related prognostic factors

• Age at diagnosis
• Gender
• Duration of symptoms
• Co-morbidity

• Patient-related factors may limit treatment for patients otherwise candidate for a certain therapy
Duration of symptoms: Impact of on local recurrences and disease-specific mortality

Table 2. Distribution of non-metastatic soft tissue sarcomas in the extremities and trunk wall according to histological types in adult patients treated at the Aarhus Sarcoma Center from 1979 to 2008 (n = 922)

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFH</td>
<td>280</td>
<td>30</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>185</td>
<td>20</td>
</tr>
<tr>
<td>WD/DD</td>
<td>71</td>
<td>7.8</td>
</tr>
<tr>
<td>MRC</td>
<td>66</td>
<td>7.2</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>46</td>
<td>5.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>164</td>
<td>18</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>65</td>
<td>7.1</td>
</tr>
<tr>
<td>MPNST</td>
<td>61</td>
<td>6.6</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>47</td>
<td>5.1</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>22</td>
<td>2.4</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>18</td>
<td>2.0</td>
</tr>
<tr>
<td>Malignant hemangiopericytoma</td>
<td>11</td>
<td>1.2</td>
</tr>
<tr>
<td>Fibromyxoid sarcoma</td>
<td>8</td>
<td>0.9</td>
</tr>
<tr>
<td>Extraosseous chondrosarcoma</td>
<td>8</td>
<td>0.9</td>
</tr>
<tr>
<td>Spindle cell sarcoma</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Malignant mesenchymoma</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>1.2</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>36</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Classified according to the WHO classification of tumors of soft tissue and bone, 3rd edition, 2002.

a Malignant fibrous histiocytoma (undifferentiated, pleomorphic sarcoma according to the 4th edition, 2013).
b Well-differentiated/dedifferentiated.
c Myxoid round cell tumor.
d Malignant peripheral nerve sheath tumor.

Figure 3. Cumulative incidence rate (solid black line) of local recurrence (panel A) and disease-specific mortality (panel B) with 95% confidence intervals (dotted gray lines).

Figure 4. Adjusted hazard ratios (HR (solid line)) with 95% confidence intervals (dashed lines) for local recurrence (panels A, C, and E) and disease-specific mortality (B, D, and F) according to age, duration of symptoms, and tumor size, based on Cox proportional hazard analyses. Adjustment covariates were selected based on Figure 2 (see Supplementary data); no covariates were included in the analysis of age; duration of symptoms was adjusted for age and grade; tumor size was adjusted for duration of symptoms and grade.

HR- Hazard ratio
Maretty-Nielsen K et al Acta Oncologica 2014
2. Tumor-related prognostic factors

**Macroscopic**
- Anatomical location
- Depth
- Compartmentalization
- Tumor size

**Microscopic**
- Histological subtype
- Vessel infiltration
- Growth pattern
- Atypia/pleomorphism
- Mitotic rate/proliferation
- Tumor necrosis

**Protein expression**

**Genetic findings**
Histological subtypes

- Histological subtypes have different prognosis
- Some sarcomas are per definition high-grade or low-grade malignant tumor
- WHO Classification of soft tissue tumours 2013
  - Benign
  - Intermediate locally aggressive
  - Intermediate rarely metastasizing
  - Metastatic
Histological subtype: Liposarcomas
n=1004

- Well. diff. liposarcoma
- Myxoid liposarcoma
- Liposarcoma all types
- Pleomorphic liposarcoma
- Dediff. liposarcoma

Bjerkehagen B
Anatomical location of the tumor

- Extremities
- Truncus: Upper and lower
- Retroperitoneum
- Intra-abdominal
- Genitalia
- Head & neck

- Location is important for mortality
- Differences between studies can be related to exclusion of different anatomical sites.
Liposarcoma: Survival according to location
Extremities vs. retroperitoneum

Extremities n=542
Includes atypical lipomatous tumors

Retroperitoneum n=127
Liposarcomas

Bjerkehagen, data from the Norwegian Cancer Registry
Depth of the tumor

- Defines the relation of the tumor to the deep fascia
  - Superficial
    - Cutaneous
    - Subcutaneous
  - Deep
    - Deep fascia
    - Intramuscular/intermuscular/extraosseous
    - Bone/periost involvement
    - Retroperitoneal and intra-abdominal

- Deep tumors tend to be larger than superficial tumors

- Dermal leiomyosarcoma (=atypical leiomyomatous tumors) has a good prognosis compared to deeper seated leiomyosarcomas
Tumor size

• Defined as largest diameter of the tumor
  • Determined on unfixed or fixed pathological specimen
  • Imaging analysis
• Categorical variable (most studies) versus continuous linear variable
• Different cut-off levels; 5 cm, 8 cm ....
• Zagars et al reported a significant impact when using 5 cm cut-off compared to 10 cm

Ref.: Zagars et al *Cancer* 2003;97(10):2530-2543
Tumor size
- categorical vs. continuous variable

Disease-specific mortality

Bjerkehagen 2012
Growth pattern: Peripheral tumor growth pattern is defined as

**Pushing:** No sign of infiltrative growth

**Infiltrative:** Tumor cells infiltrate the surrounding tissue.

Ref.: Engellau J et al. Hum Pathol 2005 36(9): 994-1002
Compartmentalization

Definition:

- Whether or not the tumor is localized in a well-defined fascial compartment.
- If the tumor grow infiltrative to more than one compartment it is considered extra-compartmental.

- Intramuscular or intermuscular tumor destroying the fascia
- Superficial tumor destroying the deep level of the fascia
- Invasion the deep level of the muscle
- Destroying the adjacent periosteum or bone
- Invasion of adjacent vascular sheaths or nerve sheaths

radiologykey.com, Enneking
Invasion to adjacent compartments

- Limited data

**Tsukushi et al:**
Histological invasion
- Independent adverse prognostic factor with HR of 2.2-2.5
- Correlation with tumor size and histological type
- Surgical procedure should take into account these factors

Ref.: Tsukushi S et al, Springer Plus, September 2014
Mitotic count

• Important with objective criteria
• Area to count: Number of high power fields versus mm²
  • 10 HPF
  • 50 HPF
• How does a mitotic figure look like? Do not count apoptotic figures!
counting PHH3 is a useful index in the diagnosis of uterine smooth muscle tumors and it can provide a more accurate index instead of the time-honored mitotic figure counts at a certain ratio.

**Phosphohistone H3** stains mitotic figures, G2 phase and prophase.
Mitotic count: PHH3

PHH3 in leiomyosarcoma

Ki67, PHH3 and mitotic count in HE in 132 uterine leiomyomatous tumors

Tumor necrosis

Definition:
- Amorphous cellular debris
- Usually a neutrophil polymorphonuclear infiltrate
- Clustering of dead cells
- Apoptotic bodies or cell ghosts

Not necrosis:
- Hyaline areas
- Edema
- Fibrinous exudates lacking tumor cells
- Acellular areas of fibrosis

Ref.: Engellau J et al Hum Pathol 2005 36(9): 994-1002
Necrosis
Necrosis

Bjerkehagen, Radiation-induced sarcoma
Vascular infiltration

Defined as:

- Tumor cells within any space having endothelial lining, whether within the tumor or in the tumor rim.
- The tumor cells have to be adherent to the vessel wall, or associated with adherent fibrin, red blood cells or leukocytes.
- Bulging of tumor into a vessel with intact endothelial lining is not accepted.

Ref.: Engellau J et al Hum Pathol 2005 36(9): 994-1002
Microscopic
- Histological subtype
- Vessel infiltration
- Growth pattern
- Atypia/pleomorphism
- Mitotic rate/proliferation
- Tumor necrosis

Macroscopic
- Anatomical location
- Depth
- Compartmentalization
- Tumor size

Malignancy grade
DIFFERENT GRADING SYSTEMS
Histological grading of malignancy

- Histological subtype for most cases gives not sufficient information

- Based on histological parameters
- Two-, 3- and 4-tired grading systems

- Broder´s grading from 1939
- The currently most accepted system is the French grading system FNCLCC
FNCLCC grading system
Federation National des Centres de Lutte Contre le Cancer

- Three-tired histological grade 1-3

Based on
- Tumor differentiation
- Mitotic count
- Tumor necrosis
FNCLCC grading system
Fédération National des Centres de Lutte Contre le Cancer

Tumor differentiation 1-3

1. Sarcoma closely resembling normal adult mesenchymal tissue e.g. well-differentiated liposarcoma
2. Sarcomas for which histological typing is certain e.g. myxoid liposarcoma
3. Embryonal and undifferentiated sarcoma e.g. synovial sarcoma
Differentiation: Atypia and pleomorphism

Score 3

Score 3

Score 1

Score 2-3

Score 2

Score 3
FNCLCC grading system
Federation National des Centres de Lutte Contre le Cancer

Table of 28 sarcomas with tumor differentiation scores according to histological subtypes.

E.G.:
Well-differentiated leiomyosarcoma 1
Myxoid liposarcoma 2
Clear cell sarcoma 3

WHO 2013
FNCLCC grading system
Federation National des Centres de Lutte Contre le Cancer

Mitotic count 1-3

- 10 high power fields (HPF)
- 1 HPF = 0.1734 mm$^2$

Score 1 0-9 mitoses/HPF
Score 2 10-19 mitoses/HPF
Score 3 >19 mitoses/HPF
FNCLCC grading system
Fédération National des Centres de Lutte Contre le Cancer

Tumor necrosis 0-2

• Score 0: no necrosis
• Score 1: <50% tumor necrosis
• Score 2: ≥ 50% tumor necrosis
FNCLCC grading system
Federation National des Centres de Lutte contre le Cancer

Histological grade 1-3
Grade 1: total score 2, 3
Grade 2: total score 4, 5
Grade 3: total score 6, 7, 8
FNCLCC grading system: n=1240 soft tissue sarcoma

Ref.: Coindre 2006 Arch Pathol Lab Voll 130
Integrated SSG models

SIN

• **SIZE** < 8 CM
• Vascular invasion (yes/no)
• **Necrosis** (yes/no)
• High-risk: 2 or more factors

SING

+ Growth pattern – pushing or infiltrative

Grading: Relation to prognosis

Soft tissue sarcoma

SIN-system

Prognostic model on internett

<table>
<thead>
<tr>
<th>Tumor size (mm)</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor necrosis</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Grade</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Depth</td>
<td>Deep</td>
</tr>
<tr>
<td>Location</td>
<td>Axis of body</td>
</tr>
</tbody>
</table>

The predicted 10y sarcoma specific survival in patients with the current profile is 26%

Out of 100 cases with the current profile 74 are estimated to die of sarcoma within 10 years from diagnosis

http://www.prognomics.org/SarcomaModel.aspx
Prognostic gene signatures

- CINSARC complexity \textbf{index} in sarcomas
- Construction of a gene panel
- Score based on 67 genes related to mitosis and chromosome arrangements
- DNA-based, fresh tissue

Next generation sequencing established on formalin-fixed paraffin-embedded blocks

RNA sequencing validation of the Complexity INdex in SARComas prognostic signature

Tom Lesluyes a,b,c, Gaëlle Pérot a,d, Marine Roxane Largeau a,b, Céline Brulard a, Pauline Lagarde a, Valérie Dapremont d, Carlo Lucchesi a,c, Agnès Neuville a,d, Philippe Terrier e, Dominique Vince-Ranchère f, Maria Mendez-Lago g, Marta Gut g, Ivo Gut g, Jean-Michel Coindre a,d,h, Frédéric Chibon a,d,*
3. Treatment-related prognostic factors

**Surgery**
- Unplanned surgery/biopsy
- Type of surgery
- Surgical margins

**Chemotherapy**
- Histological response

**Radiotherapy**
- Histological response

**Treatment in a sarcoma center**
- Multidisciplinary team with experienced specialists including pathologists and radiologists as well as research.
Biopsy should be performed at the sarcoma centre.

Local recurrence-free survival

- Untouched/cytology n=161
- Biopsy/operation performed n=477

Year after diagnosis

Data from the Norwegian Radium hospital
Surgical margins

- Standard treatment includes surgery
- What is an adequate margin?
  - Still on debate!
- Definition of margins:
  - Enneking
    - Intralional
    - Marginal
    - Wide
    - Radical
- R classification
  - No residual tumor after treatment R0
  - Microscopical residual R1
  - Macroscopical residual R2
  - Presence of residual tumor cannot be assessed
The importance of surgical margins in retroperitoneal sarcoma

Ref.: Amanda Kirane A et al, Journal of Surgical Oncology 2016;113,3,
Osteosarcoma: Histologic response to pre-operative chemotherapy

Prognostic factors
Defines risk?

Predictive factors
Which treatment is best?

Choice of treatment

Don’t under or over-treat!
Targeted therapy

Ref: Lønning PE, *Annals of Oncology* 18, 2007
Predictive factors – decides type of treatment

- Todays grading systems identify patients with high or low risk, but not effect of therapy
- Predictive factors
  - Biomarker as target for therapy
  - DNA, RNA and proteins
- Effect has to be demonstrated in clinical trials

Ref.: Italiano A, JCO, 2011, 29,35
Biomarker

Definition:
• A biological marker that is objectively measured and evaluated as an indicator of
  • Normal biologic processes
  • Pathogenic processes
  • Pharmacological responses to therapeutic intervention
• As a prognostic marker the level at diagnosis is of interest
  • Blood samples: albumin, C-reactive protein (CRP), hemoglobin, neutrophil to lymphocyte ratio and sodium, tumor DNA, …
• Can be used as a diagnostic tool, staging, prognostic factor, predicting or monitoring clinical response

Gastrointestinal stromal tumor (GIST): Model for targeted therapy

GIST has a
1. Biomarker: KIT
2. ”Drug target”: KIT tyrosine kinase
3. Treatment:
   Imatinib - a tyrosine kinase inhibitor
   – First line treatment in metastatic GIST
   – Adjuvant treatment in high risk GIST

Ref.: Joensuu H et al, JAMA. 2012;307(12):1265-1272
GIST

- The most common sarcoma in the gastro intestinal tract
- Incidence 60-100/year in Norway
- Median age 60 years at diagnosis
- Immunohistochemistry:
  - CD117+ and DOG-1+
- Risk related to:
  - Size
  - Mitotic index
  - Localization

Mutations in GIST

- Mutations in *KIT* gives constant activation signal leading to cell proliferation and tumor development
- *KIT* codes for a transmembrane tyrosine kinase receptor
- Mutation analyses:
  - Diagnostic value
  - Predictive value for treatment with imatinib
- *KIT* the most common oncogene 80%
- *PDGFRA* 8-10%
- Other mutations

Risk assessment of GIST: Location, mitoses, size, and tumor rupture (definition)


Red = high risk
Blue = low risk
White = data missing

% shows probable amount of patients som får residiv av GIST de 10 år av oppfølging.
Genomic index predicts clinical outcome of intermediate-risk gastrointestinal stromal tumours, providing a new inclusion criterion for imatinib adjuvant therapy

Lydia Lartigue a,b,c,1, Agnès Neuvile a,b,c,1, Pauline Lagarde a,b,c, Céline Brulard a, Piotr Rutkowski d, Paolo Dei Tos e, Eva Wardelmann f, Maria Debiec-Rychter g, Antoine Italiano a,b,c, Jean-Michel Coindre a,b,c, Frédéric Chibon a,b,*

Genomic index a robust marker to predict intermediate-GIST clinical outcome.

The level of genomic index, a measure of the number and type of genomic copy number alterations assessed by array CGH

A GI cut-off value (>10) was able to discriminate the good from the poor prognosis tumors.

\[ GI = \frac{A^2}{C} \]

A = total number of alterations (segmental gains or losses)
C = the number of chromosomes affected by these alterations

European Journal of Cancer 2015, 51, 75-83
Intermediate GIST

Distribution of the non-metastatic patients according to genomic index value.

Kaplan-Meier curve according to genomic index.

Ref. Lartigue et al European J. of Cancer, 2015, 51 75-83
OTHER FACTORS
Host factors - the patient’s immune system

Background:

• Increasing knowledge of the clinical importance of the patients immunological response to cancer

Soft tissue sarcoma:

• Infiltration of CD20+ B-lymphocytes is an independent positive prognostic factor in soft tissue sarcoma – not included in any of today’s prognostic grading systems

"Liquid biopsy"

- Demonstrating tumor-DNA in blood
- Correlation between tumor stage and amount of tumor DNA in blood
- Possibilities for screening, diagnostics, prognosis and follow-up?

Ref.: Crowley et al. *Nat Rev Clin Oncol* 2013
Independent adverse prognostic factors: Non-metastatic soft tissue sarcoma

French Sarcoma Group 2014
- n=3,255
- 1990-2010
- >16 years old
- R0 or R1 surgery
- Extremities and trunk, head&neck, internal trunk

Danish study 2014
- n=922,
- 1979-2008
- >15 years old
- Population based
- Extremities and trunk

Ref.: Maretty-Nielsen K et al, Acta Oncologica 2014;85 (3)
Italiano et al, Cancer November 2014
## Multivariate analysis:
Local-relapse free survival
Non-metastatic soft tissue sarcoma

<table>
<thead>
<tr>
<th>Type of prognostic factor</th>
<th>Danish study 2014</th>
<th>French Sarcoma group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient related</td>
<td>Age, Duration of symptoms</td>
<td>Age</td>
</tr>
<tr>
<td>Tumor related</td>
<td>Grade, Size</td>
<td>Grade Site Histotype</td>
</tr>
<tr>
<td>Therapy related</td>
<td>Margins, Radiotherapy</td>
<td>Radiotherapy</td>
</tr>
</tbody>
</table>

Ref.: Maretty-Nielsen K et al, Acta Oncologica 2014;85 (3)
Italiano et al, *Cancer* November 2014
Multivariate analysis: Non-metastatic soft tissue sarcoma

<table>
<thead>
<tr>
<th>Type of prognostic factor</th>
<th>Danish study Maretty-Nielsen 2014</th>
<th>French Sarcoma group Italiano 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient related</td>
<td>Endpoint: Sarcoma-specific mortality</td>
<td>Endpoint: Metastatic relapse-free survival</td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Duration of symptoms</td>
<td>Duration of symptoms</td>
</tr>
<tr>
<td>Tumor related</td>
<td>Grade Size Site</td>
<td>Grade Size Histotype Tumor depth</td>
</tr>
<tr>
<td>Grade</td>
<td>Grade</td>
<td>Grade</td>
</tr>
<tr>
<td>Size</td>
<td>Size</td>
<td>Size</td>
</tr>
<tr>
<td>Site</td>
<td>Site</td>
<td>Site</td>
</tr>
<tr>
<td>Therapy related</td>
<td>Margins Radiotherapy</td>
<td>Adjuvant chemotherapy in grade 3 sarcomas</td>
</tr>
<tr>
<td>Margins</td>
<td>Margins</td>
<td>Margins</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Radiotherapy</td>
<td>Radiotherapy</td>
</tr>
</tbody>
</table>

Ref.: Maretty-Nielsen K et al, Acta Oncologica 2014;85 (3)
Italiano et al, Cancer November 2014
Differences in the Danish and French studies:

- Different endpoints: Mortality vs. metastasis
- Prognostic factors included:
  - Denmark: Age, duration of symptoms, tumor size, site, depth, grade, margins, radiotherapy, time period of diagnosis
  - France: Age, sex, tumor size, site, depth, grade, margins, presence of bone/neurovascular invasion, histological subtype
- Statistics: Age, duration and size were continuously analyzed in the Danish study
- Included histotypes

Ref.: Maretty-Nielsen K et al, Acta Oncologica 2014;85 (3)
Italiano et al, Cancer November 2014
Should every histotype of sarcomas have their own grading system?
2016: Norwegian Society of Pathology: Recommendations of reporting of soft tissue sarcoma, 3rd ed

**Procedure:** Needle biopsy, surgical biopsy, operation specimen

**Histological subtype WHO 2013**

**Location and depth**

**Resection margins**

**Malignancy grade**

**Tumor size**

**Mitotic index**

**Necrosis**

**Vessel infiltration**

**Histological response of preoperative treatment**

**Ancillary studies:**

- Immunohistochemistry
- Genetic screening Cytogenetic analysis/NGS
- Specific molecular analysis: PCR/FISH/sequencing
Conclusion

Major development in classification of soft tissue sarcoma

- Integrated diagnostics
  - Morphological factors
  - Protein expression
  - Genetic analysis
- Prognostification is mainly based on morphology.
Conclusion

Importance for treatment and prognosis

- Malignancy grading a strong prognostic factor which identifies patients in need of adjuvant therapy
- Surgical resection status is of strong importance for outcome
- Predictive factors have relevance today only for GIST
- Currently limited impact of genomics on prognostic or predictive information
The future

Integrated diagnoses in multidisciplinary teams:

- Morphology
- Immunohistochemistry/Proteomics
- Genetics
- Bioinformatics
- Computer assisted morphological evaluation

The pathologist integrating information from several sources

2016

Morphology
Histochemistry
(Electron microscopy)
Immunohistochemistry
Genetics
Thank you!

Multidisciplinary treatment meeting at the Norwegian Radium Hospital

Department of Pathology, Oslo Cancer Cluster
The new building in 2016
The Norwegian Radium Hospital