Introduction

- Cancer is a complex disease
  - characterized by uncontrolled cell division
  - cells can undergo genetic events such as mutations influenced by inherited or environmental factors
  - primary classification is based on the embryonic origin where a tumor is derived
**Introduction**

Cancers: prognostic evaluation of patients

ONLY parameters related to the tumor are used to define:
- post-operative outcome
- rationale for adjuvant therapy

Imperfect evaluation of the severity of the disease and of the risk of relapse

**Tumoral Microenvironment**

![Diagram of Tumoral Microenvironment](image)
Introduction

- Microscopic appearance
- Serum markers
- Flow cytometry
- Microarrays
- Tissue microarrays

Objective

To analyze the quality and quantity of immune reaction at tumor site and evaluate its influence on the tumor process
Research Consortium

Inserm
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Colorectal Cancer: Patients and Materials

HEGP
Monocentric study

Digestive Surgery Department: P-H. CUGNENC, A. BERGER

- Retrospective cohort of 1006 patients (1986-2005)
- Clinical data and follow-up
- Sample materials
  - 500 Frozen tumors
  - 500 normal adjacent mucosa
  - 1006 paraffin-embedded tumors
FACS

Tissue microarrays (Kononen et al., Nat Med 4:844-847, 1998)
**Introduction**

- All investigations provide important data
- „Whole system approach“
  - Data integration using complex data management systems
    - Clinical records
    - Patient related data
    - Classical immunological data
    - High-throughput screening data

**Objectives**

- Ultimate goal
  - Design and Development of a Platform for Cancer Immunogenomics
    - enable patient classification
    - facilitate discovery and evaluation of markers applied in cancer research
    - help to unravel the immune system complexity
    - help to identify key components involved in cancer aetiology and progression
Multitier Architecture

- Enterprise services should be
  - highly available
  - secure
  - reliable and scalable
- Enterprise services are typically implemented as multitier applications
- Three principal layers
  - Presentation logic
  - Business logic
  - Enterprise Information System (EIS) layer

Java 2 Platform Enterprise Edition

- Provides a component based approach to the design and development of multitier applications
- Application model encapsulates the layers of functionality in specific types of reusable components
- Components communicate transparently
**Web Services**

- Collection of protocols and standards used to exchange data between applications in a platform independent way
  - Simple Object Access Protocol (SOAP)
  - Web Service Description Language (WSDL)
  - Universal Description Discovery and Integration (UDDI)
- Widely accepted in Bioinformatics
Immunogenomics Platform

- Microarray Data
- LIMS Data
- Clinical Data
- Flow Cytometry Data
- Immunohistochemistry

TME.db

- Provides access to data relevant to tumor biology and immunology
- Integrates clinical data sets and results from high-throughput screening technologies
  - patient information system
    - medical history, cancer, staging, surgery
  - experiment management
    - FACS phenotype, proliferation data, biological markers (IHC, ELISA)
  - sample material handling
    - treatments, used separation techniques, tube management
  - flexible queries
TME.db

- Stores sensitive patient related data
- Security mechanisms
  - encrypted storage in database
  - integration of the Authentication and Authorization System (AAS)
  - strong passwords
  - account locking
  - firewall, IP blocking
  - HTTPS access
  - login logging

Database for Clinical and Genomic Data
Role of the Immune System in Early Metastasis

- Patients with colorectal cancer (n=959)
- qPCR of 50 genes (n=75)
- Phenotypic analysis of 410 parameters using FACS (n=39)
- Tissue microarrays (n=353)
- Dedicated database for clinical and genomic data (http://tme.tugraz.at)

Early metastatic invasion and clinical outcome

Are VELIPI positive colorectal cancers associated with inflammatory mediators, immunosuppressive mediators, or both?

VE: vascular emboli
LI: lymphatic invasion
PI: perineural invasion
VELIPI: VE or LI or PI
Early metastatic invasion and clinical outcome

Absence of VELIPI is significantly and independently associated with better prognosis

VE: vascular emboli
LI: lymphatic invasion
PI: perineural invasion
VELIPI: VE or LI or PI


Immune Cell Infiltration, Inflammation, Early Metastatic Invasion, and Prognosis

n=75 patients

cytotoxic markers

T_{h1}, T_{h2} markers

Immune Cell Infiltration, Inflammation, Early Metastatic Invasion, and Prognosis

Adaptive immune response but not inflammation correlate with early tumor metastatic invasion and prognosis.

Phenotypes of Tumor-Infiltrating Immune Cells

Significantly different markers between invasion positive (VELIPI+) and negative (VELIPI-) patients

VELIPI: vascular emboli (VE), lymphatic invasion (LI), perineural invasion (PI)

Immune Cell Infiltration, Inflammation, Early Metastatic Invasion, and Prognosis

This large-scale investigation of T-cell associated markers argues for a positive role of effector-memory T-cells in the local control of tumor spread.


Effector Memory T-cells and Survival

Disease-free and overall survival of CD45RO<sup>hi</sup> patients

Conclusion

Memory T cells, in particular, $T_{EM}$ correlate with the absence of early-metastatic invasion as well as lymph node and distant metastasis, and improved clinical outcome in colorectal carcinoma.

CD45RO memory T-cells represent an independent prognostic factor.

What is the Relationship between the Type, Density, and Location of Immune Cells within Tumors and the Clinical Outcome?
Adaptive Immunity has a Beneficial Effect on Clinical Outcome

Combined Analysis of Tumor Regions Improves Prediction of Patient Survival

Combined Analysis of Tumor Regions Improves Prediction of Patient Survival

Two independent cohorts (n=119 from the same hospital and n=69 from another hospital) confirm the data.

Conclusion

Once human colorectal cancers become clinically detectable, the adaptive immune system plays a role in preventing tumor recurrence.

Type, density, and location of immune cells in colorectal cancer has a prognostic value that is superior to and independent of the those of the UICC-TNM classification.

Conclusion

The immunological criteria may lead to revision of the current indicators of clinical outcome and may help identify high-risk patients who would benefit from adjuvant therapy.

This approach may be useful for the investigation of other types of tumors (prostate, ovarian,...)