Cancer: Introduction

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Outline

1 Patient level: incidence, classification, treatment, and mortality
   - Cancers are classified into four categories
   - Cancer is treated with surgery, radiation, and medicine
   - Engineers develop tools for diagnosing and treating cancer

2 Tumor level: dysplasia, invasion, and metastasis
   - Tumors arise from normal tissues and occur in many varied host tissues
   - Hyperplasia leads to increased cell number
   - Dysplasia leads to aberrant cell organization and proliferation
   - Neoplasia implies disparate growths of cells
   - Invasion leads to local propagation of malignant cells
   - Metastasis leads to distant propagation of malignant cells

3 Cell level: cell cycle, cell survival, dna damage, immunology
   - Cancer cells proliferate abnormally
   - Cancer cells have aberrant cell cycles and respond aberrantly to growth factors
   - Cancer cells do not self-destruct when they should

Engineers can simulate tumors to study cancer
Engineers can monitor metastatic processes to study cancer
Engineers can model transport of therapeutics in the body and develop drug delivery approaches to improve therapeutic delivery

Engineers can measure cellular properties to study cancer
Engineers can take advantage of cancer cell properties to identify cancer cells
The properties of cancer are often summarized in terms of a number of hallmarks of cancer
Cancer is a disease in which cells propagate uncontrollably.

These cells can come from many different parts of the body and the reasons for the uncontrolled growth are manifold.

At the whole-body level, we think of cancer in terms of its incidence, classification, treatment, and mortality.

We want to know what types of cancer people get, how it is treated, and when it will be fatal.

Although we will not focus on it in this class, epidemiology, incidence rates, and the study of who gets cancer and why is very important.

Cancer is a disease of old age. We are living longer, so more people now get cancer and die of cancer.

Most common cancers are skin, breast, prostate, colorectal, and lung.

Cancers are classified into four categories.

Cancer can be subdivided into over a hundred different diseases based on a number of categories.

Here, we classify cancers into four broad categories that are indicative of a few key characteristics.
Patient Level | Tumor Level | Cell level
--- | --- | ---
----------------- | ----------------- | -----------------
Cancers are classified into four categories

Carcinomas are tumors of the epithelial cell layers that line organs

- Carcinomas induce 80% of cancer-related deaths in the Western world.
- Squamous cell carcinomas refer to tumors originating in sheets of cells that line a cavity and protect cells underneath, for example cells lining the skin or esophagus.
- Adenocarcinomas refer to tumors originating in sheets of secretory cells that line a glandular duct and secrete substances into the cavity they line.
- For example lung and stomach linings can give rise to adenocarcinomas.
- The most common carcinomas are shown in the figure.

<table>
<thead>
<tr>
<th>Tissue sites of more common types of adenocarcinoma</th>
<th>Tissue sites of more common types of squamous cell carcinoma</th>
<th>Other types of carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>lung, colon, breast, pancreas, stomach, esophagus, prostate, endometrium, ovary</td>
<td>skin, nasal cavity, oropharynx, larynx, lung, esophagus, cervix</td>
<td>small-cell lung carcinoma, large-cell lung carcinoma, hepatocellular carcinoma, renal cell carcinoma, transitional cell carcinoma (of urinary bladder)</td>
</tr>
</tbody>
</table>

Sarcomas are tumors forming in connective tissue cells

- Sarcomas comprise only 1% of human clinical tumors.
- These tumors derive from mesenchymal cells such as bone, muscle, cartilage, and fat cells.
- The most common sarcomas are shown in the figure.

Table 2.2 Various types of more common sarcomas

- osteosarcoma
- liposarcoma
- leiomyosarcoma
- rhabdomyosarcoma
- malignant fibrous histiocytoma
- fibrosarcoma
- synovial sarcoma
- angiosarcoma
- chondrosarcoma

Table 2.3 The Biology of Cancer (Gliae and Science 2007)
Hematopoietic malignancies consist of malignancies of the blood, including erythrocytes, plasma cells, and lymphocytes.

Lymphomas are liquid tumors and consist of uncontrolled growth of white blood cells throughout the bloodstream.

Lymphomas are tumors made from cells of lymphoid lineages that aggregate in lymph nodes to form solid masses.

The most common hematopoietic malignancies are shown in the figure.

Neuroectodermal tumors are tumors of the nervous system. Neuroectodermal tumors arise from cells from the nervous system and comprise approximately 1% of clinical tumors. The most common neuroectodermal tumors are shown in the figure.

### Table 2.3 Various types of more common hematopoietic malignancies

<table>
<thead>
<tr>
<th>Type of Hematopoietic Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute lymphocytic leukemia</td>
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<tr>
<td>acute myelogenous leukemia</td>
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<tr>
<td>chronic myelogenous leukemia</td>
</tr>
<tr>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>multiple myeloma</td>
</tr>
<tr>
<td>non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
</tr>
</tbody>
</table>

*The non-Hodgkin’s lymphoma types, also known as lymphocytic lymphomas, can be placed in as many as 15–20 distinct subcategories, depending upon classification system.*

### Table 2.4 Various types of neuroectodermal malignancies

<table>
<thead>
<tr>
<th>Type of Neuroectodermal Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>glioblastoma multiforme</td>
</tr>
<tr>
<td>astrocytoma</td>
</tr>
<tr>
<td>meningioma</td>
</tr>
<tr>
<td>neurinoma</td>
</tr>
<tr>
<td>retinoblastoma</td>
</tr>
<tr>
<td>neuroblastoma</td>
</tr>
<tr>
<td>ependymoma</td>
</tr>
<tr>
<td>oligodendroglioma</td>
</tr>
<tr>
<td>medulloblastoma</td>
</tr>
</tbody>
</table>
- At the tumor level, we are interested in how tumor masses grow, what their shape, structure, growth, invasiveness, and spreading properties are, and how different cells interact with each other to give rise to tumor behavior.

- We are also interested in the processes by which tumors affect nearby tissues.

- Tumors derive from normal tissues.

- The primary tumor is the tumor that originated and we refer to cancer types by the tissue in which the first tumor was found.

- Cancer is widely varied in many ways, including the nature of the host tissue.

- The figure shows five-year survivals for many different cancers, highlighting the huge difference between cancers.

- Hyperplasia leads to increased cell number.

- Hyperplasia is the increase in local cell number associated with deregulated proliferation.

- Hyperplasia implies, though, that the cells themselves appear normal.

- hyperplasia is typically the first step in tumor growth.
- dysplasia is the next step in tumor growth. This typically implies that cells appear abnormal and/or are in abnormal locations microscopically.

- Neoplasia is the next step in tumor growth. This typically implies that cells appear abnormal and abnormal collections of cells exist.

- Invasiveness—the tendency for cancer cells to move locally—is a hallmark of cancer cells. Benign tumors are those that invade locally but do not leave the host tissue.

- Cells that invade other tissue and spawn metastases (remote, secondary tumors) are termed malignant. Cancer cells are malignant.
Patient Level | Tumor Level | Cell level
--- | --- | ---
Cancer is staged by microscopic appearance and degree of dissemination

- Tumor staging is a system by which clinicians stage the size, invasiveness, and cellular characteristics of tumors.
- There are many systems and often multiple systems exist for a specific disease.
- Often, one system is used by surgeons, one by pathologists, one by medical oncologists.
- The TNM (Tumor–lymph Nodes–Metastasis) scheme identifies tumor size, whether it has invaded lymph nodes, and whether the tumor has metastasized.
- Other staging criteria are often focused on operability—i.e., would the patient die on the table if a tumor was removed.
- The correlation between tumor staging and survival is shown in the figure.

![Survival rates](image)

- As shown in the figure, there are multiple types of new tissue growth, namely **hypertrophy**, **hyperplasia**, **dysplasia**, and **neoplasia**.
- In different ways, these growth types all relate to (or can relate to) different aberrant cell behavior.
- Hypertrophy describes an increase in cell size; hyperplasia describes an increase in cell number.
- These can be normal behavior (for example muscle growth is hypertropy, healing is hyperplasia).
- Dysplasia denotes aberrant, disorganized growth.
- Neoplasia denotes disorganized growth with an increase in the number of dividing cells.
- Neoplasia implies a tumor. Neoplasia is the result of a loss of balance between cell growth and death.

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- Healthy multicellular organisms exert tight control on each individual cell in the body.
- Cancer is a disease in which cells evade this control and proliferate uncontrollably, and most cancer study in recent decades has been at the cellular level.
- Engineers and physicists particularly have the potential to impact cancer research in its expansion to tissue and body levels.
Normal cells grow and divide only when stimulated by growth factors (e.g., EGF and PDGF) from their environment.

This ensures that normal cells grow only when instructed to do so.

The signals from growth factors are transduced to the interior of the cell by growth factor receptors, for example EGFR and PDGFR.

Cancer cells become aberrant when their growth becomes independent of these external signals, because the growth factor receptors respond erroneously or because the cell makes its own growth factors.

Normal and aberrant growth factor signaling is shown in the figure.
Cancer cells have aberrant cell cycles. Healthy cells have a tightly regulated program for when they should die, and most cell death in humans is programmed, purposeful death. Necrosis, uncontrolled death, is relatively uncommon and usually occurs only upon injury. In contrast, apoptosis is occurring constantly in the body and is a central part of both development and normal operation.

Cancer cells do not self-destruct when they should. Cells kill themselves when they are not needed or are defective. Cells kill themselves when they are infected with pathogens or when their DNA is found to be defective. Cells somehow in the wrong place (unable to bind in a way they expect, not receiving paracrine or endocrine signals they expect) kill themselves.

Cancer cells, in contrast, typically have a disrupted apoptotic program and they do not invoke apoptosis. This has an important effect, especially when it comes to the cellular DNA. Because cells with DNA mutations kill themselves, the genetic integrity of cells is maintained. However, cancer cells often have mutations in the proteins that check DNA integrity and induce apoptosis when this integrity is compromised. Because of this, cancer cells fail to self-destruct when they should, and cancer cells can acquire significant disruptions in their DNA.

DNA mutations arise spontaneously, as DNA replication is not perfect. Further, many mutagens cause mutations to become much more common. The figure shows several simple DNA mutation mechanisms.
Cancer cells have profoundly disrupted genetic information

- In addition to small-scale mutations, cancer cells exhibit gross chromosomal abnormalities—unlike healthy cells, which are **diploid**, they often are **aneuploid**, meaning that they have chromosome copies other than two, and often incorrect repair of DNA leads to parts of different chromosomes being attached to each other—what is called **chromosomal translocation**.

- A classic example of this is the Philadelphia chromosome, an exchange of chromosomes 9 and 22 that leads to **chronic myelogenous leukemia**.

- The figure shows differences in **karyotypes** between healthy and cancerous cells.
Cancer cells have profoundly disrupted genetic information.

Cancer cells have modified adhesion/signaling/vasculature.

Cancer cells exhibit novel molecular changes.
- One is a reduction in cell adhesion proteins and gap junction proteins.
- These lead cancer cells to be less adhesive.
- Cancer cells produce proteases that help enzymatically degrade their surroundings, and secrete factors that induce **angiogenesis**.

Many pathologies relate to cancer aberrancies.

There are several hallmarks of cancer.
- Cancer can be described as a disease of cells that are independent of growth and antigrowth signals, that evade apoptosis, and retain limitless replicative potential.
- These cells form tumors that invade and metastasize, sustaining angiogenesis in response to local hypoxia.
- These properties are summarized in the figure.
There are several hallmarks of cancer:

- Sustained angiogenesis
- Invasiveness
- Limitless replicative potential
- Insensitivity to antigrowth signals
- Evasion of apoptosis
- Tissue invasion and metastasis
- Self-sufficiency in growth signals