A Manual for Medical Residents and Trainees in Medical Oncology

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The Faculty of the University of North Carolina, 2/002.
Trainees in internal medicine must understand the concept of multidisciplinary therapy of cancer. Areas of particular importance include:

1. The principles and techniques of cancer prevention and screening, including the indications for genetic screening and counseling.

2. The signs and symptoms of common cancers, their diagnostic evaluation, natural history, and therapy.

3. The principles of cancer therapy including chemo-, hormonal-, and biologic-therapy.

4. The management of common complications of therapy including myelosuppression, infection, hemorrhage, nausea, vomiting, and renal and cardiac failure.


6. The management of pain and the use of narcotic analgesics and adjunctive Medications.

7. The principles of terminal care of patients including hospice programs, ethical, and emotional issues.

8. The long term complications of cancer and its therapy.

9. The rationale for clinical trials in cancer and development of new therapies.

This manual is intended to supplement, not replace, reading from general textbooks of oncology.
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### Section I


<table>
<thead>
<tr>
<th>Cancer Statistics</th>
<th>Total</th>
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Section 2

Basic Biology of Cancer

Distinctions:
Apoptosis – programmed cell death. Present in most cells but missing in many cancer cells.
Anoikis – Forces epithelial cells to grow in aggregated clumps.

Genetic Alteration in Cancer

- Cancer develops due to multistep abnormalities at the level of DNA.
- Carcinogens may initiate the damage to the DNA. Further damage promotes the development of cancer.
- Improved knowledge about the molecular genetic alterations will be important in the diagnosis and treatment of cancer in the future.
- There are two important classes of genes, oncogenes and suppressor genes.

Oncogenes – promote cancer. They can be activated by:

  Translocation  -  The bcr-abl fusion gene is created by translocation of abl on chromosome 9 to bcr on chromosome 22 t(9;22). It is present in 95% of CMLs. It encodes a chimeric protein which is thought to deregulate growth of the stem cells.
  -  The t(8;14) or its variants (t2;8) and t(8;22) have been seen in the >80% of Burkitts lymphoma. These translocations involve transposition of the c-myc oncogene on chromosome 8 to the immunoglobulin heavy chain gene or light chain genes on chromosomes 14,8 and 22, leading to constitutive expression of myc. Myc encodes a DNA binding protein that is important in the regulation of cell proliferation.
  -  The bcl-2-Ig is a fusion gene. It is the result of joining 5'-bcl-2 on chromosome 14 to the immunoglobulin heavy chain gene on chromosome 18 t(14;18). It is present in 85% of follicular lymphoma and 20% of diffuse lymphomas. The bcl-2/Ig heavy chain hybrid mRNA transcript encodes the normal bcl-2 protein, which can block programmed cell death.
  -  In acute promyelocytic leukemia a 15:17 translocation causes a defective retinoic acid receptor (RAR) gene. The presence of the RAR receptor correlates with response to all-trans-retinoic acid.

  Amplification  -  of oncogenes encoding growth factor receptors can promote malignancy. Examples: Erb-B2 and HER-2/neu (which encode EGF receptor) in breast, ovarian and non small cell lung cancer.

  Rearrangement  -  examples: raf in lung and renal cancer
  Point mutation  -  single changes in DNA activate oncogenes. Example: ras. Ras Functions as a survival factor, preventing anoikis. Ras increases levels of VEGF causing angiogenesis (see below). Oncogenes may promote Tumor growth indirectly by causing angiogenesis (see below).
**Tumor Suppressor genes –**

- Growth Regulation
- DNA repair
- Apoptosis/cell survival
- Chromosomal stability
- Cell adhesion
- Transcription
- Think of these as several rheostats operating in paralleled to control cellular growth, stability, and death
- Rb- discovered by work on retinoblastoma. It is located on chromosome 13. An initial mutation within the Rb gene arises in a paternal germ cell. This mutated allele is transmitted to the germline of the child. Inactivation of the normal allele occurs in the target organ, typically by a gross chromosomal combination or deletion event. Presence of a homozygous mutation completely inactivates the tumor suppressor gene and results in malignant growth.
- p53 – 1) Involved in DNA repair 2) makes cells stable 3) Enables cells to undergo a potosis – mutated p53 has lost these policing actions.
- BRCA1, BRCA2 disabling mutations in either gene render an individual more susceptible to breast and ovarian cancers.
- Li Fraumeni Syndrome – A rare syndrome characterized by sarcoma in the proband early in life and two first degree relatives with cancer diagnosed by age 45. This definition is expanding as more families with abnormal germ line p53 genes are being defined.
- There are many others.

**Angiogenesis**

- Solid tumors grow slowly and in order to grow; they must develop their own blood supply. This is called angiogenesis.
- Several endothelial specific growth factors and their respective receptors have recently been discovered [e.g., 1] vascular endothelial cell growth factor (VEGF) and VEGF receptor –1 2) angiopoietin]
- Several endogenous inhibitors of angiogenesis have been discovered.
  1. Thrombospondin-1
  2. Angiostatin
  3. Endostatin
  4. Vasostatin
  5. Interferon £2a and £26
- Many existing drugs inhibit angiogenesis and many are in development.

**Existing Drugs:**

1. Antiandrogens in prostate cancer (androgens stimulate VEGF)
2. Antiestrogens in breast cancer (estrogens promote angiogenesis)
3. Paclitaxel – mechanism unclear
4. Interferon alpha
5. Thalidomide

**In development:**

1. Neutralizing antibodies to VEGF
2. Endogenous proteins inhibitors such as angiostatin or jusostatin.
3. **Ras farnesyl transferase inhibitors**

**Farnesyl transferase**

- Is a housekeeping enzyme that transfers farnesyl, a prenoid, on intermediate in cholesterol biosynthesis, to certain proteins that associate with cell membranes.
- Farnesyl transferase inhibitors (FTI’s) inhibit malignant cell growth with little effect on normal cells.
- Rho proteins regulate cytoskeletal actin organization, adhesion, and proliferation.
- FTI’s target Rho proteins.
- FTI’s are in drug development. They will likely be used to treat premalignant tumors and small tumors that haven’t developed a resistance to apoptosis.
- FTI is showing some promising results in AML and MDS.

**Special Interest**

***“Hereditary” Cancer***

- Distinguish between the terms familial and hereditary
- Familial – family members either closely or more distantly related to the proband are affected - “cancer runs in my family.”
- Hereditary cancer – refers to a situation in which the susceptibility is inherited in a Mendelian manner.
- Rare cancers are more likely to be hereditary. (e.g., The MEN syndrome)

**Colon Cancer**

- The majority of non hereditary colon cancers arise from pre-existing adenomas and proceed through stages toward cancer.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>5q</th>
<th>12q</th>
<th>18q</th>
<th>17p</th>
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<tbody>
<tr>
<td>Alteration</td>
<td>Mutation or loss</td>
<td>Mutation</td>
<td>Mutation or loss</td>
<td>Mutation or loss</td>
</tr>
<tr>
<td>Gene</td>
<td>APC</td>
<td>K-ras</td>
<td>DCC</td>
<td>p53</td>
</tr>
</tbody>
</table>

Normal Epithelium → hyperprolif. → early → intermediate → late → carcinoma → metastase

- 10-15% of colorectal cancer is hereditary
- about 1% is due to familial adenomatous polyposis
- 10-12% is due to hereditary non polyposis colorectal cancer (HNPCC) also called Lynch Syndrome
- suspect HNPCC when:
  1. early age of onset of colon cancer
  2. proximal location
  3. excess synchronous and metachronous cases.
4. Other cancers are associated with the Lynch II variant of HNPCC: endometrium>>ovary, stomach, small bowel, hepatobiliary system, ureter, renal pelvis.

- HNPCC is due to germ-line mutations in repair genes hMSH2, hMLH1, hPMS2, hPMS1, hMSH6.
- The estimated risk of colon cancer for a mutation carrier is 80-85%.
- Prophylactic colectomy in carriers is one of the options.
- Screening by colonoscopy saves lives.
- Annual colonoscopy is initiated at 25 years for mutational carriers. Females should begin endometrial screening at age 30.
- Consider chemo prevention (cox-2 inhibitors).

**Breast Cancer**

- Hereditary susceptibility to developing breast/ovarian cancer due to mutations in BRCA1 & BRCA2 genes.
- 5 to 10% of all breast cancer is hereditary.
- Presence of ovarian cancer in family with breast cancer increases likelihood of finding hereditary predisposition.
- Established risk for carrier 60-80% lifetime for breast – 20-40% lifetime for ovarian.
- Consider prophylactic bilateral salpingoophorectomy and mastectomy.
- Consider Tamoxifen as a preventive agent for breast cancer. Raloxifene is being tested for the prevention of breast cancer in the “STAR” trial.
Section 3

Chemotherapy

Chemotherapy nonspecifically damages DNA, inhibits DNA synthesis, affects RNA transcription, protein synthesis, and inhibits other functions of cells. The internist should know the main classes of chemotherapy drugs and their toxicity.

Classes of Chemotherapy Drugs

1. Alkylating Agents – Mechanism: Damages DNA. Cell-cycle phase nonspecific. However, rapidly proliferating cells are more susceptible to toxicity.

   Examples: Nitrogen mustard, cyclophosphamide, ifosfamide, chlorambucil, Melphalan, busulfan, dacarbazine, nitrosureas


   Examples: Methotrexate, 5-fluouracil (5-FU), ARA-C, fludarabine, Deoxycoformycin, 2-chlorodeoxyadenosine, 6-thioguanine, Gemcitabine, Capecitabine (Xeloda, oral 5-FU).

3. Anti-tumor Antibiotics – Mechanism: Wide range of effects on cellular processes, such as intercalation in the DNA, inhibition of the topoisomerases etc.

   Examples: doxorubicin (Adriamycin), daunorubicin, mitoxantrone (Novantrone),

4. Anti-mitotic drugs


   Examples: vinblastine, vincristine, vinorelbine (Navelbine)


   Example: paclitaxel (taxol), docetaxel (Taxotere).

5. Topoisomerase inhibitors

   Topoisomerase 1 inhibitors.

   Example: CPT-11, topotecan

   Epipodophyllotoxins – Mechanism: Inhibit nucleoside transport and incorporation into RNA and DNA. Prevent cells from entering into mitosis. Inhibits topoisomerase II

   Example: etoposide (VP-16)

Examples: Carboplatin, Cisplatin

7. Liposomal Agents – Mechanism: Traditional chemotherapy encoated in a fatty sheath. This provides more drug delivery to the target with decreased toxicity.

Example: Doxil (Liposomal Adriamycin).


Toxicity

1. **Bone Marrow Suppression**

   - Most chemotherapeutic agents cause bone marrow suppression. Drugs that cause little or no myelosuppression include bleomycin, L-asparaginase, and the vinca alkaloids.
   
   - The nadir WBC usually occurs 7-14 days after chemotherapy. A delayed nadir at 4-6 weeks occurs with mitomycin C, busulfan, and the nitrosurea (BCNU, CCNU, and MeCCNU) because they affect stem cells. This suppression affects all cell lines and lasts longer than with other agents. Treatment (see section 6 on Hematopoietic Growth Factors).

2. **Gastrointestinal**

   Nausea and vomiting – see Section 10

   Diarrhea – commonly caused by 5-FU, especially when given with folinic acid. Treated with hydration, loperamide, octreotide, and dose reduction. CPT-11 causes two forms of diarrhea. An immediate form (that occurs during chemo administration) is due to stimulation of the parasympathetic nervous system and it can be managed with atropine. The late form that is part due to hypersecretion in the intestine, must be managed carefully with loperamide and other supportive care. Mortality can occur if patients become dehydrated.

   Mucositis – oral ulceration, glossitis, esophagitis, enteritis. It can be difficult to distinguish mucositis of the esophagus from candidal esophagitis and herpes esophagitis. A biopsy may be necessary. Commonly occurs after treatment with methotrexate, 5-FU, actinomycin D, Adriamycin, and bleomycin. Treated with saline mouthwashes, topical anesthetics, nutritional support, antibiotic treatment of superimposed infection, dental prophylaxis and oral hygiene.

3. **Cutaneous**

   Alopecia - Subjectively the most disfiguring toxicity. Occurs after Adriamycin, taxol, Daunorubicin, cyclophosphamide, ifosfamide, nitrogen mustard, and
Etoposide. It also occurs, to a lesser extent, after bleomycin, ARA-C, Actinomycin D, 5-FU, hydroxyurea, methotrexate, vinblastine, and Vincristine. Hair grows back in all. When taxol is given weekly at a lower dose instead of every three weeks at the usual dose, the risk of alopecia decreases.

Drug Extravasation – Sclerosing agents – Adriamycin, actinomycin D, nitrogen mustard, mitomycin C, vincristine, vinblastine – can lead to non-healing ulcers requiring debridement and skin grafting.

Hyperpigmentation – Busulfan – generalized hyperpigmentation resembling Addison’s disease.
Bleomycin – linear streaks of pigmentation; sclerotic changes on hands.
Adriamycin – hyperpigmentation of oral mucosa and skin 5-FU – photosensitivity; pigmentation over veins
Methotrexate – photosensitivity

Radiation recall – Ranges from mild erythema to ulceration of previously irradiated sites. Occurs with actinomycin D, Adriamycin, and other agents, such as Taxol.

“Hand Foot Syndrome” – A desquamating rash on the hands and feet. Frequently associated with mucositis. Examples: Capecitabine, Doxil, prolonged infusion with 5FU.
4. **Cardiac**

Anthracycline (Adriamycin, daunorubicin)

Acute effects – Almost every arrhythmia has been reported. SVT common.
- Generally benign and reversible. More common with Adriamycin.
- Subacute – Rare. Occurs more often with daunorubicin.
- Consists of toxic myocarditis and pericarditis.
- Chronic – Cardiomyopathy can occur several years after treatment.
- Risk factors include:
  1. Cumulative dose greater than 450 mg/m²
  2. Mediastinal irradiation, especially in children
  3. Age: young children and elderly at higher risk
  4. Pre-existing heart disease
  5. Schedule: Bolus more toxic than continuous infusion.

Clinical – signs and symptoms of CHF. Patients should be followed with serial echocardiograms or radionuclide cineangiography to detect early signs.

Mitoxantrone (Novantrone), an anthracenedione, is less cardiotoxic than the Anthracyclines.

Taxol – arrhythmias, especially bradycardia and transient drop in BP during infusion.

Traztuzumab (Herceptin) – By itself, minimal cardiac toxicity, with doxorubicin it has been shown to increase the incidence of CHF.

Zinecar – A ligand that scavenges free radicals and can protect against the cardiac toxicity of anthracyclines. May decrease effectiveness of anthracyclines.

5. **Pulmonary**

Pulmonary fibrosis and infiltrates: Most commonly caused by bleomycin. Also occurs from BCNU, busulfan, ARA-C, methotrexate, and mitomycin.

Risk factors:
1. Dose related bleomycin, ARA-C, and BCNU
2. Prior or concurrent thoracic radiation
3. Age

Clinical – Patients have cough, dyspnea, fine bibasilar rales, and on X-ray, basilar infiltrates progressing to diffuse interstitial infiltrates. Mortality is 10-50%.

Therapy consists of discontinuing treatment. Steroids are often used.

Screening – Controversial. Serial FVC and DLCO are used.

Radiation recall – Adriamycin can cause a radiation recall of the lung that can present as ARDS.

6. **Hypersensitivity Reactions** – Most chemotherapeutic agents have been reported to cause hypersensitivity reactions, including anaphylaxis.

- L-asparaginase – Highest risk of anaphylaxis.
Taxoids – Anaphylaxis rarely occurs after premedication.

“First Pass” or Infusion Reactions – Can occur with Doxil and Herceptin. Premedication is suggested.

7. **Hepatic**

Some drugs are toxic to the liver. Other drugs are metabolized by the liver. They may need to be reduced or eliminated in the presence of liver impairment.

Agents that can harm the liver:

- **Docetaxel** – Liver function tests must be reviewed by the physician before giving the treatment.
- **Nitrosureas** – transiently increases liver function tests
- **ARA-C** – reversibly hepatic cholestasis
- **Methotrexate** – reversibly elevated transaminases; cirrhosis can occur with daily oral treatment.

Other agents: Adriamycin, mitoxantrone, VP-16, DTIC.

Agents that require hepatic excretion; doxorubicin, daunorubicin, epirubicin, vinca alkaloids

Mixed excretion; epipodophyllotoxins (VP16), mitomycin C.

### In patients with impaired liver function

1. Avoid hepatotoxins
2. Avoid drugs with hepatic metabolism
3. Monitor liver function frequently.

8. **Renal**

Some drugs are toxic to the kidney. Other drugs are eliminated by the kidney. Such drugs may need to be reduced or eliminated in the presence of renal impairment.

**Nephrotoxic Agents:**

- **Cisplatin** - Acute and chronic tubular necrosis may occur. Creatinine clearance is the best indicator of damage. Risk increases with other nephrotoxins. Hypokalemia and hypomagnesemia are common. Can be prevented with forced diuresis.
- **Nitrosureas** - Interstitial disease can occur years after administration
- **Methotrexate** - At high doses, metabolites can precipitate in the tubules. Can be prevented by forced alkaline diuresis.
- **Mitomycin C** - Classically associated with hemolytic uremic syndrome. Can also cause glomerular sclerosis.
- **Ifosfamide** - Hemorrhagic cystitis – preventable with Mesna. Usually reversible proximal tubular defect.
- **Cyclophosphamide** - Hemorrhagic cystitis, SIADH, nephrogenic diabetes insipidus

Renal Excretion: Bleomycin, carboplatin, Carmustine, cisplatin, 2-chloro-deoxy-adenosine, cytarabine, dacarbazine, fludarabine, hydroxyurea, idarubicin, ifosfamide, melphalan, and methotrexate.
Management in impaired renal function:
1. Always check serum creatinine
2. Avoid drugs that are toxic to kidney. Make substitutions when possible (e.g. carboplatin for cisplatin).
3. Reduce the dose for those that are eliminated by the kidney.

9. **Gonadal** Adult men – Alkylating agents are most likely to damage germ cells
Irreversible azoospermia occurs in 80% of those treated with MOPP or MVPP for Hodgkin’s disease. Risk increases with increasing age and dose. Underlying cancer causes infertility. As many as 50% of men with Hodgkin’s disease or testicular cancer are severely oligospermic or azoospermic before treatment.

Treatment – Educate male patients about the option of banking their sperm before beginning treatment.

Adult women – Alkylating agents are most toxic. Risk increases with increasing age and dose. At comparable doses, infertility is less common in women than men.

Treatment - Counsel patients before beginning treatment.
   
   No proven effective treatment.
   
   Oocyte harvest with immediate fertilization is being tried.
   
   Oocyte cryopreservation is exceedingly difficult.
   
   Oral contraceptives and LHRH analogues may arrest oocyte development and protect against infertility.

10. **Neurologic**
   
   Vinca alkaloids – Peripheral neuropathy, usually paresthesia, numbness.
   
   Cranial nerve neuropathy
   
   Autonomic neuropathy – occasionally ileus.
   
   Procarbazine - Altered consciousness. Peripheral neuropathy. “Disulfiram” like reaction to alcohol. A weak MAO inhibitor – hypertension may occur with sympathomimetics, tricyclics, or tyramine. Counsel patients about foods to avoid while on regimens containing procarbazine, such as MOPP.
   
   Cisplatin - Ototoxicity and peripheral neuropathy
   
   Taxoids - Peripheral neuropathy, often painful. Improves upon discontinuing the taxoid.
   
   ARA-C- Cerebellar toxicity
   
   Ifosfamide - Encephalopathy characterized by confusion, hallucinations, aphasia, coma. Risk factors include hypoalbuminemia and poor renal function.

4. **Second Malignancies**
   
   Acute Leukemia. Risk increases with age.
   
   Alkylators – risk increased with dose and duration.
Procarbazine – increases the risk.
VP-16, cisplatin – weakly implicated.
The combination of chemotherapy and radiation has a greater risk than chemotherapy alone. The mean interval for developing leukemia after treatment for Hodgkin’s disease is 6 years. Risk diminishes after 10 years.

Non Hodgkin’s Lymphoma – Patients treated for Hodgkin’s disease with chemotherapy and radiation are at risk for developing NHL. The median interval is 8 years after treatment.

Bladder cancer can be caused by cyclophosphamide. Radiation therapy increases the risk of a wide variety of solid tumors. The exact frequency of second malignancies is difficult to determine. Second malignancies after radiation for Hodgkin’s disease include thyroid cancer, non-Hodgkin’s lymphoma, sarcomas, lung cancer, and various adenocarcinomas. Radiation to the mantle field during the teen years leads to forty-fold increased risk of breast cancer in women.
Section 4
Biologic Therapy

**Interferons** – are a group of regulatory proteins.

Interferon α – approved in the US as either interferon alfa 2a (Roferon), interferon alpha-2b (Interon), or as recombinant multispecies interferon. At low dose, it probably works as an antiviral agent, a gene regulator, and an immune modulator. It prevents proliferation and angiogenesis and it promotes differentiation. At high dose it is cytotoxic and is used in the treatment of hairy cell leukemia (2-chlorodeoxyadenosine is preferred for hairy cell leukemia), Kaposi’s sarcoma of AIDS, condyloma acuminata, chronic hepatitis B and C, chronic myelogenous leukemia. It is also active in low-grade non-Hodgkin’s lymphoma, essential thrombocytosis, multiple myeloma, carcinoïd tumor and malignant melanoma. Combinations of interferon alpha, interleukin 2, and chemotherapy are being explored. During the first few weeks of treatment flu-like symptoms occur. Chronic dose-limiting side effects consist of anorexia, weight loss, chronic fatigue, neurologic toxicity, depression, impotence and hypothyroidism.

Interferon β – Although it has similar structure to interferon alpha, it is not widely used in cancer therapy. It has been approved by the FDA for the treatment of remitting/relapsing multiple sclerosis.

Interferon γ – Approved for chronic granulomatous disease of childhood.

**Interleukins (IL)** – A group of glycoproteins that are involved in regulation of a variety of immunological and hematopoietic processes. Interleukins 1-12 have been identified, cloned, and studied in vitro, and in some cases, in vivo. Trials are ongoing with several.

Interleukin-2 – Activates/stimulates T cells, stimulates monocytes to tumoricidal state, induces/releases other cytokines, induces non-MHC-restricted cytotoxicity. It is approved for the treatment of renal cell carcinoma. It has activity in melanoma and non-Hodgkin’s lymphomas. At high doses it causes capillary leak and can be lethal. Low dose, subcutaneous regimens are being evaluated.

**LAK cells** (Lymphokine activated killer cells)- Non-MHC restricted cytotoxicity.

**TIL cells** (Tumor infiltrating lymphocytes)- Tumor specific.

**Monoclonal antibodies** – Immunoglobulins which recognize unique protein and carbohydrate molecules.

**Diagnostic:** 1) satumomal labeled monoclonal (OncoScint®) has been approved for the detection of occult ovarian and colorectal cancer. 2) arcitu momab (CEA-scan) is a Tardiolabeled mouse M Ab’ Fab fragment that targets CEA. It is indicated in conjunction with standard diagnostic evaluation to detect the presence, location, and extent of recurrent colon cancer involving the liver extra hepatic abdomen and pelvis 3) Capromab (prostascint) is a mouse M Ab 7E11-C5.3 radiolabeled with in. It is specific for prostate cancer. It is a strong predictive test for prostate cancer in pelvic lymph nodes. The accuracy is approximately 60% 4) No fetumomab – recognizes a 40-kd glyco porein expressed on a variety of cancers and some normal tissues. It is indicated and FDA approved for patients with untreated small cell lung carcinoma.

**Therapeutic:**
1) Rituximab (rituxam™, IDEC Pharmaceuticals)- Chimeric murine/human immunoclonal antibody directed against CD20 antigen on the surface of normal and malignant B-lymphocytes. It is indicated for the treatment of patients with relapsed or refracting low grade or follicular, CD20 positive, B cell non-Hodgkin’s lymphoma. It is used in combination with CHOP chemotherapy for treatment of diffuse large B cell lymphoma in elderly patients. It had been used in post transplant lymphoproliferative lymphoma (PTLD), It has been successfully used in ITP post splenectomy and auto immune anemia.

2) Radiolabeled monoclonal antibodies:
   a. Tositumomab (Bexxar): anti-B cell (anti-CD20) mAbs conjugated to Iodine-131 (Bexxar, tositumomab) have shown promising results with limited follow-up in relapsed or refractory low grade lymphoma.
   b. Ibritumomab (Zevalin): combines an anti-CD20 mAb with the radioactive isotope Yttrium-90, has been shown to be a safe and effective alternative for outpatient therapy of patients with relapsed or refractory NHL in phase II trials.

Radiolabelled antibodies allow cross-firing where in addition to binding the receptor, the radiation can kill the adjacent cells even if they are CD20 negative. Radiolabelled AB are confined to be used in patients with less than 25% bone marrow involvement. Long term follow up is warranted to assess their long term safety.

3) Trastuzumab (Herceptin®. Genetech) is a recombinant DNA – cloned humanized monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Approximately 1/3 of patients with breast cancer has HER2 on the surface of their breast cancer cells. Herceptin as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors over express HER2 ad who have received one or more chemotherapy regimens for metastatic disease. Herceptin in combination with taxol is indicated as first line treatment for patients with metastatic disease that is HER2 positive. This treatment can double time to disease progression.

4) Gemtuzumab (Mylotarg) is an anti-CD33 antibody which is linked to calicheamicin, a potent cytotoxic agent. The drug appears to be rapidly and specifically targeted to CD33+ cells, followed by internalization and subsequent induction of cell death. Gemtuzumab was approved by the FDA (May, 2000) for use in patients age 60 or older with CD33+ AML in first relapse who are not considered candidates for cytotoxic chemotherapy. The recommended dose is 9 mg/m2 given by four-hour IV infusion, with a second dose two weeks later.

5) Alemtuzumab (campath) Anti-CD52, Food and Drug Administration approved this agent on May 7, 2001 "for the treatment of patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy. Campath was least effective in patients with bulky lymphadenopathy

**Tyrosine kinase inhibitors:**

Tyrosine kinases are protein membrane receptors with intracellular tyrosine kinase activity domain. The receptor is activated when a certain ligand binds to external domain leading to autophosphorylation and down signaling via different signaling pathway to the nucleus leading to proliferation, angiogenesis, apoptosis, etc. Tyrosine kinase receptors include epidermal growth factor
receptors (EGFR), vascular endothelial growth factor receptors (VEGF), C-kit (CD117), BCR-ABL protein.

Abnormalities of TK receptors and functions are assumed to play role in the pathogenesis of several tumors. The dysregulation of the receptor can result either from paracrine / autocrine ligand factor production stimulating the receptor or from mutations of the receptor leading to independent auto-phosphorylation.

Several TK inhibitors are being used and studied in treatment of cancer. Some of the inhibitors are monoclonal antibodies against the receptors, some inhibits the autophosphorylation of the receptors

- **BCR-ABL TKI**: Imatinib mesylate (Gleevec)-see under CML
- **C-kit inhibitors**: Imatinib mesylate in GIST (gastrointestinal stromal tumors-previously leiomyosarcoma).
- **EGFR inhibitors**:
  - Trastuzumab in breast cancer
  - C225 in head/neck cancer, colon cancer
  - ZD 1839 (Iressa) in NSCL
- **VEGF inhibitors**: studied in lung cancer, leukemia, and multiple myeloma

**Tumor vaccines**- Vaccines made from tumor tissue, common antigens, and synthetic peptides are being tested in renal cell carcinoma, melanoma, breast-, colon-, and ovarian cancer.

**Retinoids** – A family of vitamin A (retinol) derivatives which appear to have significant differentiating ability in normal and malignant tissue. They are generally well tolerated but they **must not** be given to pregnant women because they are teratogens. Other side effects are dry skin/mucus membranes, cheilitis, hypertriglyceridemia, liver function abnormalities. Retinoids have activity against oral leukoplakia, preventing secondary malignancy in patients with history of head and neck squamous cell carcinoma, preventing malignant transformation in cervical dysplasia. Dramatic remissions occur in 65-95% of patients with FAB M3 acute promyelocytic leukemia treated with all trans-retinoic acid. In APL, a 15; 17 translocation causes a defective retinoic acid receptor (RAR) gene.
Section 5
Infections in Cancer Patients

Cancers or conditions leading to host defense deficit and the likely type of infections.

- AML, ALL, chemotherapy, corticosteroids - affects phagocytic cells (granulo-cytopenia) - gram negative bacilli, staphylococci, fungi
- CLL, multiple myeloma, splenectomy* - affects B-cells (antibody defense) – encapsulated bacteria
- Hodgkin’s Disease, corticosteroids – T-cell – viruses (herpes simplex and zoster, CMV), pneumocystis, toxoplasma, bacteria (Listeria monocytogenes, nocardia, legionella), fungi (candida, Cryptococcus neoformans, Histoplasma capsulatum)

*Give pneumococcal and hemophilus vaccines before splenectomy

Febrile Neutropenia

- Febrile neutropenia is defined as oral temperature greater than 38.3 C or two oral temperatures more than 38c measured an hour apart in the setting of neutropenia (ANC < 1000/mm3)
- The risk of serious infection significantly increases when the granulocyte count is below 500/mm3.
- Most infections come from flora in the patient’s oropharynx or GI tract. Patients on chemotherapy are not susceptible to infections from casual contact. It is advised that they avoid people with contagious illnesses and crowds during anticipated times of neutropenia in order to help distinguish between a common cold and a serious bacterial illness that would require parenteral antibiotics.
- 60-70% of febrile neutropenia have no identifiable etiology. Bacteremia is seen in 10 to 20% of cases. Seventy percent of bacterial infections are gram positive.
- Antibiotics must be started promptly (even in the ED).
- The choice of empiric antibiotics is controversial.
- Monotherapy options include cefepime, ceftazidime, imipenem or meropenem while combination therapy usually includes antipseudoamoanl penicillin (e.g. piperacillin) and aminoglycoside.
- Vancomycin does not need to be given initially but have a high index of suspicion for gram positive infection (in patients with indwelling catheters) and consider adding vancomycin if patients not responding to initial empirical therapy in 3 to 5 days.
  - Oral antibiotics can be used sometimes in low risk patients.
  - Empiric antifungal treatment is considered in persistent or recurrent fever after 5 to 7 days of appropriate broad spectrum antibiotics treatment.
- Hematopoietic growth factor (see Section 6 on Hematopoietic Growth Factors).
- In afebrile patients without a source of infection, when the granulocyte count is rising and greater than 500/m³ antibiotics can be stopped. If an infection has been identified (e.g. pneumonia), customary treatment should be administered.
Section 6

Hematopoietic Growth Factors

Cytokines that promote the growth and function of target cells.

EPO – erythropoietin

- Has been approved for the treatment of anemia associated with AIDS, renal failure, and administration of chemotherapy in non-hematologic malignancies.
- In randomized trials of cancer patients, the benefit of EPO has been significant but small. Over 12 weeks the average number of transfusions dropped from 1.81 units/patient to 1.04 units/patient and hematocrit rose from 28.6 to 32.1%.
- Side effects – rapid increases in hematocrit can cause hypertension and iron deficiency.
- Serum EPO levels are often drawn because patients with levels greater than 150 U/ml will respond slowly or not at all. However, there is a considerable amount of intrapatient variability. Algorithms intended to find appropriate levels of EPO are helpful though it is better to compare EPO levels from patients with the same diagnoses.
- Administration – Start when the Hg is $< 10$. Use 40,000 units S C once a week. Treat until the Hg is $\geq 12$. Assess response no sooner than four weeks. May increase to 60,000 units once a week in patients with a poor response after an assessment of iron stores. If there has been no significant response after 12 weeks, EPO should be discontinued.
- Since treatment is costly, the value of this medication is debated. One study has shown an improvement in quality of life. There have been no cost effectiveness analyses to date.

GM-CSF – target cells: neutrophils, macrophages, and eosinophils

G – CSF – target cell: neutrophils

According to the guidelines of the American Society of Clinical Oncology (ASCO), the following are recommended uses for GM and G-CSF (CSF):

- When the risk of febrile neutropenia from a chemotherapy program is $\geq 40\%$ administer GM or G-CSF at the first cycle of treatment. The incidence of febrile neutropenia has been shown to be reduced by 50% in this setting. There is no documented survival benefit.
- After a documented occurrence of febrile neutropenia in an earlier cycle or if prolonged neutropenia is causing excessive dose reduction or delay in chemotherapy, the clinician may begin GM or G-CSF. However, the primary therapeutic option is dose reduction. With the exception of a few curable tumors (e.g. germ cell) no published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted.
- For febrile neutropenic patients with adverse prognostic factors such as pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), fungal infection, or febrile neutropenia of greater than 10 days.
- Following autologous bone marrow transplantation.
- For mobilization of autologous stem cells.
- Intermittent administration for myelodysplasia when patients have severe neutropenia and infection. Data on long-term efficacy in these patients is lacking.
Don’t use for:
- Afebrile neutropenia.
- For patients with routine febrile neutropenia who do not have adverse prognostic signs (see above).
- For dose escalation (There may be some benefit of maintaining dose intensity above 75% in certain settings such as adjuvant breast cancer. This hypothesis has not been directly tested in a randomized trial).
- Patients receiving concurrent chemotherapy and irradiation.

Administration
- 5 micrograms/kg/d of G-CSF or 250 micrograms/kg/d of GM-CSF or to the greatest vial size.
- Start between 24 and 72 hours after chemotherapy. Give until ANC is 5,000/microliter after the neutrophil nadir. There can be an initial peak in ANC after only 2-3 days of treatment followed by the nadir. Therefore, give at least 7 days of therapy.
- Schedules of lower, less frequent dose are being studied.

IL – 11
- The only commercially available thrombopoietic cytokine.
- Kinetics of platelet production is slow so the window of treatment is narrow.
- Use is limited to secondary prevention.

Long acting growth factors

Darbepoetin alfa (Aranesp) : A novel erythropoiesis-stimulating protein. The molecule contains two additional carbohydrate side chains and extra sialic acid molecules compared to erythropoietin. This modification gives the Darbepoetin its longer half- life and in vivo higher biological activity. Darbepoetin is approved in United States and Europe for treatment of anemia in adults with chronic renal failure. \(^{15}\) Darbepoetin was recently approved for chemotherapy related anemia. Recommended starting dosage for chemotherapy related anemia is 200 mcg/ SC q 2 weeks

Pegfilgrastim (neulasta)

Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxy polyethylene glycol. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared to Filgrastim. It was approved by the United States Food and Drug Administration in January 2002 for use in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy drugs associated with a clinically significant incidence of. A single fixed dose of 6 mg sc is used per cycle.
Section 7

Oncologic Emergencies

Superior Vena Cava Syndrome

- Occlusion of the SVC causes an increase in upper body venous pressure and forces blood to return to the right atrium via collateral venous channels
- Patients present with dyspnea made worse on recumbency, or feeling of fullness in the head, lethargy, cough, and dysphagia
- Physical findings include thoracic and neck vein distention, edema of the face with cyanosis, tachycardia, and edema of the upper extremities. If enough time has elapsed, collateral veins can be seen on the chest.
- The diagnosis can be confirmed by radionuclide scan or CT scan.
- Unless the clinical condition is unstable, a biopsy is the first and most important step (if the diagnosis is not known!)
- 90% of SVC obstructions are due to cancer. Small cell and squamous cell carcinomas of the lung are the most common primary tumors followed by lymphomas. Breast cancer is the most common metastatic tumor.
- Most tumors are treated with radiation therapy. Small cell carcinoma can be treated with radiation or chemotherapy but chemotherapy is preferred. Lymphomas can also be treated with chemotherapy.
- Except for SVC syndrome caused by a clot from an indwelling catheter, there is no proven benefit of heparin or lytic agents.
- There is no proven benefit to decadron or diuretics.

Metabolic

Hypercalcemia:

Hypercalcemia is the most common life-threatening metabolic disorder in patients with cancer. It occurs in 10-20% of cancer patients.

The differential diagnosis and mechanism are not discussed. Please see a general medical text for these.

Treatment

- Calcium less than 12 mg/dl; patient minimally symptomatic; oral hydration, mobilization, and antitumor therapy. Consider starting pamidronate.
- Calcium greater than 12mg/dl; patient moderately to severely symptomatic; treat with vigorous hydrion with normal saline, 6 to 10L/24 hours. Be certain that the patient is well hydrated before starting furosemide. Begin bisphosphonates promptly. The preferred agent is zolendronate 4mg intravenously over 15 minutes. Consider maintenance zolendronate every 3 to 4 weeks. Note that hydration is not a substitute to definitive therapy. Calcitonin has a very rapid onset of action and can be helpful in severe and symptomatic hypercalcemia.
- Corticosteroids are helpful in tumors responsive to steroids such as lymphomas.
- Symptoms of Mild hypercalcemia: nausea, anorexia and vomiting, constipation, thirst and polyuria.
- Severe hypercalcemia: dehydration, drowsiness, confusion, coma, and cardiac arrhythmias.
**Tumor lysis syndrome:**

- Refers to a constellation of metabolic alterations: hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Can lead to renal failure and sudden death. It occurs after treatment with chemotherapy.
- The tumors that are prone to causing this are lymphomas (particularly Burkitt’s lymphoma) and acute leukemia.
- Preventative therapy includes allopurinol 300 to 600 mg/d for 1 to 2 days before chemotherapy, with a maintenance dose of 300 mg/d after the first dose of chemotherapy while the tumor burden is still high. Patients should be hydrated with 4 to 6 liters of fluid per 24 hours for the first several days. The fluid should contain sodium bicarbonate (e.g. 1/4 normal saline with 2 amps of NaHCO3/L) in order to bring the urine pH to 7 or more. If the urine pH remains low, add acetazolamide (diamox). Switch to saline hydration when the phosphate begins to rise. Over zealous alkalinization of the urine could lead to phosphate precipitation in the renal tubules. If metabolic parameters cannot be controlled or if there are signs of renal impairment, begin dialysis.
- Electrolytes, BUN, creatinine, uric acid, calcium, phosphate, and lactate dehydrogenase (LDH) are monitored for several days.

**Hyponatremia:**

- Cancer patients are susceptible due to poor health, medications, fluid shifts, etc. Please review a general medical test on this topic.

**Syndrome of inappropriate secretion of ADH (arginine vasopressin) = SIADH**

- an abnormal production of ADH causes hyponatremia.
- Seen most commonly with small cell lung cancer

**Diagnosis**

- Hyposmolality (<280 mosm/kg).
- Urinary osmolality > the plasma (>500 mosm/kg)
- Continued urinary excretion of sodium (>20mEg/L) although taking no diuretics.
- Absence of signs of volume depletion.
- Normal renal function.
- Normal adrenal and thyroid functions.
- No diuretic use
- Low serum uric acid can be a helpful clue

**Treatment**

- When possible, treat the underlying tumor.
- For symptomatic hyponatremia and sodium levels <130 mEg/L, treat with fluid restriction to allow plasma osmolality to correct slowly. For severe symptoms (e.g. coma) treat with hypertonic saline and furosemide.
- In patients who have relapsed and who have recurrent SIADH with no or minimally effective anti-cancer treatment, demeclocycline can be tried.
Spinal Cord Compression: (SCC)

- SCC can result in paralysis.
- Early diagnosis and treatment of SCC are essential to preserve neurologic function.
- A high index of suspicion is needed for SCC in a patient with malignancy. If the patient has back pain, sensory loss, autonomic dysfunction, radicular pain, or weakness, appropriate diagnostic tests, frequently including a MRI of the spine should be done.
- Prompt treatment is essential if function is to be maintained. Neurologic status is the most important factor influencing outcome. We generally recommend radiation therapy to all patients. Retrospective analysis has NOT shown an advantage for patients managed by laminectomy and radiotherapy over radiotherapy alone. Surgical therapy is now performed less frequently. Surgery is indicated when:
  1) tissue is needed for diagnosis
  2) the vertebral column is structurally unstable
  3) there is SCC in a previously radiated field
  4) the tumor is resistant to radiation
  5) an epidural abscess or hematoma needs to be ruled out.

- Dexamethasone 10 mg followed by 4 mg every 6 hours may decrease edema and relieve signs and symptoms. Higher dexamethasone doses are associated with more complications and no extra benefit. The steroid can be tapered as the patient stabilizes.

Brain Metastases

Incidence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>33%</td>
</tr>
<tr>
<td>Lung</td>
<td>25%</td>
</tr>
<tr>
<td>Breast</td>
<td>15%</td>
</tr>
<tr>
<td>Kidney/Bladder</td>
<td>10%</td>
</tr>
<tr>
<td>Colon</td>
<td>5%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
</tr>
<tr>
<td>Liver</td>
<td>5%</td>
</tr>
<tr>
<td>Testicular</td>
<td>5%</td>
</tr>
<tr>
<td>Prostate</td>
<td>5%</td>
</tr>
</tbody>
</table>

Diagnosis

- In a patient with known malignancy and new CNS symptoms or signs urgent brain CT or MRI is indicated. Biopsy is necessary if there has been a long interval between cancer and the abnormal CT/MRI. A biopsy is also necessary for patients with abnormal CT/MRI and no history of cancer. Although the scan may have the classic appearance of metastasis, primary CNS tumor, infection, lymphoma, granuloma are in the differential.

Treatment

- Dexamethasone to reduce intracranial pressure, and whole brain radiation.
- Surgical resection is indicated for solitary metastasis with Karnofsky performance score greater than or equal to 70, and controlled systemic disease. Post operative radiation therapy will delay death due to neurologic causes but probably not affect overall survival.
- Stereotactic radiosurgery (SRS) is a term applied to various techniques that deliver three-dimensional external beam radiation. It delivers small volume radiation with minimal deposition outside the target volume. It is ideal for solitary tumors up to 3 cm in size.
- Antiepileptics are indicated only if the patient has had a seizure.

Prognosis
• 1 month without treatment, 2 months with steroids, 3 to 6 months with whole brain therapy. There is an occasional long-term survivor after resection of a solitary metastasis. The local control with SRS has ranged from 83% to 94% and the median survival has been 11 to 12 months. Prospective trials are needed to compare whole brain irradiation with SRS and surgical resection with SRS.

**Cardiac Tamponade:**

• up to 21% of autopsied cancer patients have pericardial involvement.
• Clinical symptoms of tampanade include anxiety, chest pain, and dypnea.
• Clinical signs: peripheral edema, hypotension, pulsus paradoxus, increased jugular venous pressure, softened heart sounds, and pericardial friction rub. Enlarged cardiac silhouette on CXR. Electrocardiographic changes include low QRS and non-specific ST/T wave changes. Echo shows pericardial effusion.
• Treatment: depends on the histologic diagnosis and the patient’s cardiac status. If the patient is hemodynamically unstable or has had prior chest irradiation, pericardiocentesis or pericardiac window is done. It can be done percutaneously. In many cases, drainage for several days with an indwelling catheter alleviates the effusion without recurrence. Chemotherapy or radiation therapy is effective in lymphoma, leukemia, and breast cancer. Sclerotherapy with tetracycline or bleomycin is effective and has a low morbidity. Prognosis in general is poor.
Section 8  Palliative Care

Pain Management

Diagnosis

- Careful medical history
- To determine the cause of the pain
- To determine co-factors that would influence treatment choice/route
- Laboratory
- Blood tests, bone scans, CT scans, MRI

Pathophysiology

Pain is perceived on the skin surface by nociceptors. Unlike other sensory receptors, nociceptors are only activated when a painful stimulus is present. The message is sent via type C (small) fibers mainly to the dorsal root ganglion and after this synapse, the fibers transmitting pain ascend in the lateral spinothalamic tract to the level of the mid brain where an interaction occurs such that the message may be modified by outflow down that spinal cord. This input may be transmitted through the sympathetic system. Pain messages are then transmitted up the brain stem to the thalamus and again modified by input from the cortex. Various neurotransmitters are involved but in particular excitatory amino acids may be released. Among these are NMDA (N methyl d aspartate). This amino acid is released at the level of the cord and receptors with a shift in voltage and the binding of glutamate, in order to activate the receptor. Activation of the NMDA receptor may account for the phenomenon of “wind-up” where the continued firing of the neurons occurs even if the stimulus is removed. This observation has important implications for chronic pain. Attempts to prevent “wind-up” may prevent the development of chronic pain.

Pain categories include nociceptive pain occurring with bone metastases; visceral pain perceived as deep, poorly localized, arising with bowel obstruction; neuropathic pain, occurring with nerve injury; and complex regional pain, arising after injury which persists – probably due to sympathetic fiber involvement. In patients with cancer combinations of these types of pain can be seen. In general, 75-85% of pain in the cancer patient is due to disease. The remaining causes of pain are due to treatment, and occasionally to non-malignant causes, such as a herniated disc.

Poor prognostic features of pain include incidental pain (movement related), history of substance abuse, psychiatric history, escalating does of current medication [tolerance], neuropathic pain, and cognitive impairment.

Pain at the end of life is often “global pain” and may involve psychic or existential pain, anxiety and depression. These issues need to be addressed also.
# Treatment
## A Stepwise Approach

<table>
<thead>
<tr>
<th>Mild Pain</th>
<th>Moderate Pain</th>
<th>Severe Pain</th>
<th>Coanalgesics/Adjuvants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Codeine (Tylenol #3 = acetaminophen + codeine)</td>
<td>Morphine (Dilaudid)</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>(Tylenol #3 = acetaminophen + codeine)</td>
<td>Hydromorphone (Duragesic)</td>
<td>Antidepressant</td>
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<tr>
<td>NSAID</td>
<td></td>
<td></td>
<td>Bisphosphonates</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Narcotic infusions</td>
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<td></td>
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<td>Chemotherapy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone (Lortab = acetaminophen + hydrocodone)</td>
<td>Fentanyl (Duragesic)</td>
<td>Biofeedback/Biorelaxation</td>
<td>TENS units</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone (Percodan = aspirin + oxycodone and Percocet = acetaminophen + oxycodone)</td>
<td></td>
<td>Nerve blocks – neurosurgery</td>
<td>Radiation therapy</td>
</tr>
</tbody>
</table>

### Principles of Prescribing Analgesics:

- Analgesics should be prescribed on an “around the clock” basis rather than “as needed” to prevent rather than treat pain.
- No ceiling for analgesic use in cancer patients
- Patients may be started on short-acting analgesics. Total 24 hour doses are calculated and converted into a long-acting formulation.
- Breakthrough medicine (which can be the same medication as the “around the clock” medication) should also be prescribed. Breakthrough pain is intermittent pain that occurs spontaneously or with activity. Patients can be instructed to take their breakthrough medication prior to activities that cause pain. Breakthrough doses are usually 20% of the total dose of the long-acting formulation.
- Learn the pharmacology (the duration of action, side effects, cost, and routes of administration) of a few analgesics. The common side effects of narcotics are constipation, sedation, nausea and vomiting, and respiratory depression. When using stronger opioids, a laxative regimen is usually needed.
- Explain to patients the importance of following a scheduled regimen. Reassure them that they are not likely to become addicted by taking strong narcotics, early treatment will not result in loss of efficacy later, and that sometimes very large doses of medication are required to control their pain.
- Use drug combinations to provide additive analgesia and reduce side effects. For example, nonsteroidal antiinflammatory drugs can be given with narcotics to reduce bony pain. Antidepressants or antiepileptics can be given with narcotics to reduce neuropathic pain. Glucocorticoids reduce the edema associated with brain and epidural metastases.
- If tolerance develops, switch to an alternative drug or increase the dose until pain is controlled. Use the equianalgesic tables. Remember oral or parenteral. Decrease by 20% for cross tolerance.

### Morphine

- Morphine can be given by oral, subcutaneous, intramuscular, intravenous, and rectal routes.
- Immediate release oral morphine has a short half-life. It should be given every 2 to 3 hours. Sustained release morphine (MS Contin) should be given “around the clock” every eight hours.
hours or every twelve hours.

• Subcutaneous, intramuscular, and intravenous routes have equivalent potency. The half-life is short; the medication should be given every 2 to 3 hours. Continuous IV. or sq administration via a pump is very effective for patients with refractory pain.

• When using the parenteral route use one half to one third of the same drug.

• The nausea and sedation that occurs with morphine usually subsides after the first few days of treatment.

• No tachyphylaxis for constipation.

• Constipation should be prevented with a regular laxative, stool softener or both.

• A morphine concentrate of 20mg/ml may be given sublingually and is very useful in terminally ill patients who cannot or are too tired to swallow. Dose would range from 5 to 20mg q 2 hours prn.

• Methadone is a long acting opioid. It is the only opioid that is not cleared renally.

End of Life Care

• Hospice Care

The word hospice comes from the Latin root for hospitality and hospitable. The Irish Sisters of Charity viewed death as one stage of a journey. They opened a hospice in Dublin in 1879 and another in London in 1905. These were places where dying people could be cared for, when they could not be managed at home.

Today most hospice care occurs at home. Sometimes hospice care occurs in hospice centers when the nursing needs of the patient or the burden on their caregivers is too great to continue at home. Hospice focuses on palliative care. It:

1. Affirms life and regards dying as a normal process.
2. Neither hastens nor postpones death.
3. Provides relief from pain and other distressing symptoms.
4. Integrates the psychological and spiritual aspects of patient’s care.
5. Offers a support system to help the family cope during the patient’s illness and their own bereavement.
• Pain Control – covered in the preceding section.
• Dyspnea Control – If the patient is near to death, morphine may help relieve distress. For specific situations:
  1. Bronchospasm – nebulized albuterol or oral steroids.
  2. Rales – diuretics are occasionally needed. (If pneumonia seems likely, decide whether an antibiotic will rehabilitate the patient or just prolong the dying process.)
  3. Effusion – consider thoracentesis or pleurodesis if the patient is ambulatory.
  4. Thick secretions – nebulized saline, transderm scopolamine patches, oxybutynin ( Ditropan )
  5. Anemia – occasionally a blood transfusion can add energy and reduce dyspnea for a few weeks.
  6. Anxiety – change position, relaxation techniques, benzodiazepines. Benzodiazepines should be given continuously in a patient on opioids.
• Nausea and Vomiting – covered in the next section.
• Fear- Pay attention to physical care and symptoms. Determine what will make transition to death more acceptable and less fearful. e.g. religious beliefs, gathering friends, reviewing life, additional professionals in the home?
• Anorexia – loss of appetite and progressive cachexia are among the most frequently encountered symptoms. One should treat complicating conditions:
  
  A ches and pains
  N ausea
  O ral Candidiasis
  R eactive (or organic) depression
  E vacuation problems (constipation, retention)
  X erostomia (dry mouth)
  I atrogenic (radiation or chemotherapy)
  A cid-related gastritis or peptic ulcers
• Occasionally a patient will benefit from an appetite stimulant:
  1. Megestrol 800mg/d PO (Megace oral suspension 20 cc q am)
  2. Medroxyprogesterone 500mg/d IM
  3. Dexamethasone 3-6 mg/d PO
  4. Marinol 2.5 to 10 mg per day.
• Eventually the patient and the family should accept anorexia as part of the dying process. Artificial feeding, except during active treatment (which is not part of hospice care), with NG tubes, total parenteral nutrition, IV fluids, does not prolong life.
• Constipation – prevent with a regular laxative, stool softener or both. Some ideas include: Senna as a laxative, colace as a stool softener and lactulose as a nonabsorbable solute in the event that senna and colace do not work. The “right “amount will very from individual to individual.
  Restlessness and Delirium are common in the final stage of life. Look for easily treatable causes unless the patient is near death. For severe agitated delirium can cause more clouding of the sensorium. Benzodiazepines are to be avoided. Consider low dose of haldol.
Section 9
Controlling Nausea

- The incidence of nausea and vomiting varies among patients.
- A young age, female, history of nausea, history of emesis during pregnancy and a tendency to get motion sickness increase the risk.
- A history of significant amount of alcohol consumption is associated with decreased risk.
- Emesis results when the vomiting center is stimulated from:
  1. Chemotherapy trigger zone (CTZ) in the area postrema of the fourth ventricle
  2. Afferent fibers of the cerebral cortex
  3. GI tract (especially duodenum)
  4. Heart
  5. Vestibular apparatus
  6. The periphery via the vagus nerve and other autonomic nerves.
- Common causes of nausea and vomiting in the cancer patient are antineoplastic agents, GI tract tumors, GI obstruction, infections, medications, (particularly narcotics and psychogenics) intracranial tumors, high intracranial pressure. Metabolic: uremia, hypercalcemia.

**Chemotherapy Agents with high likelihood of emesis**

<table>
<thead>
<tr>
<th>Highest emetogenic potential</th>
<th>Moderately high potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin &gt;50mg/m2</td>
<td>BCNU</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>*Nitrogen mustard</td>
<td>Hexamethylmelamine</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>Cisplatin &lt; 50mg/m2</td>
</tr>
<tr>
<td>Cyclophosphamide &gt; 1.5 gram/m2</td>
<td>Cyclphosphamide</td>
</tr>
<tr>
<td></td>
<td>Actinomycin D</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
</tr>
<tr>
<td></td>
<td>Cytarabine &gt;100mg/m2</td>
</tr>
</tbody>
</table>

*Probably the highest
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Do</th>
<th>Intervals (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>depresses dopamine receptors In the CTZ</td>
<td>10mg PO or 10-15mg spansules</td>
<td>4-8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25mg rectally</td>
<td>8</td>
</tr>
<tr>
<td>Granisetron (Kytril)</td>
<td>inhibits 5-HT3, a serotonin receptor</td>
<td>1-2mg PO</td>
<td>once a day</td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>inhibits 5-HT3, a serotonin receptor</td>
<td>24mg PO</td>
<td>once a day</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>inhibits 5-HT3, a serotonin receptor</td>
<td>0.15mg/kgIV</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8mg PO</td>
<td>4-6</td>
</tr>
<tr>
<td>Tetrahydrocannabinol (Marijuana/Marinol)</td>
<td>unclear-patients should be “high” to get an effect</td>
<td>5mg/m² PO</td>
<td>1-3 hr before then 2-4 hr after up to six times total</td>
</tr>
<tr>
<td>Dexamethasone (Ativan)</td>
<td>unclear, amnesia, sedation</td>
<td>10mg IV or PO</td>
<td>2-4</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td></td>
<td>1-2mg IV or PO</td>
<td>6-8</td>
</tr>
<tr>
<td>Prometrazine</td>
<td>depresses dopamine receptors in CTZ</td>
<td>12.5-50mg PO</td>
<td>4</td>
</tr>
<tr>
<td>Meboclopramide</td>
<td>depresses dopamine receptors in CTZ</td>
<td>0.5mg 1kg PO</td>
<td>6</td>
</tr>
</tbody>
</table>

Prophylaxis or rx of delayed emesis (d 2-5 with chemo rx)
Prochlorperazine 10-25 mg po or pr q 6-12h O
Decadron 4-8 mg po q 8-12 hours
Lorazepam 0.5-1 mg po q 8-24h

**Guidelines**

- Patients should be cautioned to take their antiemetics at home for a day or two after receiving their chemotherapy.
- Patients should receive primary prophylactic anti-emetic regimen according to emetic potential of chemotherapy.
- Breakthough antiemetics are added if patients develop emesis inspite of prophylaxis.
- Some patients experience a “delayed” nausea up to 5 days after cisplatin. A short course of Dexamethasone can be helpful in preventing this.
- Prescribe tetrahydrocannabinol for severe nausea and vomiting only when other modalities have failed.
Section 10
Clinical Trials

- Cancer treatment cannot improve without cancer trials
- Clinical trials are done to test cancer treatments. They can be done on an institutional basis such as at the Lineberger Cancer Center or the James P Wilmont Cancer Center or by large cooperative groups such as ECOG (Eastern Oncology Cooperative Group), SWOG (South western oncology group), NSABP (National Surgical Adjuvant Breast and Bowel Project), and CALGB (Cancer and Leukemia Group B). Large cooperative groups are made up of several institutions that agree to work on ideas. The Lineberger Cancer Center belongs to the NSABP and CALGB.

Traditional types of trials:
- Phase 1: Tests the side effects and establishes the maximum tolerated dose (MTD) of drugs by gradually increasing the dose. These are usually done in patients where there are no effective therapies.

- Phase 2: Tests the effectiveness of a drug(s) in decreasing the burden of cancer. Tumor size before and after treatment is measured. The dose established in phase I is usually used in phase II.

- Phase 3: Compares an established treatment with one that was effective in phase II. These are usually done with large populations of patients in cooperative groups. For example, comparing leupron to leupron plus flutamide in prostate cancer patients.

- Phase 4: Tests an existing therapy in the medical community.

Target - Based Therapy

- New target based antineoplastic compounds have minimal toxicity and are envisioned to be effective at doses well below those leading to severe toxicity.
- Traditional phase 1 studies are not necessary.
- Traditional phase 2 studies many not be useful because target based agents many work by preventing disease progression or improving quality of life. Clinical trials are being redesigned to evaluate these drugs.

Vaccine Trials - seek to develop the most immunogenic way to give the vaccine.

Prevention trials - are being conducted. For example, The “STAR” study is comparing Tamoxifen versus Raloxifene in the prevention of breast cancer.
Section 11  Cancer in the Elderly

Epidemiology

- Cancer is the second overall leading cause of death in the United States for persons over the age of 65.
- More than 60% of all cancer occur in the approximately 12% of the population over age 65.
- The number of people over the age of 65 will double in the next 50 years. The number of people over the age of 85 will quadruple.

The Frail Elderly patient

- It is estimated that there are 4 million frail persons in the United States and that 300,000 of them are affected by cancer
- The life expectancy is excess of years.

Table 1. Criteria for Establishing the Diagnosis of Frailty

<table>
<thead>
<tr>
<th>Activity of daily living dependence</th>
<th>+ Three co-morbid conditions</th>
<th>+ One geriatric syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Delirium</td>
<td>Depression</td>
</tr>
<tr>
<td>Falls</td>
<td>Incontinence</td>
<td></td>
</tr>
</tbody>
</table>

BIRTH --------→ ADULTHOOD--------→ SENILITY --------→ FRAILTY ---→ DEATH

- Puberty  GFR  Age ≥85
- Ossification  Cystine/Cysteine  ≥3 comorbid conditions
- Height  Functional Reserve  ADL dependence
- Maturity  ≥ Geriatric Syndrome

Complicating Factors in Treating Elderly patients

- Physiologic changes
- Comorbidity
- Balance between expected side effects and patient benefit (in terms of quality of life and life expectancy)

Physiology of aging

- Renal function declines with age (Adjust the dose for cisplatin, carboplatin, methotrexate, bleomycin, carmustine, cladribine, camptothecin, cytarabine, fludarabine, ifosfamide)
- Hepatic Function is modified by aging due to decreased blood flow, decreased albumin production, decreased cytochrome P450 function.
- Modification of lean body mass occurs with a proportional increase in total body fat by 15 to 30% of body weight implying that lipophilic drugs will have an increased volume of distribution. The clinical consequences of these changes are unclear.
- Bone Marrow Reserve– declines. Unpredictable myelotoxicity occurs in frail elderly patients.
- Neurotoxicity – more common. Increased neuropathy, ototoxicity and CNS toxicity.

Assessment of the older patient.
• Take a multi dimensional assessment.
• Comorbidity
• Functional status
• Depression (misdiagnosed in one half of all cases)
• Mental status (Cognitive disorders are missed without screening) Use the mini-mental state scale for screening
• Medications – polypharmacy can lead to interactions with oncology treatments.
• Nutrition
• Social support

Table 2. Minimum Suggested Assessment of Older Cancer Patients
• Complete History and physical (including psychiatric, visual, and auditory problems)
• Formal assessment of orientation and short-term memory
• Detailed medication history
• Obesity/Cachexia, weight changes, brief dietary screening
• Screening for frailty
• Social Support evaluation
• Creatinine clearance
• Patient opinion (even if it is limited)
• Osteoporosis
• Failure to thrive
Section 12
Positive Emission Tomography

- The positron is a subatomic particle that represents the positively charged, antimatter equivalent of the negatively charged electron.
- Positron emission is one of the processes by which radionuclides convert a proton to a neutron. The positron interacts with an electron in a process known as annihilation. The mass released in this process is converted to energy. PET scanners detect this energy.
- The information derived from recording a large number of annihilation reactions can be reconstructed to form radiographic pictures. This is the same general approach used in computed tomography (CT).

Advantages
- Evaluates physiology and biochemistry as well as anatomy.
- Should have the ability of detecting disease at an earlier stage.

Disadvantages
- A Cyclotron or other particle accelerator must be at or near the site (PET radionuclides have a short half-life).
- There are regulatory problems because of the radioactive decay.
- It is expensive.

2-(f-18) fluro -2 -deoxy-D-glucose
- FDG
- Is a glucose analogue that is accumulated and becomes trapped in metabolically active cells.
- It is the most common radionuclide used.
- Since malignant cells use more glucose than normal cells, there should be a greater release of FDG by the malignant cells than the nonmalignant cells in the annihilation reaction.

Use of PET scans with FDG in the following tumor types:
1. Primary Brain Tumors – detects the presence of viable tumor versus scar after radiation treatment.
2. Lung Nodules – separates benign from malignant nodules with a sensitivity of 90-95% for cancer.
4. Colorectal cancer – PET is more accurate than CT in staging and assessing recurrent disease.
5. Lymphomas – PET is more accurate than CT for staging.
   Can determine if a residual mass after treatment is disease versus scar tissue. PET scanning has a high negative predictive value of relapse if negative after treatment for Hodgkin’s disease.
6. Head and Neck – staging, detecting recurrence, and possibly detecting unknown primary sites.
7. Melanoma: high sensitivity and specificity.
8. Diseases under study: breast, ovarian, pancreatic, sarcoma, and thyroid. PET may be useful in breast cancer patients in sorting out benign from malignant radiographic findings.

Cancers where FDG-PET is not useful:
Prostate, hepatocellular carcinoma, and tumors of the genitourinary tract, low grade lymphoma.
Part II - Specific Cancers

Section 1

Breast Cancer

Incidence

- Most common cancer in women
- Second leading cause of cancer death in women
- 205,000 cases expected in 2002 in the USA
- Approximately 50,000 deaths/year in the USA
- Female: male 100: 1

Risk Factors – (70% women with breast cancer do not have risk factors)

- A positive family history
  Hereditary breast cancer, BRCA1, BRCA2
  Familiar tendency
- Reproductive endocrine Variables
  Late pregnancy
  Early menarche
  Late menopause
  Prolonged exposure to postmenopausal estrogen (> 10 years)
  Possibly prolonged exposure to oral contraceptives
- Obesity.
- Fatty diet
- Radiation therapy
  Patients who have been treated for Hodgkin’s disease with mantle field radiation are at increased risk.
- Other cancers
  Patients with ovarian, uterine, or breast cancer are at increased risk.

Incidence of Breast Cancer in the US by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1:19,608</td>
</tr>
<tr>
<td>30</td>
<td>1:2,525</td>
</tr>
<tr>
<td>35</td>
<td>1:600</td>
</tr>
<tr>
<td>40</td>
<td>1:217</td>
</tr>
<tr>
<td>45</td>
<td>1:93</td>
</tr>
<tr>
<td>50</td>
<td>1:50</td>
</tr>
<tr>
<td>55</td>
<td>1:33</td>
</tr>
<tr>
<td>Over</td>
<td>1:8</td>
</tr>
</tbody>
</table>

Pathology

- Majority are adenocarcinomas
- 70 to 80% are infiltrating ductal carcinomas
Prognostic Features

Nodal status – the greater the number of positive nodes, the worse the prognosis
Tumor size – the greater the size, the worse the prognosis
Estrogen and Progesterone – prognosis improves with positive ER, PR, or both
Histopathology – infiltrating ductal and infiltrating lobular carry the same prognosis.
	Other types are better
DNA factors – a high S phase which measures proliferation is a poor prognostic factor.
HER-2/neu- epidermal growth factor receptor.
	1/3 of women will have HER-2/neu on the surface of their cells. Positivity predicts for a more aggressive tumor.

Screening

- Women over age 20 should perform breast self-examination every month.
- Women should have a yearly examination by a physician.
- Women between 40 and 50 should discuss a screening mammogram with their physician and decide if it is right for them.
- Women over 50 should have annual mammography.
- Recommendations have not been made for elderly women.

Clinical Presentation

Diagnosis:

- Most breast cancers present as painless masses.
- Most breast masses should be biopsied (One exception is a possible cyst that is followed through a menstrual cycle and disappears at the patient’s next visit about a month later).
- Once the diagnosis of breast cancer has been made, a complete history and physical examination should be done. Chest x-ray, complete blood count and screening liver chemistries are done on all patients. A bone scan is indicated if the patient has bone pain.

Local Regional Therapy

- Breast cancer is a systemic disease; variations in local-regional therapy are unlikely to affect survival.
- Breast conservation: local excision of the tumor (lumpectomy, segmentectomy, excisional biopsy or quadrantectomy) followed by radiation therapy to the breast offers comparable 5-year survival to more extensive surgery (mastectomy).
- In many cases breast conservation cannot be done.

Tumor factors:
	Tumor size is too large relative to the breast size (consider neoadjuvant therapy)
	There is extensive ductal carcinoma in situ.
	There is inflammatory breast cancer
	The biopsy margins are consistently positive for disease

Patient Factors:

- Prefers a mastectomy.
- Lives too far from a radiation facility or is too frail to get there
- Prior chest radiation
- Significant connective tissue disease
- Pregnancy (Defer radiation until after delivery if possible)
**Axillary Lymph node dissection**

- A dissection of nodes on the side of the tumor has been done to help determine prognosis and choose treatment.
- In the late 1990’s this procedure has been questioned because:
  1. There is morbidity – numbness – a risk of arm edema (lymphodema) – general anesthesia is required.
  2. The results of the procedure may not change therapy – a postmenopausal patient may get Tamoxifen regardless of nodal status (see below)
- “The Sentinel Lymph Node Biopsy” identifies the first node that drains the tumor with a combination of dye and radiotracers. In most cases, if the sentinel lymph node is negative the rest of the nodes are negative. If it is positive, a full axillary dissection should be done. The procedure requires expert training and experience in order to be reliable. It is not done for very large tumors, for patients with inflammatory disease, for patients who have had multiple biopsies in the breast, after neoadjuvant therapy. Sentinel lymph node biopsy is becoming the standard procedure in most instances.

**Staging**

- Is based on a TNM system
- T describes the size of the tumor and it may describe characteristics such as skin and chest wall involvement
- N refers to the axillary lymph nodes on the side of the affected breast.
- M refers to the presence or absence of distant metastases.

**Adjuvant Therapy**

“Adjuvant” means as an adjunct to surgery. This is the treatment given after local therapy to increase the chance eliminating micrometastatic disease.

- The decision to give adjuvant therapy is based on the patient’s general health, age, stage of disease, and prognostic variables of the tumor.
- Treatment can consist of hormonal therapy, chemotherapy, or both.
- Hormone receptors. Estrogen receptor (ER) and progesterone receptor (PR) are important in determining responsiveness of breast cancer to endocrine therapy.
- The hormonal therapy for postmenopausal women is antiestrogens or aromatase inhibitors. Tamoxifen is the most common antiestrogen prescribed in the United States. A large trial called the ATAC study was presented in 12/2001 and it showed that the aromatase inhibitor, anastrozole, is slightly more effective than tamoxifen but the follow up in this study is short. So unless there are contraindications to tamoxifen (blood clotting risks or exceptionally high risk of uterine cancer), tamoxifen is still the treatment of choice. The hormonal therapy for premenopausal is ovarian ablation (either by castration, medical therapy, or radiation), antiestrogens, or both.

**Tamoxifen**

- It competitively binds to the estrogen receptor and deprives the breast cancer cells of proliferative estrogen stimulation. After the antiestrogen receptor complex translocates to the cancer cell nucleus, direct cell injury may occur.
- Disadvantages:
  1. Only 3% of patients discontinue treatment because of toxicity. Side effects are hot flashes and mild nausea. Rare side effects are nausea, rash, vaginal discharge, thrombocytopenia.
  2. The “tamoxifen flare” can occur in patients being treated for metastatic disease. In this, bone pain increases and hypercalcemia can occur.
Because tamoxifen paradoxically acts as an estrogen in the body, it has increased the risk of endometrial cancer in women over 50. Women are cautioned to report any pelvic symptoms, especially unusual vaginal bleeding. They are to have a yearly pelvic examination, including pap smear. Screening for endometrial cancer is not indicated and it is costly.

An increased incidence of deep venous thrombosis occurs. Approximately 1 percent per year

Tamoxifen may hasten the development of cataracts in elderly patients.

- **Advantages:** Decreases systemic recurrence of breast cancer by approximately \( \frac{1}{2} \) in postmenopausal patients and \( \frac{1}{3} \) in premenopausal patients.
  - Decreases the incidence of contralateral breast cancer
  - Prevents bone loss in post menopausal women
  - Lowers total cholesterol by lowering LDL-cholesterol

### Choosing Adjuvant Therapy

- Almost every patient gets adjuvant therapy
- The one group that **does not** have tumors <1.0 cm, low histologic grade, node negative, ER/PR positive
- Adjuvant chemotherapy has been shown to increase survival in most patients. The survival benefits decrease as the age of the patient increases and are undetectable after the age of 70 years.
- Younger and premenopausal patients derive more benefits from adjuvant chemotherapy because:
  1. They tend to have more aggressive disease
  2. They tend to have fewer side effects
- Older women derive more benefits from tamoxifen
- In women <50 or pre menopausal, the chemotherapy of choice is “anthracycline-based”. The most common regimen is called “A/C” and consists of Adriamycin and cytoxan given intravenously every 3 weeks for four treatments. When “A/C” is medically contraindicated or when patients insist on a more mild alternative “CMF” --- cytoxan, methotrexate, and 5 FU may be used. There are many different regimens of CMF but the most effective is called “classic CMF” and it consists of oral cytoxan and IV M,F.
- In women > 50 who are node negative, tumors less than 2cm, and ER/PR positive, the chemotherapy is CMF, MF, or A/C.
- In women >50 who are node positive, studies that have shown a survival advantage with chemotherapy, have used an adriamycin-based program. If and anthracycline is medically contraindicates or the patient refuses, CMF could be presented.
- In all cases that are ER/PR positive TAMOXIFEN is given for 5 years! When tamoxifen is given with chemotherapy the risk of blood clots increase but many national studies prescribe it this way. Alternately the tamoxifen is given when all of the chemotherapy has been completed.
- **REMEMBER,** the benefit of chemotherapy decreases with age so older postmenopausal women could be treated with tamoxifen alone.
- Chemotherapy programs can be more complicated than those described above:
  1. When patients have node positive, ER/PR negative disease 4 A/C followed by 4 cycles of a taxane (taxol or taxotere) may be given
  2. Studies in the year 2002 demonstrated an advantage for dose-dense chemotherapy for women with higher risk, early stage disease. This is chemotherapy given at the usual dose, more frequently along with growth factor support. For example, four doses of Adriamycin every 2 weeks, followed by 4 cycles of cyclophosphamide every two weeks, followed by four doses of paclitaxel every two weeks OR four cycles of A/C every 2 weeks followed by four doses of paclitaxel every 2 weeks.
  3. When neoadjuvant programs are given for very large tumors
  4. When patients have inflammatory breast cancer (see below)
5. When patients have >4 lymph nodes positive they may be encouraged to go on more aggressive chemo regimens.
   • Whenever possible enroll patients onto clinical trials.

### Table 1: Common side effects of A/C versus CMF

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>A/C</th>
<th>CMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Complete</td>
<td>10%</td>
</tr>
<tr>
<td>Bone Marrow Suppression</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Cardiac Toxicity</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Equal</td>
<td>Equal*</td>
</tr>
<tr>
<td>Risk of Menopause**</td>
<td>40-50%</td>
<td>50-90%</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>possible</td>
<td>possible</td>
</tr>
</tbody>
</table>

*But the treatment takes longer so fatigue can be the most disturbing side effect.  ** Risk goes up with age

**Metastatic Recurrent Disease**

- Approximately 50% of patients will develop a recurrence in their lifetime.
- Metastatic/recurrent disease is generally incurable. In MD Anderson’s long term experience, the estimated cure rate was 5%. The same can be said with selected patients who have undergone bone marrow transplantation.
- The average survival after recurrence is approximately 24 months but many individuals can live much longer than that and 10% can live for more than 10 years.
- The most common site of recurrence is local/regional followed by bone > lung > liver. CNS metastases (brain, leptomeninges, spine) are rare.
- Patients with local/regional or bone only disease tend to have an indolent course whereas patients with visceral disease, especially liver, tend to have an aggressive course.
- Treatment depends on:
  1. The site(s) of recurrence
  2. The pace of the disease
  3. The ER/PR status
  4. A patients age and general health
• In general:
  Local regional recurrence ➞ surgery possible ➞ treat with surgery followed by radiation
  Surgery impossible ➞ radiation
  Consider changing or adding hormone treatment

Bone recurrence ➞ hormone treatment plus bisphosphonate (zolendronate)

Lung recurrence ➞ course is variable => assess tempo ➞ chemo or hormone therapy

Liver recurrence ➞ chemo

Brain => Solitary metastasis with systemic control ➞ surgical resection and radiation.
non solitary or no systemic control ➞ whole brain radiation

**Hormone Treatment**

**Concept:**
1) Estrogen is made by the ovaries and by the adrenal glands. Adrenal glands make androgens which are converted to estrogens.
2) Premenopausal women still have estrogen production by their ovaries. Post menopausal do not.
3) Post menopausal women derive estrogen from the adrenal glands.

**Premenopausal:**
Oophorectomy (medical, surgical, or by radiation to the ovaries) (add tamoxifen if not previously treated with tamoxifen)

  ↓
  Tamoxifen
  ↓
  Progestins (mechanism is unclear)

**Post Menopausal**
Tamoxifen

  ↓
  Aromatase inhibitors (block peripheral conversion of androgens to estrogens)
  ↓
  Progestins

Androgens (mechanism unclear) New emerging data point that aromatase inhibitors are better as first line treatment for metastatic breast cancer, however, long term follow up is warranted before changing standards of treatment.

Fulvestrant (Faslodex) a "pure" antiestrogen, has a steroid structure that blocks ER dimerization, inhibits DNA binding, increases ER turnover, and inhibits nuclear uptake of the receptor. As a result, it blocks ER function before coactivator binding, theoretically overcoming resistance that is driven by the agonist properties of tamoxifen. It is administered as a monthly intramuscular injection. The United States Food and Drug Administration approved it in April 2002 for treatment of hormone receptor-positive postmenopausal women with disease progression following antiestrogen therapy.
Table 2: Active Agents in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Doxorubicin (adriamycin)</th>
<th>Paclitaxel (taxol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (taxotere)</td>
<td>Mitoxantrone (Novantone)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>5 FU</td>
<td>Doxil (liposomal Adriamycin)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Navelbine</td>
</tr>
<tr>
<td>Capecitabine (xeloda)</td>
<td></td>
</tr>
</tbody>
</table>

Chemotherapy Treatment

- There are many effective programs
- Adriamycin and the taxanes are equally effective
- Single agent treatment can be just as effective as combination therapy and have fewer side effects.
  Many studies show a higher response rate with combination therapy but no increase in survival. Use
  combination therapy when a quick response is needed.
- Longer durations of therapy are more effective than shorter duration
- Capecitabine is an oral 5FU that is effective in patients who fail adriamycin and taxol

Special Issues in Metastatic Disease

1) Bone Mets – Don’t forget bisphosphonates for bone disease. Pamidronate, 90 mg IV over 90
   minutes every 3-4 weeks. It decreases bone pain, spinal cord metastasis and orthopedic
   procedures.

2) Herceptin – Is a monoclonal antibody to Her-2neu, which is present on the cancer cells in 1/3
   of patients. It is indicated to treat metastatic disease in patients who test positive for this
   protein by the fluorescence in situ hybridization (FISH) test. It is being studied in earlier
   stages of breast cancer. It may be combined with Taxol, Taxotere, Navelbine or given as a
   single agent. The most important side effect is cardiac dysfunction.

Special Issues in Breast Cancer

Breast Cancer during pregnancy

- 2 to 3 % of patients with breast cancer are pregnant or lactating.
- These tumors are difficult to detect. Late diagnosis is common.
- Chemotherapy except anti-metabolites can be used after the first trimester. Radiation is postponed
  until after delivery.

Inflammatory Breast Cancer

- This is clinical description of an erythematosus, warm breast and the pathologic proof of
  adenocarcinoma.
- It is treated with chemotherapy followed by radiation and surgery.
- It should not be misdiagnosed as mastitis.

Carcinoma in Situ
• Carcinoma in situ means “Cancer in Place”. There are two types, ductal carcinoma in situ (DCIS), and lobular carcinoma in situ, (LCIS). This refers to the location in the breast where the tumors arise.
• DCIS is being diagnosed more commonly because of a true increased incidence and because it shows up easily on mammogram as a calcified area.
• Treatment of DCIS is surgical excision. Most excised DCIS should be followed by breast radiation.
• Tamoxifen has been shown to decrease local/regional recurrence and contralateral disease.
• LCIS is usually and incidental finding. The presence of LCIS slightly increases the risk of breast cancer in the contralateral breast. Women should be warned of their increased risk of contralateral disease and consider tamoxifen as a preventative therapy

**Prevention**

• Tamoxifen is indicated as a chemo preventive drug in high risk patients.
• Risk is calculated by the “Gail Model” and looks at:
  1. Race
  2. Age
  3. Age at first menses
  4. Age at live birth
  5. Number of mother/sister(s)/daughter(s) with breast cancer
  6. Number of previous breast biopsies
• Were any of these atypical hyperplasia?
• Lobular carcinoma in situ?
• A relative risk is calculated from these factors. A number of doctors have risk assessment calculators in their practices. Alternatively, the NCI has a web page for this. A risk of 1.67 or greater could qualify a woman for treatment.
• In high risk patients, Tamoxifen decrease the chance of breast cancer by 50%, decreases the incidence of hip fractures, and lowers cholesterol.
• Serious and life – threatening side effects are rare and could occur in women > 50 years. These are an increased incidence of uterine cancer, deep venous thrombosis, stroke, and pulmonary embolism.
• The “STAR” or P2 trial began in 1999 and is comparing Tamoxifen vs. Raloxifene in postmenopausal women.

**Bone Marrow Transplantation**

• Is not an effective adjuvant treatment for patients with > 10 positive lymph nodes.
• It is not better than standard treatment for metastatic disease. It is more costly and has more toxicity.
Section 2

Colorectal Cancer

Incidence

• 148,000 cases expected in the US in 2002
• over 50,000 people die of the disease per year
• Males>Females, but not true for all populations

Risk Factors

• Age (peak onset age 65)
• High fat diet increases the risk
• Family History
• Colon polyps (villous greater risk than tubular adenomas)
• Gardener’s syndrome, ulcerative colitis, Crohn’s colitis
• NSAIDS may decrease risk
• Exercise may decrease risk

Genetic Alterations

See Part I section 2

Pathology

• Majority are adenocarcinomas

Staging- The following is the modified Dukes system*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Confined to mucosa and submucosa</td>
<td>95%</td>
</tr>
<tr>
<td>B1</td>
<td>Penetration into the muscularis</td>
<td>85%</td>
</tr>
<tr>
<td>B2</td>
<td>Extension through serosa</td>
<td>75%</td>
</tr>
<tr>
<td>C1</td>
<td>Positive lymph nodes; tumor within the bowel wall</td>
<td>65%</td>
</tr>
<tr>
<td>C2</td>
<td>Positive lymph nodes; tumor extends through serosa</td>
<td>60%</td>
</tr>
<tr>
<td>D</td>
<td>Involvement of adjacent organs or distant metastases</td>
<td>&lt;5-10%</td>
</tr>
</tbody>
</table>

*Remember “C” disease = lymph node involvement

The TNM system is preferred. Generally, T3 = B disease. N1 = C disease
R=inadequate resection (positive margins, insufficient nodal dissection)

Screening

• The American Cancer Society recommends:
  1. Annual digital exam and fecal occult blood testing for patients over age 40.
  2. Proctoscopic exams every 3 to 5 years after two initial negative tests q 1 year for people over age 50. In truly high-risk patients, such as those with familial polyposis and ulcerative colitis, a full colonoscopy is indicated.
Treatment of Colon Cancer (including the proximal 1/3 of the rectum)

- Adjuvant chemotherapy is recommended for all patients with stage III (lymph node positive) colon cancer. The standard of care is 6 months of chemotherapy with 5FU and leucovorin. The three drug regimen of 5FU, leucovorin and irinotecan (Saltz regimen) is being studied.
- The NSABP and a pooled analysis of trials offer different opinions on Stage II disease. Impact B2 recommends no adjuvant treatment. NSABP states that there’s a reduction in death rate with adjuvant treatment. Subset of patients with bowel obstruction or perforation at diagnosis may benefit from adjuvant chemotherapy. Whenever possible, enroll patients on a clinical trial, especially if they have B2 disease.

Treatment of Rectal Cancer

T1-local excision only
T2-local excision followed by post op radiation therapy
T3-Radical surgical resection, 5FU chemotherapy, radiation therapy
- optimal order of treatment is unknown
- adjuvant versus neoadjuvant treatment is being studied
- Neoadjuvant Chemo/radiation can down stage approximately 80% of low rectal cancers to enable a resection with coloanal anastomosis as an alternative to abdominoperineal resection

Metastatic Disease

Isolated Liver Metastases

- Offer resection when there are few mets or mets isolated to one lobe of the liver. Alternatives include radiofrequency ablation, cryoablation, or alcohol injection.
- Studies have shown improved survival with intrahepatic FUDR and systemic chemotherapy following liver resection.
- In selected patients with liver metastasis who cannot undergo resection, treatment with intrahepatic FUDR with Decadron and with or without leucovorin
- In other patients, offer systemic chemotherapy

Widespread disease

- Chemotherapy improves quality of life compared to best supportive care
- First line chemotherapy treatments are 5 FU based with or without irinotecan (CPT-11). The Saltz program showed improved survival compared with 5FU/leucovorin but it is very toxic. Newer programs look at infusional 5 FU with CPT-11 or oxaliplatin. Oral 5FU treatments are new in 1999 and may be preferred over intravenous treatments in some patients.
- Single agent irinotecan (CPT-11) is second line treatment
- Oxaliplatin has been FDA approved for patients who have progressed on CPT-11.
- Whenever possible, enroll patients onto a clinical trial

Chemotherapy Side Effects

- 5FU/Leuvorin- When each drug is given once a week at 500mg/m2 the most common side effects are diarrhea and decreased blood counts.
- 5FU/Leucovorin- when each is given as an intravenous push on Monday through Friday once a month mucositis is the most common side effect. Cryotherapy (ice chips) during the treatment helps decrease the incidence of mucositis.
- Infusional 5FU- 1000mg/m2/day Monday-Friday or 350mg/m2/day every day for month is associated with mucositis and the hand/foot syndrome. Hand/foot ranges from a mild discomfort to peeling and pain.
- Oral 5FU- Hand/foot syndrome, mucositis
- Irinotecan (CPT-11)- By itself there are two forms of diarrhea, acute and chronic. The acute reaction can occur during the infusion and is associated with sweating. It is treated with atropine. The delayed reaction can be life threatening if not properly treated and prevented with loperimide. In the adjuvant trial of Irinotecan, 5FU and Leucovorin, there has been an excess of morbidity due to diarrhea, sepsis and thrombosis.
Section 3
Lung Cancer

Incidence
- Approximately 170,000 cases will be diagnosed in 2003. Approximately 155,000 deaths will occur.
- Leading cause of cancer death for men and women

Causes
- Cigarette smoking increases the risk of all types of lung cancer except bronchioloalveolar cancer
- A 20-pack year history of smoking produces a 10% lifetime risk of dying of lung cancer
- Heavy metals: arsenic, chromium, nickel Gases: nitrogen mustard, coal, radon (uranium and iron miners are exposed to high levels of radon)
- Previous lung injury by inflammatory process increases the risk for bronchioloalveolar lung cancer
- Chlorethyl ethers
- Asbestos -- acts synergistically with smoking
- Patients with chronic obstructive pulmonary disease have increased risk

Pathology

<table>
<thead>
<tr>
<th>Histology</th>
<th>Incidence</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small-cell carcinoma</td>
<td>25%</td>
<td>central</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>30%</td>
<td>central</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>30%</td>
<td>peripheral</td>
</tr>
<tr>
<td>Large-cell carcinoma</td>
<td>15%</td>
<td>peripheral</td>
</tr>
</tbody>
</table>

- In the last few years there has been a decrease in squamous cell cancer and an increase in adenocarcinomas. This may be due to the relative increase in women with lung cancer (adenocarcinoma is more common in women) or the use of filtered cigarettes. The later allow smaller articles to reach the peripheral airways. Peripheral airways are the location of bronchioloalveolar lung cancer, a form of adenocarcinoma.
- The most important task for the pathologist is to distinguish small cell carcinoma (SCLC) from non-small cell carcinoma (NSCLC) since the treatment is vastly different. It is believed that lung cancers arise from a common stem cell; occasionally tissue types are “mixed”
- In SCLC abnormal expression of p53 tumor suppressor gene occurs. Deletion of the short arm of chromosome 3 is common. In NSCLC, point mutations in ras oncogenes are associated with poor prognosis.

Clinical Presentation
- Squamous cell has the greatest tendency to remain localized.
- Small cell has the greatest tendency to spread.
- Central, endobronchial lesions can produce cough dyspnea, hemoptysis, wheezing, stridor, or post obstructive pneumonia
- Superior sulcus (Pancoast) tumor - apical pain. Symptoms of shoulder pain radiating down the arm. Can be associated with Horner’s syndrome. May be missed on an ordinary chest x-ray. Check lordotic view and/or chest CT scan.
- Mediastinal tumors can cause superior vena cava syndrome, hoarseness (involvement of the recurrent laryngeal nerve), paralysis of the diaphragm (involvement of the phrenic nerve), and dysphagia (compression of the esophagus).
These tumors can metastasize anywhere. Brain mets (in 30% of patients with SCLC at diagnosis and up to 80% during follow-up). Adrenal mets do not cause symptoms unless they are bilateral.

**Paraneoplastic syndromes**

**Small cell**
- SIADH (see Part I, section 7)
- Ectopic ACTH - muscle weakness, hypokalemia, metabolic alkalosis, and moderate elevations in glucose. They lack the physical characteristics of classic Cushing’s syndrome
- Eaton Lambert – weakness and fatigability of proximal muscles, often with a dry mouth, dysarthria, peripheral paresthesias, ptosis, blurred vision, and muscle pain.
- Cerebellar degeneration

**Non small cell**
- Adenocarcinoma - thrombophlebitis, hypertrophic osteoarthropathy
- Bronchioloalveolar - marantic endocarditis
- Squamous cell - ectopic PTH production – hypercalcemia
- General – poliomyelitis or dermatomyositis: progressive proximal mm, weakness, increased sedimentation rate, increased muscle enzymes

**Lung cancer, in general**
- Cerebellar degeneration
- Dermatomyositis,
- Acanthosis nigricans
- Anemia
- Granulocytosis

**Diagnosis**
- The American Cancer Society does not recommend any screening for lung cancer
- Central lesions - bronchoscopy is most likely to provide a tissue diagnosis and it can assess patency of the airways and operability
- Solitary peripheral nodule - surgical removal (even for SCLC).
- Multiple peripheral nodules - percutaneous transthoracic needle aspiration
- If sputum cytology, bronchoscopy, and/or needle aspiration fail to yield a diagnosis, and a search of readily accessible sites of metastatic disease is unproductive, a surgical procedure is necessary.
  - scalene node biopsy
  - mediastinoscopy and mediastinotomy
  - thoracotomy
Staging

**Tx**  Primary tumor cannot be assessed or tumor proven by malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

**T0**  No evidence of primary tumor

**Tis**  Carcinoma in situ

**T1**  Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus, (i.e., not in the main bronchus)

**T2**  Tumor with any of the following features of size or extent:
- More than 3 cm in greatest dimension
- Involves main bronchus, 2 cm or more distal to the carina
- Invades the visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

**T3**  Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

**T4**  Tumor of any size that invades any of the following: Mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.

Regional Lymph Nodes (N)

**NX**  Regional lymph nodes cannot be assessed

**N0**  No regional lymph node metastasis

**N1**  Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor

**N2**  Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

**N3**  Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or0 supraclavicular lymph node(s)

Lung Cancer Stage Groups by TNM Subsets

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
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<td>Stage I A</td>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I B</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III B</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
**Treatment of NSSLC**

Criteria for Inoperability

**Tumor Related:**
- Stage IIIB: Vocal cord paralysis
- Phrenic n. paralysis: Pleural effusions due to malignancy
- Bulky Mediastinal disease: SVC syndrome

Medical contraindication:
- General debilitation FEV < 800-1000 mL

**Stage I, II, IIIa**
- Surgical resection whenever possible
- Direct extension into the chest wall and pericardium are not contraindications to surgery

**Locally Advanced NSSLC**
- Disease that is too extensive for primary surgical resection, sited to the thorax, and technically allows inclusion of the entire tumor within a radiation field.
- Includes IIIB, Bulky IIIa, excludes malignant pleural effusion
- Standard of care for good performance status and little weight loss is chemotherapy and thoracic irradiation (RT)
- Several studies favor concurrent chemo/radiation over sequential treatment for increased survival local toxicity (mucositis) may be greater.
- Questions:
  1. Added value of new chemotherapy agents?
  2. Are there effective strategies for reducing esophagitis?
  3. What is the role of altered fractionation RT in conjunction with chemotherapy?
  4. What is the role of three-dimensionally planned RT?
  5. What is the optimal management of low performance status patients?

**Stage III b with pleural effusion, stage IV**
- Chemotherapy is the standard of care for good performance status (ECOG less than or equal to 2), weight loss less than 10%.
- Platinum-based chemotherapy results in prolongation of survival, symptom control, and superior quality of life compared to supportive care alone.
- 1990s---new agents have been developed: paclitaxel and docetaxel, topoisomerase I inhibitors (irinotecan), novel analogs (vinorelbine and gemcitabine). But no combination of “new agent” plus platinum has proved superior to another “new agent” plus platinum.
- Two agents are superior to single agent, however, three agents are more toxic but not more effective.
- Novel therapeutic approaches to NSSLC are currently in clinical trials:
  1. Hypoxic cytotoxins (tirapazamine)
  2. Monoclonal antibodies to tumor growth (trastuzumab)
  3. Signal transduction modulators (bryostatic, UNC-01, R115777)
  4. Matrix metalloproteins inhibitors and antiangiogenic agents (marimastat and others)
  5. Gene replacement therapy
- Elderly patients with good performance status can tolerate platinum-based combination. Patients with poor performance status should be considered for single agent treatment.
Treatment of SCLC

- The key point is that SCLC has early metastatic spread. Chemotherapy is given to everybody, regardless of the stage.
- Prognosis: The average survival for limited stage disease without treatment is approximately 4 months and with treatment, approximately 1 year. A small number will have a prolonged disease free survival with aggressive combined modality treatment.
- The average survival for extensive stage disease without treatment is approximately 6 weeks and with treatment, 7 to 9 months. There are virtually no cures.

Surgery - Has a limited role in SCLC. Occasionally, a patient with SCLC presents with a peripheral coin lesion. These patients should undergo surgical resection followed by adjuvant chemotherapy.

Chemotherapy - This is the main form of treatment. It is used to palliate, or possibly cure, limited stage disease.

Many combinations of chemotherapy are used. Some examples are cisplatin/VP16, ifosfamide/VP16, Taxol, oral VP16 and CPT-11. A study done in Japan showed that cisplatin plus irinotecan was superior to cisplatin and VP-16.

Radiation - Has three roles:
1. It is added to chemotherapy for limited state disease. Many trials have demonstrated that combined modality treatment produces a slight benefit in survival.
2. It is used to palliate metastases (example, in a vertebral body with signs of spinal cord compression).
3. It can be given to the whole brain to prevent brain metastases in patients with limited stage disease who have achieved a complete clinical response.
Section 4

Prostate Cancer

Incidence
- 189,000 cases expected in 2002
- The most common cancer in American men.
- 80% of cases are found in men over 65 years old.
- 16% lifetime probability of developing prostate cancer in men (1 in 6).
- Second leading cause of cancer death in men (31,500 deaths in 2001)
- Cause is unknown. In some way related to testosterone stimulation.
- Twice as common in African Americans compared to Caucasian Americans.

Pathology
- Almost all are adenocarcinomas
- The Gleason score correlates with prognosis. In this system, the primary and secondary patterns are scored from 1 (well-differentiated) to 5 (poorly-differentiated). Adding the two scores gives a number from 2 to 10. Scores of 2 to 4 are low grade, 5 to 7 intermediate, 8 to 10 high grade. High grade tumors are more likely to spread outside of the prostate and relapse following therapy.
- Extent of involvement by tumor should be estimated (eg, number of core biopsies involved, percentage of tissue replaced by tumor, linear length of cancer).

Screening
- Controversial. The value of routine screening is not established.
- The prostate-specific antigen, PSA, is the most sensitive test for early detection of prostate cancer, but is limited by insensitivity and lack of specificity (elevated with benign prostatic hyperplasia, prostatitis).
- A multicenter trial sponsored by the National Cancer Institute is underway to test the value of early detection on mortality. The united states preventive services task force (USPTF) have not endorsed routine screening. The American cancer society, however, recommends screening with PSA and DRE to men 50 years or older with more than 10 years life expectancy. Screening is recommended at age of 45 for higher risk patients.
**Staging**

- TNM staging

T1 tumor not palpable or visible by imaging
  - T1a Tumor incidental finding \( \leq 5\% \) of tissue resected.
  - T1b Tumor incidental finding > 5% of tissue resected.
  - T1c Tumor identified by needle biopsy alone (after PSA elevation)

T2 Tumor confined to the prostate
  - T2a Tumor involves one lobe
  - T2b Tumor involves two lobes

T3 Tumor extends through the prostatic capsule
  - T3a extracapsular extension
  - T3b tumor invades seminal vesicles

T4 tumor fixed or invades adjacent structures other than seminal vesicles.

N0 no regional lymph node metastasis
N1 regional lymph node metastasis.

M0 no distant metastasis
M1 distant metastasis

**Stage Group**

I  T1a, N0, M0 any Gleason score
II  T1a, N0, M0 GS 2,3, or 4
    T1b,c N0, M0
    T2 N0 M0
III  T3 N0 M0
IV   T4 N0 M0
    Any T N1 Mo
    Any T, any N, M!
Bone mets from prostate cancer are characteristically osteoblastic in appearance. Bone is the predominant site of metastasis and the only site of metastasis in the majority of patients. Skeletal complications (eg, pain, spinal cord compression, pathologic fracture) are common. However, hypercalcemia from prostate cancer is uncommon. Also, retroperitoneal or pelvic soft tissue masses can cause hydronephrosis and renal failure.

**Treatment**
- Nomograms using three factors (clinical stage, Gleason score, and pretreatment PSA) have been developed for estimating the probability of organ-confined disease and are helpful for planning treatment.
- Patients with PSA <10 (unless T3/T4 tumor or Gleason 8 or greater) do not need bone scan for initial staging as yield is extremely low.
- Due to the long natural history of prostate cancer, life expectancy of patients (co-morbid conditions, etc) should be taken into account.

**Surgery**
- Radical retropubic prostatectomy or radical perineal prostatectomy is performed. The retropubic approach has the advantage of gaining access to the pelvic lymph nodes. Due to better ability to predict lymph node involvement using nomograms, pelvic node dissection is done less frequently.
- Side effects of prostatectomy: impotence, urinary incontinence. With nerve sparing prostatectomy, the incidence of impotence is reduced (compared to older operations).

**Radiation Therapy**
- External Beam - based upon plain radiographs with bony landmarks
- Three-dimensional conformal radiotherapy - computer tomography and software create 3-dimensional treatment. It is the new standard of care in major centers.
- Side effects of radiation therapy: impotence, bladder irritation (urgency, pain, frequency), rectal irritation (diarrhea, urgency, tenesmus, bleeding)

**Overview of Treatment by Stage**

**T1a:** Observation (surgery or radiotherapy could be recommended for Gleason 7 or greater, men with life expectancy greater than 20 yrs)  
**T1b, T1c, T2:** Radiation, Surgery or Observation. Observation is recommended for men with a life expectancy of less than 10 years and low Gleason grade (6 or less). Younger men and men with a high Gleason grade benefit form treatment. Radiation therapy is given to the prostate field. Relative efficacy of surgery and radiation therapy is controversial in the absence of data directly comparing treatment modalities prospectively, but for younger patients, prostatectomy is the gold standard. Older patients and patients with more advanced tumors have traditionally been treated with radiation and this may skew the results unfavorably. Both radiation therapy and surgery can cause substantial side effects in a significant number of patients.

**T3, T4:** Radiation to prostate and pelvis (+/- hormonal therapy). Adjuvant hormonal therapy with radiation should be strongly considered as addition of hormonal therapy has been shown to increase survival compared to radiation alone.

**Hormonal Treatment of Metastatic Prostate Cancer**
- Initially, prostate cancer growth is dependent on testicular androgens and androgen deprivation leads to regression of tumor in most patients.
- For hormonal treatment of prostate cancer, surgical castration with bilateral orchiectomy and medical castration with an LHRH agonist such as Leuprolide are equally effective in decreasing circulating testosterone to the castrate level and represent the standard of care with equivalent clinical outcome. Most studies show no advantage of combined androgen blockade (surgical or medical castration combined with an antiandrogen like Bicalutamide or Flutamide).
• Addition of an antiandrogen is indicated for the first month when the LHRH agonist is started, to prevent "flare". The LHRH agonist initially causes a surge in the testosterone level due to the stimulation of the LHRH receptor in pituitary. Over three weeks, testosterone eventually falls to the castrate level due to loss of LH secretion from pituitary. This initial flare can cause worsening symptoms, such as paralysis in patients with spinal cord compression. Therefore, monotherapy with the LHRH agonist is contraindicated in patients with spinal cord compression.

• The major side effects of androgen deprivation therapy (surgical and medical) include loss of libido, impotence, gynecomastia, hot flashes, loss of muscle mass, osteoporosis, anemia and fatigue.

Hormone Treatment of metastatic disease
• The common treatments, their mechanisms, and their major side effects are listed below:

  Orciectomy
Mechanism: decreases circulating testosterone by removing the organ in which 95% of testosterone is produced.
Advantage: inexpensive, no compliance issue, acts immediately without flare (especially advantageous for treatment of cord compression).
Disadvantage: psychological trauma

  LHRH analogues (Leuprolide (Lupron) and Goserelin available as depo prep given every 3 months)
Mechanism: Decrease LH & testosterone after an initial flare. Feedback to inhibit LH secretion from pituitary.
Advantage: Avoids psychological trauma and thrombotic complications of estrogens.
Disadvantage: Flare, expensive, need for parenteral administration.

  Antiandrogens (Flutamide (Eulexin), Bicalutamide (Casodex))
Mechanism: Inhibit binding of testosterone to the androgen receptor
Advantage: Antiandrogen alone is the only agent that does not cause impotence. Has been used for potency-sparing androgen deprivation (not standard treatment).
Disadvantage: Very expensive, diarrhea, increased LFT's, gynecomastia.

• Hormonal treatment is clearly indicated for palliation of symptomatic metastatic disease (eg, painful bone mets, obstructive uropathy). However, when to start hormonal therapy in asymptomatic patients (early vs delay till symptoms appear) is controversial. Arguments in favor of early hormonal treatment: decreased complication rates (eg, pathologic fracture, cord compression), survival advantage in locally advanced disease and pelvic node involvement. Against early treatment: no definitive survival benefit in metastatic disease, side effects of hormonal treatment (see above) without symptoms to palliate.

Treatment of Hormone-Refractory Prostate Cancer
• Hormone-refractory disease is defined as progression despite having a castrate level (<50 ng/dl) of testosterone. Most patients will progress on androgen deprivation therapy after a median of 18-24 months. Thereafter, the median survival is about one year.

• For patients who have been on antiandrogen, the first step is to stop antiandrogen as it leads to improvement with PSA drop in 15-20% of patients (antiandrogen withdrawal phenomenon).

• Second-line hormonal manipulations such as 1) addition of antiandrogen, 2) ketoconazole (inhibition of adrenal androgen production), 3) low dose steroids, can be tried for patients who are not good candidates for chemotherapy, but responses are short-lived.

• Traditionally considered chemo-resistant disease. However, this picture is changing. Mitoxantrone has been shown to improve pain and quality of life without increasing overall survival. A combination of estramustine and taxanes (docetaxel or paclitaxel) has shown encouraging activity with PSA responses in 60-70% of patients and is becoming the de facto standard therapy in hormone-
refractory prostate cancer patients. PSA is a good tumor marker to follow to assess response to therapy.

- Palliation of painful bone mets can be achieved with radiation therapy (indicated for spinal cord compression, painful sites) or systemic administration of bone-seeking radioactive isotopes (Samarium-153).
- Always think about the possibility of spinal cord compression in any patients with prostate cancer and increasing back pain. Loss of ambulation and bowel/bladder incontinence are late symptoms that are usually irreversible despite treatment. Ideally, patients should be diagnosed and treated before these advanced symptoms appear.

**Role of Bisphosphonates**

- A recent randomized trial of zoledronic acid (vs placebo) in hormone refractory prostate cancer patients with bone mets shows a benefit of zoledronic acid 4 mg IV q3 weeks in delaying skeletal complications of bone mets (i.e. path fx, cord compression, RT for pain relief/impending fx, etc.). Therefore, administration of the newest and potent bisphosphonate zoledronic acid may be beneficial in this population whereas such data is lacking for pamidronate.
Section 5
Testicular Cancer

Incidence
- a rare tumor
- 1% of cancer in men
- 7,500 cases expected in 2002
- most common cancer in men in the 15 to 35 age group
- very rare in African American men

Risk Factors
- History of testicular cancer is the highest risk factor for subsequent cancer (500 fold).
- cryptorchidism
- Klinefelter syndrome (germ cell tumor)
- isochrone 12 p is common

Pathology
Seminoma Nonseminoma Mixed
  embryoonal carcinoma teratocarcinoma
  choriocarcinoma yolk sac tumor

Stage
- I Disease limited to the testes
- IIA Microscopic positive retroperitoneal lymph nodes at lymphadenectomy
- IIB Macroscopic positive retroperitoneal lymph nodes (2-5cm)
- IIC Palpable retroperitoneal lymphadenopathy
- III Supradiaphragmatic or vesicular involvement

Diagnosis
- Ultrasound can identify testicular masses from extratesticular masses.
- Testicular biopsy is **not** recommended. Orchiectomy is the preferred method of diagnosis as well as treatment once a testicular mass is identified. 95% of testicular masses are malignant. A biopsy may lead to aberrant lymphatic drainage from the tumor.

Markers
- Human chorionic gonadotropic (B-HCG) - elevated in 50% of patients with non seminoma and 10% of patients with seminoma
- Alpha-fetoprotein (AFP) – may be elevated in patients with non seminoma but never in patients with seminoma. It may be produced by embryonal carcinoma teratocarcinoma, yolk sac tumor, or combined tumors.
- When the HCG is elevated in a patient with seminoma, the pathologist should make sure that no nonseminomatous component exists
- LDH has prognostic significance

Treatment of Seminoma
• Extremely radiosensitive
• Stage I, IIA, IIB is treated with radiation therapy to parotic and ipsilateral iliac lymph nodes (hockey stick field). 10% of patients with IIB will recur in the mediastinum but they can be cured with chemotherapy. Patients with stage I seminoma can be observed as in non-seminoma below; about 15% will have persistent disease after orchiectomy and can be salvaged with chemotherapy
• Stage IIC -- chemotherapy
• Stage III - chemotherapy
Treatment of Non seminoma

Clinical Stage I

Clinical Stage I

Choice

observation  retroperitoneal lymph node dissection (RPLND)

75 to 80%         20 to 25%
- nodes  + nodes
probably cured          ½ were     ½ relapse
cured by the surgery chemotherapy with a high likelihood of cure

Summary

Observation: avoids unnecessary surgery but it requires compliance on the part of the patient and doctor. Patients are seen every month for the first year, every two months for the second year and every 6 months or more frequently for years 3 to 5. A chest x-ray, tumor markers (AFP, HCG, LDH), and physical examination is done with each visit. Patients who do not have elevated AFP or HCG should be considered for chemotherapy instead of observation.

RPLND: Surgery alone cures approximately 10% of clinical state I patients. Retrograde ejaculation used to be a common complication of RPLND. In the 1990s RPLND has become the preferred treatment over observation because the surgical technique has improved, making retrograde ejaculation a rare complication.

Immediate Chemotherapy: may be given to patients with clinical Stage I testicular cancer who have poor prognostic signs --- angioinvasion, lymphatic invasion, or embryonal histology.

Stage II

• Pathologic Stage II (patients with “Pathologic Stage II disease” had positive lymph nodes discovered on RPLND) could be treated with observation or adjuvant chemotherapy. Half of the patients who choose observation will relapse so the compliance on the part of the patient and doctor must be very high. The same tests and visits are followed as in Observation for Stage I disease. Adjuvant chemotherapy is preferred over observation because the disease is easily cured this way, side effects of chemotherapy have decreased over the last 8 years, and the issue of compliance with observation is avoided.

• Clinical Stage II should be treated with standard chemotherapy.

Stage III

• Good risk (no nonpulmonary mets, low serum markers such as AFP<1000 ng/ml, hCG<5000 IU/L and LDH<1.5XULN): >90% longterm cure. 3 cycles of BEP (Bleomycin, Etoposide, Cisplatin) is equivalent to 4 cycles of EP (Etoposide, Cisplatin).
• Intermediate risk and poor risk: 75% and 40% cure with 4 cycles of BEP.

**Standard Chemotherapy**

- For good risk disease, consists of three cycles of Cisplatin, Bleomycin, and Etoposide. The Cisplatin and Etoposide are given for 5 days in a row every three weeks and the Bleomycin is given weekly for nine treatments. Alternatively, four cycles of Cisplatin and Etoposide may be given.
- Bleomycin may cause irreversible pulmonary toxicity and should **not** be used in patients with pre-existing lung disease. Bleomycin may also cause Raynaud’s disease.

**Final Pearls**

- Regardless of the treatment (observation, RPLND, chemotherapy) used for any stage of disease, follow-up should be monthly for the first year and bimonthly for the second with physical examination, serum markers, chest x-ray, and other appropriate laboratory tests.
- Surgery is indicated for marker negative residual disease following chemotherapy for nonseminomatous testicular cancer. If persistent cancer is found at the operation, two additional cycles of chemotherapy are given.
- Other side effects of treatment include bone marrow suppression, alopecia, ototoxicity (cisplatin), renal failure (cisplatin if proper hydration is not followed), leukemia (etoposide when higher doses are used)
- Surgery is indicated for marker negative residual disease following chemotherapy for non-seminomas testicular cancer. If persistent cancer is found at the operation, two additional cycles of chemotherapy are given.
Section 6

Ovarian Cancer

- This section covers ovarian cancer of epithelial origin. Tumors of the germ cells are rare and will not be discussed

Incidence
- 23,300 cases expected in the U.S. in 2002
- 13,900 will die due to the disease
- 1 in 70 American women will develop it
- Fourth most common cause of cancer death

Reduces Risk Increases Risk
Pregnancy Infertility
Hysterectomy Late menopause
Tubal ligation Breast cancer
Oral contraceptives Talc
Family history Asbestos

Presentation

- Unfortunately early symptoms and signs are unusual and most case present at an advanced state.
- The tumor spreads by fine intraabdominal seeding along peritoneal surfaces. Thus, ascites and pleural effusions are common.

Ca-125
- Is a monoclonal antibody that is elevated in over 80% of patients with ovarian cancer.
- It is generally not elevated in early stage disease
- It can also be elevated in patients with endometriosis or other benign gynecologic conditions, and in cancer of the pancreas, lung, breasts, endometrium and colon.

Staging
Stage I - a Tumor limited to one ovary; capsule intact
b Tumor limited to both ovaries, capsules intact
c Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
Stage II Tumor in one or both ovaries with pelvic extension
Stage III Tumor in one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and or regional lymph nodes
Stage IV Distant mets

Treatment
Surgery is a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Pelvic node sampling + paraaortic node sampling. Optimal cytoreductive surgery correlates with improved survival.

Stage IA, grade1- Surgery only
Stage Ib through IIIC - surgery and adjuvant chemotherapy
Stage IV- surgery and chemotherapy. Outcome depends on the volume of cancer following surgery.

Stage IV patients who are poor candidates for surgery because of older age, poor health, site of metastases (predominantly lung, for example) could be treated with chemotherapy alone.

**Chemotherapy**

- In the mid 90s Taxol/Carboplatin is the standard of care for adjuvant therapy. In 2001 data from the ICON-3 study showed no difference between carbo versus taxol/carbo. The choice of adjuvant chemotherapy, therefore, is controversial. Offer the patient a clinical trial whenever possible.

Treatment of the patient with recurrent disease:
- Use platinum-containing regimens in patients who responded to the initial platinum-based therapy and relapse after a platinum-free interval.
- Use therapy for platinum resistant patients in those who failed to respond to platinum. Choices are taxol, oral etoposide, topotecan, tamoxifen, gemcitabine, navelbine, ifosfamide, and possible liposomal doxorubicin. There’s no evidence that combinations of these drugs are more effective than single agent therapy.

**Secondary cytoreduction**
- Good clinical data is lacking

**Dose Intensity (Stem cell transplant/Bone marrow transplant) in second line theory**
- It is not standard therapy
- Seven randomized trials are currently in progress

**Familial Ovarian Cancer** (see also part I, section 2)

- 5% of ovarian cancer is hereditary
- There are three types of “hereditary”
  1. Site specific ovarian cancer
  2. Ovarian cancer in conjunction with breast cancer due to a mutation in BRCA1 or BRCA2
  3. The “cancer family syndrome” (Lynch Syndrome II also called hereditary non polyposis colorectal cancer --- HNPCC) with a high concentration of colon, endometrial, and ovarian cancer in the same family

Screening for these women is controversial. People at risk for BRCA1 or BRCA2 should see a genetics counselor. For others, screening with biannual pelvic examinations and yearly pelvic ultrasounds should begin at age 30. Some doctors do serial Ca-125 (but Ca-125 does not diagnose early disease). Some women choose to have prophylactic oophorectomy. But ovarian cancer may still occur, (Perhaps microscopic ovarian cancer has already spread at the time of the prophylactic oophorectomy or perhaps the peritoneum itself can give rise to this malignancy).

Section 7
**Malignant Melanoma**

**Incidence**
- 51,400 cases expected in 2001
  - 1930: 1 in 500
  - 1989: 1 in 125
  - 2000: 1 in 90
- Highest concentration occurs in the legs in women and the interscapular in men and women.
- Be able to recognize the various forms of malignant melanoma and to distinguish malignant lesions from benign ones. (see Scientific American Medicine for photographs)

<table>
<thead>
<tr>
<th>Benign Nevi</th>
<th>Dysplastic Nevi</th>
<th>Melanoma</th>
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<tr>
<td>Numerous begin nevi</td>
<td>Larger than ordinary nevi</td>
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<tr>
<td>smooth border</td>
<td>irregular border</td>
<td>Superficial Spreading</td>
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<td>uniform color</td>
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**Dysplastic Nevi Syndrome**

Features:
1. >100 lesions, ranging in size from 6mm to 15 mm in diameter
2. Absent at birth; number of nevi increases at age 5 or 6; at puberty the number and appearance of moles may change drastically
3. These are the most common precursors of melanoma; 8 to 12% of melanoma cases are with the dysplastic nevi syndrome.
**Risk factor for melanoma**

Sun Exposure  
Sunburn in Childhood  
Changing mole  
Adulthood  
Irregular pigmented lesion  
Congenial nevus  
White race  
Personal or family history  
Immunosuppression

Genes implicated: 9p21, 9p22

**Diagnosis:**

- Use ABCD for differentiating early melanoma from benign mole:
  - A: asymmetry
  - B: border irregularity
  - C: color is variegated, black
  - D: diameter usually more than 6mm

- The preferred way of diagnosis is excisional biopsy, if large size lesion then incisional or punch biopsy.

**Staging**

- Clark’s staging is based upon the depth of epidermis or dermis that is involved by tumor.
- Breslow’s system measures the depth of invasion in mm.
- The thickness of invasion (Breslow’s System) correlates with the prognosis better than the location of invasion (Clark’s System).

**Treatment**

- Consists of a wide excision. Margins should be 2cm for melanomas of 1mm or greater in thickness.
- There’s no survival benefit to prophylactic lymph node dissection. But, a lymph node dissection is therapeutic in patients with involved nodes. A sentinel lymph node procedure can identify occult metastasis. It is usually done for melanomas that are 1 mm or greater in thickness with non-palpable nodes. If identified, a full therapeutic lymph node dissection is in order.
- Adjuvant immune treatment is under investigation. Melanomas greater than or equal to 4mm in thickness or melanomas associated with positive lymph nodes may be treated with adjuvant interferon. At least one large randomized study showed improved survival with interferon.
- Metastatic disease may be treated with palliative care alone. Selected patients may benefit from chemotherapy or biologic treatment. Active chemotherapy drugs are cisplatin, dacarbazine, carmustine, taxanes, temozolamide, and fotemustine. A study showed that combination chemotherapy with DTIC, cisplatin, Tamoxifen, and BCNU (Dartmouth) was no more effective than single agent chemotherapy. Biologic treatment with interferon alpha, interleukin–2 and vaccine may be given. A 1999 report showed that there is no benefit to combining biologic therapy and chemotherapy.

**Section 8**
**Head and Neck Cancer**

- Includes tumors in the oral cavity, pharynx (oropharynx nasopharynx, hypopharynx), larynx, and paranasal sinus
- More than 90% are squamous cell carcinomas

**Incidence**

- In 2002 it is estimated that head and neck cancers will account for 2 to 3% of all cancers. It is estimated that 20,300 cases of oral cavity, 8,900 cases of laryngeal cancer, and 8,600 cases of laryngeal cancer will be seen.
- More in males.

**Risk Factors**

- poor oral hygiene
- chronic irritation form ill-fitting dentures
- tobacco smoking and tobacco chewing*
- betel nut
- heavy alcohol use*
- 15% have a second primary cancer in the lung or esophagus
- nasopharyngeal cancer, a relatively common tumor in South east Asia, appears to be associated with the Epstein-Barr virus

* Both are synergistic risk factors

**Clinical Features**

- Symptoms are usually related to the location of the primary
- Symptoms are often ignored until the disease is far-advanced because patients are often indigent and are without good access to health care. This cancer is not uncommon, however, in well-educated employed, insured patients with adequate access to health care.
- Otalgia, unilateral hearing loss, dysphagia, odynophagia, voice change, anorexia, weight loss and neck mass are the most common symptoms for head and neck cancer.
- Most remain localized. 10-20% present with distant metastases. Cancer in the vocal cords rarely metastasizes. Lung, liver and bone comprise the most common metastatic sites.
- A solitary pulmonary nodule in a patient with a history of head and neck cancer could represent a primary lung cancer (1/3), a metastasis (1/3), or a benign lesion (1/3).

**Staging**

- Panendoscopy: laryngoscopy, nasopharyngoscopy, esophagoscopy with biopsy
- Computed tomography, magnetic resonance imaging, and PET scanning can all be used.
- Chest x-ray
- Body CT, bone scan as clinically indicated
- Complete blood count, chemistries.

**Treatment**

**Definitions:**
1). Accelerated fraction eradication: shortens the total time of treatment. Theoretically should increase the probability of local control by reducing tumor repopulation.

2). Hyperfractionated irradiation: multiple small fractions of radiation are given each day to increase total dose but not risk long-term toxicity.

- Localized, early stage disease (Stage I and II): treated with surgery and radiation therapy
- Localized, advanced disease (Stage III/IV, resectable): treated with either surgery/radiation, or concomitant chemoradiation for organ preservation based on sites of primary (mainly larynx, hypopharynx, oropharynx)
- Localized, advanced (Stage III/IV, unresectable): Hyperfractionated irradiation has been shown to improve local control and survival compared to conventional, external-beam irradiation. Hyperfractionated radiation with concomitant cisplatin/5FU chemotherapy might be more effective than hyperfractionated radiation alone (RR = 60-80%, CR = 45-60%, 5 yr DFS = 20-25%).
- Recurrent/Metastatic: treated with standard chemotherapy and/or radiation with cisplatin, 5FU or carboplatin, paclitaxel. Use single agents for patients with poor performance status, including methotrexate. Salvage surgery should also be considered for recurrent resectable disease and can cure a small percentage of patients. Clinical trials available with EGFr antagonist, cdk inhibitors and viral agents.
Section 9

Gastrointestinal malignancies

Esophagus

- 13,100 cases in U.S. in 2002. Incidence is high in China
- Risk factors: alcohol, tobacco, Barrett’s esophagus (the most important risk factor for adenocarcinoma, please refer to general medical text for definition and recommended follow up), Plummer-Vinson syndrome, tylosis, achalasia, lye ingestion, gluten-sensitive enteropathy, and radiation therapy for other conditions.
- The incidence of adenocarcinomas in the distal esophagus and gastric cardia is increasing. SCC occur in the middle esophagus.
- Dysphagia to solids is the most common early symptom. Later, dysphagia to liquids occurs.
- Patients with esophageal cancer are also at increased risk for lung and head and neck cancer. Triple endoscopy (bronchoscopy, laryngoscopy, and esophagoscopy) is recommended by some.
- Treatment of localized disease consists of surgery alone (patients with no metastasis, no lymph node involvement, and no direct invasion of adjacent organs). The mortality of surgery is 5-10%. The two-year survival is only 15%. In patients who are not surgical candidates, the treatment is radiation plus chemotherapy (usually 5FU and cisplatin). Triple modality treatment is being studied.
- Treatment of metastatic disease is palliative.

Gastric

- 21,600 cases in U.S. in 2002. The incidence has been decreasing in the U.S
- more common in males.
- Major problem in Japan
- Risk factors: Helicobacter pylori gastric infection, older age, male gender, ingestion of nitrates and nitrites, chronic atrophic gastritis, gastric adenomas, diffuse gastric polyposis, pernicious anemia.
- Most are adenocarcinomas.
- Lymphomas comprise approximately 5%.
- Presenting symptoms are non specific including early satiety, nausea/vomiting, weight loss, and upper GI bleeding
- Physical exam may reveal left supraclavicular lymphadenopathy (virchow’s nodes), umbilical nodules (Sister mary joseph nodules), and palpable peritoneal implants on rectal exam (Blumer’s shelf)
- Paraneoplastic syndromes - gastric cancer is the most common malignancy associated with acanthosis nigricans. Also seen: coagulopathies---DIC, TTP, and migratory superficial thrombophlebitis---Eaton Lambert, dermatomyositis and polymyositis.
- Treatment consists of surgery if possible. Adjuvant chemoradiation is the standard of care after surgical resection ( 5FU, leucovorin and radiation). Neoadjuvant treatments are showing encouraging results but still under trials. Radiation and/or chemotherapy may be given to palliate patients with metastatic disease. Palliative resection should be reserved for patients with continued bleeding
Pancreatic

- 30,300 cases in 2002
- Rapidly increasing incidence
- More common in elderly and African Americans.
- Adenocarcinoma is the most common histologic type
- Five-year survival is (3%) for all stages, among the lowest of all cancers.
- Risk factors: cigarette smoking, alcohol, certain occupations (chemists, petroleum workers, coke and metal workers, gas plant employees)
- Abdominal pain, jaundice, anorexia, and weight loss are the usual presenting symptoms. A palpable gallbladder the Coursvoisier sign is seen in 25% of patients. Patients with pancreatic cancer are at very high risk for thrombosis.
- Determine if the disease is resectable for cure. Standard staging studies to determine resectability include spiral CT of the abdomen, EUS, MRI, laparotomy and/or laparoscopy.
- After surgery treat exocrine pancreatic deficiency with pancreatic enzymes.
- In patients with localized disease who are not surgical candidates, treatment usually is radiation therapy with 5 FU-based chemotherapy.
- In patients with distant disease consider chemotherapy with gemcitabine (the standard of care) or 5FU. Gemcitabine was approved by the FDA on the basis of improved pain control and quality of life. Consider palliative procedures such as celiac nerve block, surgical bypass, and biliary stent placement.
Section 10  AIDS Associated Malignancies

- Malignancies occur in approximately 40% of AIDS patients.
- Rates had declined since introduction of active HAART medications
- Certain cancers -- Kaposi sarcoma, non-Hodgkin’s lymphoma, Hodgkin’s disease, and cancers of the anogenital region, squamous cell carcinomas of the head and neck and cervical cancer -- occur more frequently in patients with the human immunodeficiency virus.

**Kaposi Sarcoma**  - There are 5 types
1. Classic KS - older men of Mediterranean heritage
2. Endemic KS - in central Africa. Indolent course
3. Iatrogenic KS - from immunosuppression such as with therapy to prevent rejection of transplanted organs.
4. Epidemic KS in HIV infected patients.
5. Non-Epidemic gay-related KS - no HIV is detected. Indolent and cutaneous with new lesions appearing every few years.

**Epidemic KS**
- Be able to recognize KS (see Scientific American Medicine)
- Lesions range in color from faint pink to reddish brown or blue and occur as macules, papules or nodules in the skin or oral mucous membrane.
- gamma herpes virus, human herpes virus type 8 (HHV-8), was identified in KS tissue biopsies from all patients with classic, African, transplant related, AIDS associated, but absent from non involved tissue.
- 95% diagnosed in homosexual or bisexual men.
- There is a decreasing incidence from 1981 to 1999
- This trend may be impart from HAART (highly active antiretroviral therapy)
- Multifocal, widespread lesions at the onset
- Skin, oral mucosa, lymph nodes, and visceral organs.
- Almost all patients develop disseminated disease.
- The treatment is palliative. Therefore, the most effective treatment with the least morbidity should be the goal. When possible, local treatment for symptomatic or disfiguring KS such as radiation, liquid nitrogen, and intralesional chemotherapy should be applied.
- Systemic treatment should be given for disseminated cutaneous disease or life threatening visceral disease, such as pulmonary involvement. The first line therapy is liposomal anthracycline eg, pegylated liposomal doxorubicin. Other effective chemotherapy is doxorubicin, bleomycin, vinblastine, vincristine, etoposide, and paclitaxel. Interferon alpha is used.
- Control of HIV infection with an active HAART regimen is essential.
- Poor prognostic factors include:
  - Visceral involvement
  - CD4 counts < 150/mm³
  - History of other opportunistic infection.
  - B symptoms
  - Poor performance status

Non-Hodgkin’s Lymphoma
• The incidence of intermediate and high grade NHL has significantly increased since the AIDS epidemic began.
• NHL occurs in 4 to 10% of patients with HIV. 60 times higher than general population.
• Majority of patients have advanced disease with median CD4 between 100 to 200 cells/mm3 while CD4 counts below 50 cells/mm3 is found nearly in all patients with CNS lymphoma.
• Pathology - most are B-cell lymphomas. Most are high grade (Burkitt’s lymphoma, immunoblastic lymphoma), diffuse large B cell lymphoma accounts for 30% of AIDS lymphoma, most CNS lymphoma are diffuse large B cell. Body cavity-based lymphoma / primary effusion lymphoma is an entity seen in HIV patients, occurs predominantly in males, may co-exist with KS, highly associated with HHV-8 and EBV.
• Features of AID-NHL that are uncommon in non-AIDS cases:
  - extranodal involvement
  - Most patients present with advanced stage
  - "B symptoms” are difficult to distinguish from underlying HIV
  - Central nervous system lymphoma is common (0.5% of AIDS patients)
  - Poor prognosis, even with treatment
• It is impossible to distinguish CNS lymphoma from toxoplasmosis on the basis of CT findings. Both are ring enhancing. A therapeutic trial on anti-toxoplasmosis medications is often given.
• Prognosis is associated with stage, severity of the underlying immunodeficiency (as measured by CD4), performance status, and prior AIDS diagnosis.
• Treatment should be systematic even if dissemination is not confirmed on routine evaluation.
• EPOCH regimen seems to be superior regimen to others but no randomized trials in between various regimens.
• CNS prophylaxis with intrathecal chemotherapy decreases CNS relapse.
• Active HAART is essential in treatment.

Hodgkin’s Disease
Hodgkin’s disease is commonly diagnosed in patients who have HIV. But, Hodgkin’s disease is NOT an AIDS-defining illness.
Features of Hodgkin’s disease in HIV infected patients that are uncommon in non-HIV infected patients:
  - extranodal involvement
  - Advanced stage
  - More aggressive
  - Poor prognosis
Section 11

Carcinoid Tumors
Incidence is 1-2 per 100,000 population in the U.S.
The appendix is the most common site followed by the rectum, ileum, lungs, bronchi, and stomach.

Pulmonary Carcinoid Tumors
- 2% of primary lung tumors.
- Typical pulmonary carcinoids are well-differentiated tumors that rarely cause carcinoid syndrome and have an indolent course. The 5-year survival is greater than 90 percent.
- Atypical carcinoids are more accurately classified as well-differentiated neuroendocrine tumors. They are more aggressive. The 5-year survival is between 40-60 percent.

Gastric Carcinoid Tumors
- Less than 1 percent of gastric neoplasms
  Three types:
  1). Associated with chronic atrophic gastritis-- and half of these are associated with pernicious anemia -- Treat with surgery
  2). Associated with Zollinger-Ellison syndrome
- Occur almost exclusively in patients with multiple endocrine neoplasia type 1, an autosomal dominant genetic disorder associated with the loss of MEN1, a putative tumor suppressor gene located on chromosome 11q13. MEN1 is characterized by tumors of the pituitary gland, pancreatic islet cells, and parotid glands.
  indolent course
  surgical resection
  3) Sporadic
- Aggressive with a poor prognosis
- Associated with atypical carcinoid syndrome, manifest by flushing and thought to be mediated by histamine.

Carcinoid Tumors of the Small Intestine
- 1/3 of small-bowel tumors
- 6th or 7th decade of life
- Vague abdominal pain for many years
- Prognosis correlates with stage. Five-year survival is 65% for localized or regional disease and 35% for those with distant mets.
- 5 to 7% present with the carcinoid syndrome

Appendiceal Carcinoids
- Occur at a younger age
- Curable by surgery

Carcinoid Tumors of the Colon
- Less than 1 percent of colonic tumors
- Majority of patients are treated with radical colectomy

Rectal Carcinoids
- 1-2% of rectal tumors
- Treatment is individualized, taking into account the patient’s age and coexisting conditions.
Metastatic Carcinoid Tumors
- Abdominal CT to check for liver metastases
- 5-HIAA in a 24 hour urine collection
  sensitivity = 73%
  Specificity 100%

Carcinoid Syndrome
- occurs in more than half of the patients with liver involvement. Rarely occurs when the liver is not involved.
- Characterized by flushing, diarrhea, wheezing
- Right-sided endocardiac lesions can cause tricuspid and pulmonic valvular damage
- Diagnostic studies include imaging studies CT/MRI and a 24-hour urine test for 5-hydroxyindoleac acid (5-HIAA). Octreotide scan has have been shown to have a higher sensitivity for detecting metastasis especially extrahepatic disease. It may predict who will respond to octreotide analogues.

Treatment of Bulk disease
Surgery
- Appendiceal carcinoids: if tumor less than 2 cm appendectomy, if tumor more than 2 cm then hemicolecctomy.
- Small and rectal carcinoids: resection with a wedge lymphadenectomy.
- Patients with limited liver metastasis may benefit from debulking, ablation with cryo or radiotherapy. Transplant after resection may be considered in patients with good performance

Treatment with Somatostatin analogues
- Somatostatin is 14-amino acid peptide that inhibits the secretion of a broad range of hormones, including growth hormone, insulin, glucagon, and gastrin.
- Somatostatin receptors are expressed on 80% of carcinoid tumors.
- Octreotide is an eight-amino acid long-acting somatostatin analogue used for detection and treatment.
- Scintography with radiolabeled octreotide has been used to determine extent of disease.
- Octreotide can treat the diarrhea, flushing and wheezing associated with carcinoid syndrome.
- A depot, LAR octreotide, can be given one a month. Chronic use is associated with cholelithiasis, fluid retention, and glucose intolerance.
- High dosages may be associated with anti-tumor activity.

Management of Hepatic Metastases
- Surgical resection for those with minimal disease
- Hepatic artery occlusion or embolization for those who are symptomatic. There may be many side effects and the result may be short-lived.

Medial Management of Metastatic Disease
• Streptozocin and fluorouracil is the chemotherapy of choice. Response ranges are 20-30% and side effects can be substantial.
• Systemic chemotherapy may be of more benefit for patients with aggressive variants of carcinoid tumors, called neuroendocrine tumors.
• Radiolabeled somatostatin analogues with yttrium 90 are being studied.
Section 12

**Soft Tissue Sarcoma** The following section primarily deals with adult soft tissue sarcoma of mesenchymal origin. This is a rare tumor in adults (7% of all malignancies). In 2002, 8,300 new cases are estimated with and 3900 patients will die. More than 50% of cases occur after age of 60. There is a slight male predominance

**Etiology**

- Usually unknown
- Late complications of radiation therapy, chemotherapy, and chemical exposure.
- 13 q 14 – abnormal suppressor gene in retinoblastoma; p53 mutations common.
  - Genetic factors: neurofibromatosis, tuberous sclerosis, Gardener’s syndrome, Li-Fraumeni syndrome.
- Chronic lymphedema.

**Diagnosis:**

- A needle biopsy or incisional biopsy is made for diagnosis, not excisional! An inappropriately performed biopsy may preclude a limb-sparing procedure. If a sarcoma is suspected it may be wise to refer the patient to an orthopedic surgeon who specializes in this disease to do the biopsy.
- Pathology: note tumor markers (reticulin, vimentin, and S-100) and grade.
- Stage with a chest CT (bone scan if suspicious).

**Pathology**

More than 100 subtypes, malignant fibrous histiocytoma (MFH) is the commonest subtype. The tumor grade and tumor size are of major importance in prognosis rather than histologic subtype. Synovial cell sarcoma, embryonal rhabdomyosarcoma, angiosarcoma and epithelioid sarcoma are the subtypes with tendency to spread via lymphatic system.

**Staging** TNM staging depends on the size (< or > 5 cm), lymph node involvement, metastasis and grade of differentiation.

**Clinical presentation**

- Sites:
  - Extremities 60%
  - Retroperitoneal 15%
  - Visceral 15%
  - Head and neck 15%
- Lump and pain are the commonest presenting symptoms.
- MRI or CT scan are the imaging procedures of choice.
- Imaging for metastatic disease, only a CXR for patients with tumors less than 5 cm in size while chest CT scan is needed for tumors with large size.
- Any soft tissue mass in adult should be biopsied if enlarging or more than 5 cm in size.

**Prognosis**

- Better features: low histologic grade, small primary, extremity location, and no metastases
• 5 year survival 60%

**Local Treatment**

• Wide local surgical excision is key.
• When possible, a limb sparing operation (as opposed to amputation) preceded or followed by radiation therapy is offered. With this approach recurrence rates for lesions of the distal extremity range from 5 to 13%; recurrence usually occur within 30 months
• A meta analysis of soft tissue sarcomas showed that adjuvant doxorubicin-based chemotherapy improved the time to local and distant recurrence and overall recurrence – free survival. Overall survival was not statistically better. Chemotherapy (Ifosfamide/Doxorubicin) can be used to “debunk” tumors prior to surgery and is often considered for large, high grade tumors.
• Rhabdomyosarcoma is, however, treated with adjuvant chemotherapy.

**Treatment of metastatic disease**

• Surgical excision of pulmonary metastases is preferred over chemotherapy. The role of chemotherapy is unclear; it clearly can be used for palliation when other options are not available.
Section 13

Bladder Cancer

Incidence/Epidemiology

Pathology
More than 90% of bladder carcinomas are transitional cell carcinomas derived from the uroepithelium. About 6% to 8% are squamous cell carcinomas, and 2% are adenocarcinomas.

Presentation

Stage

TNM

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Ta: Noninvasive papillary carcinoma
- Tis: Carcinoma in situ: “flat tumor”
- T1: Tumor invades subepithelial connective tissue
- T2: Tumor invades muscle
- T3: Tumor invades perivesical tissue
- T4a: Tumor invades prostate, uterus, vagina
- T4b: Tumor invades pelvic wall, abdominal wall.

Regional lymph nodes are those within the true pelvis; all others are distant lymph nodes.

- NX: Regional lymph nodes cannot be assessed
- No: No regional lymph nodes metastasis
- N1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node, more than 2 cm but not more than 5 cm or multiple lymph nodes, none more than 5 cm
- N3: Metastasis in a lymph node more than 5 cm in greatest dimension

Distant metastasis (M)

- Stage 0a: TaN0M0
- Stage 0is: TisN0M0
- Stage I: T1N0M0
- Stage II: T2N0M0
- Stage III: T3N0M0 or T4aN0M0
- Stage IV: T4bN0M0 or any regional positive lymph node, or M1 disease

Treatment

Stage 0 and Stage I
- Readily cured although the risk of new tumor formation is high.
- Risk of recurrence increases with increasing size, poor differentiation, multiple tumors, p53 overexpression, Tis, dysplasia of grossly uninvolved bladder.
- Transurethral resection and fulguration are the most common treatments
- Intravesical therapy with BCG, thiotepa, mitomycin, doxorubicin, is used for multiple tumors, recurrent tumors, or as prophylaxis in high-risk patients.

Stage II and Stage III
- Radical cystectomy is considered standard treatment
- In highly selected cases the cancer may be controlled by transurethral resection.
- External-beam irradiation in non-surgical candidates.
- One trial presented by the SWOG in May 2001 showed that neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) showed a survival benefit. It took several years to accrue
patients to this study so there may be a selection bias. Other studies have shown that adjuvant chemotherapy is important. It is likely that patients who can tolerate chemotherapy should receive it before or after their surgery.

Stage IV
- Only a small fraction of patients with stage IV disease can be cured. Cure is likely restricted to patients with involvement of pelvic organs by direct extension (T4b disease) or patients with small volume in regional lymph nodes.
- Focus is on palliation of symptoms
- Urinary diversion may be indicated for palliation and preservation of renal function
- When chemotherapy is indicated many choices are available. The MVAC regimen was compared to Cisplatin and Gemcitabine. These regimens were equally effective and the quality of life was better with the Cisplatin and Gemcitabine. Paclitaxel and carboplatin, ifosfamide are active drugs.

Surgery
- Radical cystectomy includes removal the bladder, perivesical tissues, prostate and seminal vesicles in men and the uterus, tubes, ovaries, anterior vaginal wall, and urethra in women and may or may not be accompanied by pelvic lymph node dissection. Studies suggest that racial cystectomy with preservation of sexual function can be performed in some men and that new forms of urinary diversion obviate the need for an external urinary appliance.
Section 14

Renal Cell Carcinoma (Material below applies to adenocarcinomas)

Incidence/Epidemiology
- 2 percent of all cancers
- 31,800 cases in 2002
- Twice as common in men
- Most cases are diagnosed in the fourth to sixth decade
- Risk Factors:
  - Smoking
  - Obesity
  - Hypertension
  - Unopposed estrogen therapy
  - Petroleum products
  - Heavy metals
  - Asbestos
  - Acquired cystic disease associated with chronic renal insufficiency

Pathology
- Renal cell adenocarcinomas account for 80-85%. Clear cell is a common form of adenocarcinoma.
- Transitional cell of the renal pelvis accounts for 15-20%
- Wilms tumor (nephroblastoma) in children
- Other: sarcoma, lymphoma, metastatic carcinoma

Genetic Abnormalities:
- Familial clear cell: breakpoint of the short arm of chromosome 3. Gene for von Hippel-Lindau syndrome is at 3p25
- Loss of 3p25 occurs in as many as 97% of sporadic cases. This suggests that it is a classic tumor suppressor gene.

Presentation
- Multiple presenting signs and symptoms
- Small-localized tumors rarely produce symptoms and for this reason the diagnosis is often delayed until the disease is advanced.
- Most common symptoms are hematuria, abdominal pain, and palpable mass. When these three occur together it is called the “triad.” But the triad is only seen 15% of the time.
- Widespread application of CT scans and ultrasounds for other indications has led to increased detection of renal cell carcinoma as an incidental finding.
- 25 to 30% have metastases at presentation. Common sites are lung, bone, liver, and brain.
- Paraneoplastic syndromes occur in approximately 5%. Erythrocytosis, hypercalcemia, hepatic dysfunction, amyloidosis.

Stage
- TNM and Robson are used
- The Robson stages:
  - I. Confined to the kidney: 65 - 85%
  - II. Extending through the renal capsule: 45 - 80%
    Renal vein involvement or nodal involvement
    Five year survival
III. Direct extension into organs  15 - 35%
IV. Distant metastases  0 - 15%

**Treatment**

**Surgery**
- Radical nephrectomy is the standard surgery and it includes resection of the kidney, perinephric fat, and ipsilateral adrenal gland.
- Lymphadenectomy is not helpful
- Partial nephrectomy is indicated for patients with bilateral tumors or a functioning solitary kidney

**Surgery in Patients with Metastatic Disease**
- Nephrectomy may be justified when the intention of surgery is to improve local symptoms. Nephrectomy does not cause spontaneous regression of metastatic disease.

**Systemic Therapy**
- There are no effective adjuvant systemic or radiation therapies after nephrectomy.
- There are no effective hormone or chemotherapy treatments for advanced disease.
- Interferon alpha by itself has a low response rate.
- High dose inerleukin-2 is effective but toxic. Response rate around 15% with 5% durable response.
- Non-myeloablative stem cell transplnat showed some encourage early results and is under testing.
- Responses are also seen with low dose interleukin -2.
- New combinations of biologic response modifiers are being studied.
- Systemic therapy may be delayed until symptoms appear or there is evidence of progression of disease.
- Palliation with radiation, surgery and medications (analgesics, appetite stimulants, antidepressants, etc) can be extremely important.
Section 15

Carcinoma of Unknown Primary

- 10 to 20% of oncology practice

Guidelines

1). A focused logical diagnostic strategy is important

<table>
<thead>
<tr>
<th>Location of Metastasis</th>
<th>Possible Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axilla in women</td>
<td>Breast</td>
</tr>
<tr>
<td>Left supraclavicular node (Virchow’s node)</td>
<td>GI primary</td>
</tr>
<tr>
<td>Cervical Node</td>
<td>Head and neck</td>
</tr>
<tr>
<td>Squamous histology above the diaphragm</td>
<td>Head and neck/esophagus</td>
</tr>
<tr>
<td>Skin</td>
<td>Breast, lung, and kidney</td>
</tr>
<tr>
<td>Inguinal nodes</td>
<td>Pelvis, lower extremities</td>
</tr>
<tr>
<td>Periumbilical (Sister Mary Joseph’s nodule)</td>
<td>Stomach</td>
</tr>
<tr>
<td>Peritoneal thickening in women</td>
<td>Ovarian</td>
</tr>
<tr>
<td>Lower cervical/Supraclavicular</td>
<td>Lung</td>
</tr>
</tbody>
</table>

(2) Look for primary sites that are curable or treatable.

<table>
<thead>
<tr>
<th>Curable Cancers</th>
<th>Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomas</td>
<td>Immunohistochemistry, Flow (markers)</td>
</tr>
<tr>
<td>Germ Cell tumors</td>
<td>Alpha-feto protein and B-HCG</td>
</tr>
</tbody>
</table>

“Treatable Cancer” (with a > 50% response rate to chemotherapy)

- Breast
  - Physical examination
  - If palpable axillary lymph nodes, order a mammogram
- Prostate
  - Digital rectal exam, PSA
- Ovarian
  - CA-125
- Thyroid
  - Physical examination, Fine needle aspiration
- Head and Neck
  - Indirect laryngoscopy

Workup

History - Smoking, asbestos, and toxin exposure, removal of pigmented skin lesions, biopsy of tumors, any unusual bleeding

Physical examination - Should include a pelvic examination in women, testicular examination in young men, rectal examination with fecal occult blood testing, and careful examination of optic fundi, oral cavity, lymph nodes, breast, prostate, and thyroid. An evaluation of the head and neck by an
otolaryngologist is required when cervical adenopathy or supradiaphragmatic squamous cell carcinoma is present.

**Laboratory Tests**

Screening: CBC, urinalysis, liver profile, LDH, chest x-ray, and CAT Scan of the abdomen

Pathology: The biopsy of the “unknown primary” is the most important part of the work up.

- 60% are adenocarcinomas
- 5% are squamous carcinomas
- 35% are poorly differentiated tumor or undifferentiated malignancy. The clinician should provide the history and physical findings to the pathologist (e.g. If the patient is having night sweats, could the tumor be lymphoma? Was the cancer recovered from the supraclavicular lymph nodes in an asbestos worker? Could it be mesothelioma?) Special stains, immunohistochemistry, cell markers, hormone receptors, and electron microscopy may be ordered by the pathologist. Occasionally repeat biopsy is necessary to get more tissue.

**Diagnostic tests:** Avoid ordering too many tests! The board examination loves to deduct points for doctors who spend too much money. Bear in mind: 1) In a substantial number of patients, the primary will not be found and, 2) the median survival of these patients is about 3 to 7 months, with less than 25% alive at one year and less than 0% alive at 5 years.

**DO NOT:**

- Get Upper GIs, endoscopies, ERCP, barium enemas, colonoscopies, unless there are signs of an occult primary in the GI tract such as abdominal pain, change in stool caliber or bowel habits, iron deficiency anemia, gross or occult GI bleeding.
- Get head and neck CT scans without cervical adenopathy, squamous cell histology or neurological signs or symptoms.
- Get an IVP unless there is hematuria
- Get tumor markers such as CEA (Colon), Ca -125 (ovarian), Ca 27-29 (breast), Ca 19-9 (pancreas). There is no such thing as a diagnostic tumor marker. These tests can be ordered if the primary site is found. Markers are used to help follow a patient’s course on treatment or used after treatment to help diagnosis an early recurrence.

**Treatment** (When the primary site is still not found)

**Adenocarcinoma**

1. Women with peritoneal carcinomatosis - treat as epithelial ovarian cancer.
2. Women with axillary lymph node metastases -
   --and no other site of disease: treat like stage II breast cancer.
   --and other sites of disease: treat like stage IV breast cancer.
3. Men with elevated PSA or blastic bone metastases - treat like prostate cancer with hormone therapy.
4. Single peripheral lymph node - excision, local radiation, or both (occasional long-term survivors).
5. All others:
   - good performance status: trial of chemotherapy for 6 to 8 weeks, continue for 6 months in those who respond.
   - poor performance status: palliative care.
Squamous Carcinoma

1). If the cervical lymph nodes are involved and the diagnostic evaluation does not reveal a primary site in the head, neck, or lung, treatment should be with radiation therapy of the involved neck region.
2). If the inguinal lymph node: are involved and the diagnostic evaluation does not reveal a primary site in the perineal or anorectal area, treat with an inquinal lymph node dissection with or without radiation therapy.

Poorly Differentiated Carcinoma

1). If pathologic work up is consistent with lymphoma, treat as lymphoma.
2). In young men with mediastinal or retroperitoneal tumors with or without elevated HCG or AFP treat as germ-cell (testicular) tumor.
3). Neuroendocrine Tumors: treat with cisplatin-based chemotherapy.

Empiric chemotherapy:

- Mostly used for adenocarcinoma, but minority of patients had poorly differentiated carcinoma.
- No regimen is considered standard
- Most old regimens produced response rates 20-35% and median survival duration of 5 to 8 month.
- Newer regimens including taxanes, gemcitabine, and topoisomerase I inhibitors had produced higher response rates with 14% 3 year survival.
- Carboplatin/paclitaxel, Carboplatin/paclitaxel/ettopside, or Carboplatin/paclitaxel/gemcitabine are some of the new regimens used
Part III The Hematologic Malignancies

Section 1 Non Hodgkin’s Lymphoma

Incidence and Epidemiology

- 53,900 cases expected in 2002, and 24,400 will die of the disease. It accounts for 4.5% of all cancer diagnosis.
- NHL is slightly higher in males.
- Median age at diagnosis of all subtypes is + 50 years. Low-grade lymphoma account only for 16% of cases below age of 35 years.
- Most histologies are more common in white but mycosis fungoides and other peripheral T cell lymphoma are more common in black.

Etiology:

- Chromosomal translocations and molecular rearrangements
  - The most common abnormality is t(14;18)(q32;q21) seen in 85% of follicular lymphoma and 28% of high grade lymphomas. The translocation results the juxtaposition of bcl-2 apoptotic inhibitor to the heavy chain region of the immunoglobulin.
  - In Burkitt’s lymphoma 85% of the cases will have t(8;14)(q24;32) and the rest will have t(8;22)(q24;q11) or t(2;8)(p11-12;q24). All the translocations involve the c-myc oncogene.
  - In MALT lymphoma t(11;18).
  - In mantle cell lymphoma t(11;14)
- Viruses:
  - EBV: Burkitt lymphoma, post-transplant lymphoproliferative disorders, other B and T cell lymphoma
  - HTLV1: adult T cell leukemia / lymphoma
  - Hepatitis C: clonal B cell expansion and NHL
  - HHV-8: cavity based lymphoma and castleman’s disease
- Environmental:
  - Chemicals, chemotherapy, radiation
  - Certain occupations seem to have increased risk ( farmers, pesticide applicators, painters, etc)
- Immunodeficiency
  - Congenital
  - Acquired: HIV, PTLD, autoimmune diseases
- GI lymphoma:
  - H.pylori: MALT
  - Celiac disease
  - Crohn’s disease

Pathogenesis

- In the normal lymph node, B cells enter the germinal center when antigen is encountered during the secondary immune response and undergo a process known as activity maturation, which is designed to increase the production of antigen specific B cells. In the germinal center, most of these cells express bcl-6 protein. After somatic mutation, some cells up regulate bcl-2, allowing them to survive, exit and differentiate into memory B cells or plasma cells.
- Several oncogenic events are thought to be involved in B cell Non Hodgkin’s lymphomas, including
t (14,18) t (3; 14), t (8; 14), implicating the bcl-2, bcl-6, and myc oncogenes, respectively.

**Diagnosis**
- Microscopic appearance
- Marker analysis (often helpful when the diagnosis isn’t clear)

  CD Markers: - T-cell markers CD 2,3,4,5,7,8  
  - B-cell markers CD 5,10,19,20,21,22,38, CALLa (CD10)
- Clinical picture (eg extranodal, vs. nodal; mediastinal location; skin)

**Classification**

Table 1. Classification of Non-Hodgkin’s Lymphomas

<table>
<thead>
<tr>
<th>Working Formulation</th>
<th>Rappaport</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Grade</strong></td>
<td></td>
</tr>
<tr>
<td>A. Malignant Lymphoma, diffuse small lymphocytic</td>
<td>Well-differentiated Lymphocytic</td>
</tr>
<tr>
<td>Consistent with CLL</td>
<td></td>
</tr>
<tr>
<td>B. Malignant lymphoma, follicular predominantly</td>
<td>Nodular, poorly differentiated</td>
</tr>
<tr>
<td>Small cleaved</td>
<td></td>
</tr>
<tr>
<td>C. Malignant lymphoma, follicular mixed, small</td>
<td>Nodular, mixed</td>
</tr>
<tr>
<td>Cleaved and large cell</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Grade</strong></td>
<td></td>
</tr>
<tr>
<td>D. Malignant lymphoma, follicular predominantly</td>
<td>Nodular, histiocytic</td>
</tr>
<tr>
<td>Large cell</td>
<td></td>
</tr>
<tr>
<td>E. Malignant lymphoma, diffuse small cleaved cell</td>
<td>Diffuse, poorly differentiated</td>
</tr>
<tr>
<td>F. Malignant lymphoma, diffuse mixed small and large cell</td>
<td>Diffuse, mixed</td>
</tr>
<tr>
<td>G. Malignant lymphoma, diffuse large cell</td>
<td>Diffuse, histiocytic</td>
</tr>
<tr>
<td><strong>High Grade</strong></td>
<td></td>
</tr>
<tr>
<td>H. Malignant lymphoma large cell, immunoblastic</td>
<td>Diffuse, histiocytic</td>
</tr>
<tr>
<td>I. Malignant lymphoma lymphoblastic</td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td>J. Malignant lymphoma small noncleaved cell Burkitts</td>
<td>Non-Burkitts</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>Mantle Zone Lymphoma</td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
<td>MALT Lymphomas</td>
</tr>
<tr>
<td>True Histiocytic Lymphoma</td>
<td>Unclassifiable</td>
</tr>
<tr>
<td>Extramedullary plasmacytoma</td>
<td></td>
</tr>
<tr>
<td><strong>B-cell neoplasms</strong></td>
<td></td>
</tr>
<tr>
<td>Mediastinal (thymic) - arises from normal B cells in the thymus</td>
<td></td>
</tr>
<tr>
<td>T-cell-rich-B-cell-shows a biological overlap with nodular lymphocyte -predominant Hodgkin’s disease.</td>
<td></td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma - CD 30+.  B cell cases have a poor prognosis</td>
<td></td>
</tr>
</tbody>
</table>

**The new WHO classification:**
recognizes more subtypes of lymphoma and classify them according cell of origin
THE INDOLENT LYMPHOMAS — Indolent lymphomas represent 35 to 40 percent of the NHLs diagnosed in Western countries, including approximately 24,000 people in the United States in 1999. The most common subtypes are follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, and marginal zone lymphoma, comprising 22, 6, 6, and 5 percent of all NHLs, respectively. In comparison, lymphoplasmacytic lymphoma, mycosis fungoides/Sezary syndrome, and splenic marginal zone lymphoma are rare diseases, comprising 1 percent or less of all NHLs. Indolent malignant lymphoproliferative diseases may arise from B-cell, T-cell, or NK-cell lines.

B-cell neoplasms

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma — The committee of oncologists agreed with the pathologists that B-cell chronic lymphocytic leukemia (B-cell CLL, B-CLL) and small lymphocytic lymphoma (SLL) are one disease at different stages, rather than two separate diseases.

B-cell prolymphocytic leukemia — Prolymphocytic leukemia can present as a disease in its own right, or can occur as a malignant transformation of previously-diagnosed B-CLL.

Lymphoplasmacytic lymphoma — Lymphoplasmacytic lymphoma is a disorder that is indistinguishable from Waldenstrom's macroglobulinemia.

Hairy cell leukemia — Hairy cell leukemia (HCL) is an uncommon chronic B-cell lymphoproliferative disorder originally termed "leukemic reticuloendotheliosis" and named HCL in the 1960s because of the prominent irregular cytoplasmic projections of the malignant circulating lymphoid cells.

Plasma cell myeloma/plasmacytoma — (see section on multiple myeloma). These are malignancies of the plasma cell.

Follicular lymphoma — Follicular lymphomas (FL) are the most common type of indolent NHL, and morphologically recapitulate normal germinal centers (GC) of secondary lymphoid follicles. This disorder was previously called follicle center lymphoma. FL of grades I and II is an indolent NHL, while FL of grade III behaves more like one of the aggressive lymphomas.

Marginal zone B-cell lymphoma — Three subtypes of marginal zone B-cell lymphoma (MZL) are recognized as distinct entities. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) or MALT-type lymphoma. This condition refers only to the low-grade tumor and not to the diffuse large B-cell lymphoma (DLBCL) which can also occur in these tissues. Splenic marginal zone B-cell lymphoma. This condition is the tissue counterpart of splenic lymphoma with circulating villous lymphocytes. Nodal marginal zone B-cell lymphoma. In the nodal MZL, the tumor cells cytologically resemble "normal" monocytoid B-cells and often involve lymph node sinuses. Phenotypically these tumors are similar to hairy cell leukemias.

Mantle cell lymphoma — Mantle cell lymphoma (MCL) has been previously referred to as intermediate lymphocytic lymphoma, mantle zone lymphoma, centrocytic lymphoma; and lymphocytic lymphoma of intermediate differentiation. These tumors are neoplastic counterparts of naive "mantle zone" B-cells. Mantle cell lymphoma is generally classified as an indolent lymphoma, since survival of the untreated disease is measured in years. However, in many ways, this disease behaves as an aggressive lymphoma.

T-cell neoplasms

T-cell large granular lymphocyte leukemia — The term T-cell large granular lymphocyte (LGL) leukemia was proposed for this disorder, based upon demonstration of invasion of bone marrow, spleen, and liver by clonally expanded LGLs. It is an indolent disease that is treated with immunosuppressive therapy such as methotrexate or prednisone or both.

Mycosis fungoides — Mycosis fungoides (MF) is one of the cutaneous T-cell lymphomas, with Sezary syndrome being an erythrodermic, leukemic variant of MF.
T-cell prolymphocytic leukemia — T-cell prolymphocytic leukemia (T-cell PLL or T-PLL) is a distinct subtype of PLL with a clinical course different from that of B-PLL. It is not clear whether the disorder previously called T-cell chronic lymphocytic leukemia (T-cell CLL or T-CLL) is a distinct disease, a small-cell variant of T-PLL, or whether it represents patients who should have been classified as having T-cell LGL.

Natural killer cell neoplasms
Natural killer cell large granular lymphocyte leukemia — The clinical presentation of natural killer (NK) cell LGL leukemia is more aggressive than in T-cell LGL leukemia.

THE AGGRESSIVE LYMPHOMAS —
Aggressive lymphomas represent about 50 percent of the NHLs diagnosed in Western countries. The most common subtypes are diffuse large B-cell lymphoma, and peripheral T-cell lymphoma, comprising 31 and 6 percent of all NHLs, respectively. Anaplastic large cell lymphoma is a rare diseases, comprising 2 percent of all NHLs. The aggressive lymphomas can arise from B-cells, T-cells or null-cells.

B-cell lymphomas
Diffuse large B-cell lymphoma — Diffuse large B-cell lymphoma (DLBCL) was previously called diffuse histiocytic lymphoma in the Rappaport classification. The disease is currently subclassified into centroblastic, immunoblastic, and anaplastic variants. However, it was felt that neither reliable pathologic or biologic criteria, nor treatment recommendations could be made for these subclassifications at this time. Other common variants of DLBCL include:
- Intravascular large B-cell lymphoma
- Primary mediastinal (thymic) large B-cell lymphoma
- Large B-cell lymphoma, lymphomatoid granulomatosis type
- T-cell rich/histiocyte-rich large B-cell lymphoma

T-cell lymphomas
Anaplastic large cell lymphoma — Anaplastic large-cell lymphoma of T-cell or null-cell type has been divided into two subtypes, cutaneous and systemic. Distinction between relatively indolent and more aggressive variants of the cutaneous type was not felt to be reliable at this time.

Peripheral T-cell lymphoma — The category of mature peripheral T-cell lymphoma (PTCL) includes a number of entities within the REAL classification. Among these are: PTCL, unspecified; angioimmunoblastic T-cell lymphoma, angiocentric T/NK-cell lymphoma; subcutaneous panniculitis-like T-cell lymphoma, intestinal T-cell lymphoma, and hepatosplenic gamma/delta T-cell lymphoma.

THE HIGHLY AGGRESSIVE LYMPHOMAS — Highly aggressive lymphomas as a group represent about 5 percent of the NHLs diagnosed in Western countries. These diseases are all uncommon, each one constituting <2 percent of all NHLs. The highly aggressive lymphomas can arise from B-cells or T-cells.

B-cell lymphomas
Burkitt's lymphoma — Burkitt's lymphoma is also called Burkitt-cell leukemia. It includes a variant, Burkitt-like lymphoma, as well as three subcategories (endemic, nonendemic, and immunodeficiency-associated)

Precursor B lymphoblastic leukemia/lymphoma — This condition is also called precursor B-cell acute lymphoblastic leukemia (ALL). It was agreed that precursor B-cell ALL and lymphoblastic lymphomas were a single disease with different presentations.

T-cell lymphomas
Adult T-cell lymphoma/leukemia —

Precursor T lymphoblastic leukemia/lymphoma — Precursor T-cell lymphoblastic lymphoma is also called precursor T-cell ALL

Table 2. Non-Hodgkin’s Lymphomas: Ann Arbor Staging System
Stage I: Involvement of a single lymph node region
Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm
Stage III: Involvement of lymph node regions on both sides of the diaphragm
Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement.

The subscript E (e.g. IE or IIE) is used to denote involvement of an extralymphatic site primarily or by direct extension, rather than by hematogenous spread, as in the case of a lymphoma arising in the gastrointestinal tract.

The presence (B) or absence (A) of fever, night sweats and/or unexplained loss of 10% or more of body weight in the six months prior to admission are denoted by the corresponding suffix letters B and A.

Modification of the Staging System - IPI (International Prognostic Indicator)

An international non-Hodgkin’s lymphoma project has developed a model for aggressive lymphomas. The following factors are associated with poor survival. These factors are added to determine risk group.

- A : Age over 60
- P : Poor performance status (ECOG performance status > 2)
- L: Abnormal LDH
- E: Two or more extranodal sites
- S: Stage III or IV disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>0-1</td>
</tr>
<tr>
<td>Low-intermediate risk</td>
<td>2</td>
</tr>
<tr>
<td>High-intermediate risk</td>
<td>3</td>
</tr>
<tr>
<td>High risk</td>
<td>4-5</td>
</tr>
</tbody>
</table>

Work up - Dependent on histological type and treatment goals

*** Diagnostic sampling of lymph node should always be excisional biopsy if possible since architecture of the lymph node is important in determining the subtype.

**Indolent Lymphoma**

- CBC, diff, liver profile, LDH, baseline chest x-ray (CT of the chest if the chest x-ray is suspicious). Consider CT of the abdomen. SPEP, Coombs for WDLL

- The bone marrow will be involved in 40-100% of WDLL. Since this won’t change the treatment or prognosis it is not necessary to do a bone-marrow biopsy.

**Aggressive Lymphoma**

- CBC, diff, liver profile, LDH, baseline chest x-ray, CT of the chest, abdomen and pelvis, bone marrow aspirate and biopsy

- The bone marrow is involved in 5-15% of patients. Involvement of marrow connotes an increased chance of CSF involvement and a poorer prognosis. Some doctors recommend obtaining a spinal tap
in patients with a positive bone marrow biopsy. Spinal tap is also indicated for patients with nasopharyngeal NHL, HIV-associated NHL, and CNS symptoms or signs.

- Preauricular involvement may indicate Waldeyer’s ring involvement

**Treatment**

**Indolent Lymphoma**

Indolent tumors with long survival but in general not curable by current methods of treatment.

**Stage I/IIa**
- Observation
- Radiation

**Stage IIb/IV**
- Observation/ close watching if asymptomatic
- Chemotherapy: multiple options including CVP (cyclophosphamide, vincristine, prednisone), chlorambucil, and fludarabine based regimens
- On going studies are evaluating the role of CHOP + rituximab

**Relapsed or refractory disease**
- Rituximab: monoclonal antibodies targeted against CD20, approved by FDA for treatment of refractory or relapsed lymphoma with approximately 50% response rate and 1 year median duration of response
- Radioimmunotherapy: monoclonal antibodies linked to iodine –Tositumomab (Bexxar) or Yttrium (Zevalin) are used in rituxan refractory disease and undergoing clinical trials.
- Autologous stem cell transplant may be used in selected cases of indolent relapsed or refractory lymphoma especially in young age.

**Aggressive Lymphoma**

Aggressive tumors but potentially curable (approximately 40%)

- Phase III intergroup studies compared cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) to “third generation” regimens such as MBACOD, and others. The third generation regimens are more toxic and expensive than CHOP and did not prolong survival. CHOP, therefore, is the standard of care.

- Further studies have shown that response to CHOP depends on the International Prognostic Group (IPI) risk factors. Patients with a low risk IPI should be treated with CHOP. Those with a high risk IPI should be identified for clinical trials.

- New therapeutic approaches for high-risk patients are in development such as adding high dose therapy with stem cell support and using drugs to overcome resistance to chemotherapy. The monoclonal antibody, rutuximab in combination with chemotherapy is being studied. Studies in Europe showed better results with CHOP/rituxan combination in elderly patients.

- For stage I/II disease CHOP 3-4 cycles with radiation is the treatment while in advanced stages CHOP 6-8 cycles is used.
- For relapsed or refractory disease salvage chemotherapy followed by autologous transplant is superior to only salvage chemotherapy if possible.
Highly aggressive Lymphoma

- The high-grade lymphomas - lymphoblastic, small noncleaved, Burkitt, require urgent diagnosis and treatment with aggressive combination chemotherapy. Treatment should be started promptly after stabilizing the patient and continued on a continuous schedule.

Specific subtypes

- MALT lymphoma: if associated with H.pylori can be treated with eradication of H.pylori infection especially in absence of chromosomal abnormalities
- Mantle cell lymphoma treatment is difficult, it has aggressive features of higher grade lymphoma but still noncurable as low grade lymphoma. Probably patients should not treated with CHOP alone and enrolled in clinical trials when possible.
- Cutaneous T cell lymphoma: treatment options includes PUVA, topical chemotherapy, photopheresis, external beam radiation, systemic chemotherapy, Ontak (anti-CD 25 toxin), and bexarotene a rexinoid approved for refractory to at least one previous treatment.
Section 2
Hodgkin’s Disease
7,400 cases expected to be diagnosed in 2002, more than 80% of all newly diagnosed cases can expect a disease free long survival.

- **Epidemiology**: Higher in developed countries and with higher socioeconomic status.
- Male: female 1.3:1
- Bimodal age peaks in the third decade and a smaller one after age of 50.
- More common in Caucasians.

**Etiology:**
Genetic predisposition: monozygotic twin sibling has 99 x higher risk for Hodgkin disease
Viral: EBV

**Pathology:**
Reed-sternberg cell is the diagnostic tumor cell. It is a large cell with binucleated large eosinophilic nucleoli. Cells are CD15, CD30 positive. RS cells are B cell in origin

**Classification**
- Classical (95%)
  - 5% lymphocyte predominant
  - 70% nodular sclerosis
  - 20-25% mixed cellularity
  - 5% lymphocyte depleted
- Nodular lymphocyte predominant Hodgkin lymphoma (5%)

**Staging**
The staging system is the same as the Ann Arbor system shown in Table 2 under NHL.

**Diagnostic Tests**
- H and P, CBC, SMA 12, Sed Rate, CXR, chest and Abd CT, bone marrow, gallium scan, Early studies have shown that PET scan has a strong negative predictive value of relapse after tretment if it was negative.
A staging laparotomy is not done anymore with the advanced imaging studies and introduction of chemotherapy treatment for early disease. Pearls
  - Pleural effusion does not necessarily represent pleural involvement.
  - Involvement of the bone should not be equated with involvement of the bone marrow unless there is widespread disease.

**Clinical Presentation**
- Usually asymptomatic adenopathy
- B symptoms – fever, night sweats, >10% weight loss
Depressed cellular immunity (low CD4/CD8 ratio, high CD8) is a lifetime characteristic of Hodgkin’s patients. Patients with a history of Hodgkin’s Disease are at increased risk to develop Zoster infections compared to the general population. The presence of Zoster does not mean that the disease has reoccurred.

**Treatment** is guided by the clinical stage (CS) and prognostic factors as follows:

**Stage I/II with favorable prognosis**
- A very favorable prognostic group, consisted of CS IA women less than 40 years of age with an ESR under 50 mm/h, no B symptoms, the absence of large mediastinal adenopathy, and nodular sclerosis or nodular lymphocyte predominant histology.
- A favorable prognostic group: age 50 or under; without large mediastinal adenopathy; an ESR of less than 50/h and no B symptoms or an ESR of less than 30 mm/h with B symptoms; and disease limited to one to three regions of involvement.
- Treatment options include
  - ABVD for four to six cycles, followed by involved field or mantle irradiation with 25 to 30 Gy to prophylactic regions and 36 Gy to regions of initial involvement. This approach has the lowest relapse rate (10 to 15 percent) but is more toxic and may be associated with a higher rate of late complications.
  - Mantle irradiation to 30 Gy with a total dose of 36 to 40 Gy to regions of initial involvement, followed by paraaortic and splenic irradiation to 30 Gy. This regimen has a relapse rate of 20 to 25 percent but is easier to salvage after first relapse than the above regimen. However, the risk of second malignancies may be increased with these large radiation fields.

Mantle irradiation to 30 Gy with a total dose of 36 to 40 Gy to regions of initial involvement. Selected patients may not require the laparotomy (see above). This regimen is particularly attractive for CS/PS I patients where the risk of recurrence is only 10 to 15 percent. With this regimen, it is easier to salvage after first relapse, and it should be associated with a lower risk of second malignancy than the second regimen.

**Stage I/II with unfavorable prognosis**
- An unfavorable prognostic group defined as those having any one of the following features: large mediastinal adenopathy; four or more sites of involvement; B symptoms and an ESR over 30 mm/h; an ESR over 50 mm/h without B symptoms; or age over 50.
- Treatment is combined chemotherapy & radiation

**Stage III/IV**
- For advanced HD, doxorubicin-containing chemotherapy is the standard against which newer treatments must be compared. With ABVD, 60 to 70 percent of patients will be alive and free of disease at five years. As described above, ABVD is much less likely to cause severe myelotoxicity, acute leukemia, or sterility compared to treatment regimens, such as MOPP

**Chemotherapy**
MOPP is no longer considered standard of care! ABVD (Adriamycin, bleomycin, Velban, DTIC) is the standard of care. The intergroup trial comparing ABVD with a MOPP/ABV. Hybrid closed early due to increase toxicity of the hybrid arm. Since the aim is cure, doses of the drugs should not be compromised. Long term risks of MOPP were sterility and leukemia. ABVD has an increase of pulmonary fibrosis of 2-6%.

**Bulky Mediastinal Disease**

- Is a common presentation
- By definition, it is disease occupying 1/3 or greater the chest diameter or a bulk of disease 10cm or greater
- It is treated with “combined modality”: chemotherapy and radiation

**Treatment of relapsed or refractory Hodgkin’s**

1. Relapse after radiation – Rx with systemic chemotherapy
2. Relapse after being in chemotherapy – induced complete response for 1 year or more – may use the same chemo regimen again or switch to a non-cross resistant regimen.
3. Minimal response, no response, or progression while on treatment – Treat with a second line regimen to try to obtain a response and then consider a bone marrow transplant.
Section 3

Chronic Lymphocytic Leukemia

Definition – a neoplastic disorder of mature lymphoid cells, usually of B cell origin. The diagnosis requires a peripheral blood lymphocytosis of greater than 5,000/mm3, mature-appearing lymphocytes, and a lymphocytic infiltration in the bone marrow. In the absence of a bone marrow exam, flow-cytometry can be done. CLL has positive surface immunoglobulin, either Kappa or lambda light chain predominance, various B-cell markers such as CD19, CD 20 CD22 or CD 24, and a specific T-cell marker, CD5. CLL cells are CD23 positive where as Mantle cell lymphoma is CD 23 negative.

Epidemiology

CLL is the commonest leukemia in adults in the western countries. The median age of diagnosis is 65-70 years; CLL is seen more in males (2:1 ratio)

Etiology – unknown

• Approximately 50% of patients have chromosomal abnormality. Common abnormalities are t (11; 14), t (14;19), t(14;18) with expression of the respective oncogenes: bcl-1, bcl-2, bcl-3. Trisomy 12 is also common.
• ATM gene located on the long arm of chromosome 11 at 11q 22-23 has been recently identified and associated with more aggressive disease and poor survival. Increased incidence in Families (2 to 7 fold increased risk).

Clinical presentation:

• 20% of patients are asymptomatic and diagnosis is discovered on routine blood testing.
• Lymphadenopathy, hepatosplenomegaly are common at diagnosis
• Infection, autoimmune phenomena (anemia, thrombocytopenia) can be seen as presentation

Rai Staging System:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Features</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Absolute lymphocytosis</td>
<td>150</td>
</tr>
<tr>
<td>I</td>
<td>Lymphocytosis plus adenopathy</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis plus enlarged liver or spleen or both</td>
<td>70</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis plus anemia (Hg &lt;11g/dl)</td>
<td>20</td>
</tr>
<tr>
<td>IV</td>
<td>Lymphocytosis plus thrombocytopenia (platelets &lt; 100,000)</td>
<td>20</td>
</tr>
</tbody>
</table>

Other prognostic factors include elevated B2-microglobulin and CD38 expression.

Indications for Treatment

• Constitutional symptoms referable to CLL
Symptomatic hepatosplenomegaly
Anemia (hemoglobin < 10g/dl)
Thrombocytopenia (platelets < 100,000)
Possibly WBC > 300,000
Possibly Refractory autoimmune disease
Possibly frequent infections.

**Therapy**

- Fludarabine is first line treatment; Fludarabine has better response rates and disease free survival compared to chlorambucil but no all over survival. Ongoing studies are evaluating combination treatments like FCR (fludarabine, cytoxan and rituxan), FNR (fludarabine, novantrone and rituxan)
- Initial treatment with an alkylator (chlorambucil) for elderly patients, those with co-morbid conditions that limit survival, individuals with renal insufficiency.
- PCP prophylaxis to those who receive fludarabine plus prednisone (see below)
- Allogeneic transplant only for young patients with refractory disease

**New Approaches (In clinical trials)**

- Purine analogues (fludarabine) and alkylator
- Purine analogues and monoclonal antibodies
  - CAMPATH – 1H (Alemtuzumab) anti CD-52 monoclonal antibody approved by FDA for treatment of refractory CLL.
  - Rituximab
- New agents
- Autologous Transplant with purging

**Special Issues**

- Richter’s syndrome is the transformation of CLL, characterized by rapid enlargement of lymph nodes, hepatosplenomegaly, fever, and weight loss. Therapy of Richter’s syndrome is the same as that recommended for diffuse large cell lymphoma.
- Waldenstrom’s macroglobulinemia should be distinguished form CLL, by hyperviscosity and elevated IGM. Patients with hyperviscosity will have sausage-like segmentation of retinal veins.
- Coombs-positive autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are common complications of CLL, regardless of the stage. If AIHA occurs while on treatment with fludarabine, pentostatin or cladribine, these drugs should be stopped as they may be causing the hemolysis.
- Prolymphocytic leukemia is a rare variant of CLL characterized by massive splenomegaly and large lymphocytes usually greater than 100,000/mm³. Treatment is chemotherapy, usually with fludarabine.
- Infections are common in CLL and frequently the cause of death. There are several reasons:
  1. Hypogammaglobulinemia is a complication of CLL because the neoplastic B cells do not produce a normal amount of IgG.
  2. Treatment for CLL is immunosuppressive.
  3. Fludarabine is cytotoxic to normal and malignant B cells and T lymphocytes. A high incidence of opportunistic infection is observed when fludarabine is combined with prednisone.
Section 4

Chronic Myelogenous Leukemia

Section 16 (revised 11/02)

Chronic Myelogenous Leukemia

Definition:
A clonal myeloproliferative disorder characterized by Philadelphia chromosome translocation and its resultant bcr/abl protein

Epidemiology:
- Accounts for 15% of all leukemias, 4700 cases will be diagnosed in 2001.
- Male: Female 1.4-2.2:1
- Median age is 65 years

Diagnosis

95% of patients will have the Philadelphia Chromosome, a translocation of chromosome 22 to chromosome 9. This translocation creates a fusion gene called bcr/abl, which encodes a chimeric protein with unusual tyrosine kinase activity.

Clinical

- The clinical course follows three phases:

  →                      →                      →

  Chronic phase  accelerated phase  blast crisis

  I------years------I   I---months---I

- In the chronic phase (3.5-5 years) patients have an elevated leukocyte count consisting of neutrophils, bands, metamyelocytes, myelocytes, and a small percentage of promyelocytes and myeloblasts. Anemia is mild. Splenomegaly is present. Platelet count is normal, elevated or depressed. The leukocyte alkaline phosphatase (LAP) is decreased. (The other condition with a decreased LAP is paroxysmal nocturnal hemoglobinuria, PNH.) Bone marrow blasts do not exceed 5%.

- Imatinib mesylate (Gleevec)(STI571) a potent inhibitor of tyrosine kinase bcr/abl has become the standard of care first line treatment. The drug was associated with 98% hematological response and more importantly 31% major cytogenetic response in patients previously treated with interferon. Imatinib is given orally, myelosupression, and peripheral/periorbital edema are major side effects. Various methods of monitoring response are in development including quantitative RT-PCR for bcr/abl, cytogenetics by FISH technique. Long-term survival data are yet to be determined. Imatinib is approved for treatment of GIST tumors (gastrointestinal soft tissue tumors- previously known as leomyosarcoma).

- Stem cell transplantation in young patients remains curative option especially as the long-term outcome with Imatinib is yet unknown. Other options of treatment includes interferon, interferon with low dose ara-c, busulfan and hydroxyurea that is used to control high white blood cell counts.
• In the accelerated phase, the white count increases rapidly and the bone marrow is characterized by fibrosis and a shift to blasts. Increased basophils and constitutional symptoms

• Blast crisis is a fulminant leukemia, which is resistant to standard leukemia regimens. Imatinib at higher doses had 34% hematological response rate and 15% cytogenetic response.
Section 5
Acute Lymphoblastic Leukemia (ALL)

Epidemiology:
- More common in children

Diagnosis
- Elevated white blood cell count with abnormal differential, abnormal hemoglobin/hematocrits and platelet counts and signs/symptoms of the disease (lymphadenopathy may be present, fever, weight loss)
- Blasts greater than 5% on the bone marrow biopsy
- Markers: 50% are positive for CALLA (common lymphocyte antigen), 95% are TdT positive.
- Myeloperoxidase negative (But, M0 and M7, two subtypes of AML can be neg as well)

Subtypes: There are FAB types L1, L2, and L3
- L1-more mature-appearing lymphoblasts, 30% of cases
- L2 more immature-appearing lymphoblasts, 60% of cases
- L1 and L2 can be T or pre-B cells. T cells are CD 2,5,7,10 and 34. B cells are CD10,19,20,22, and 34
- L3-increased tendency to have CNS involvement. Associated with translocations of the e-myc protooncogene to the immunoglobulin gene locus such as t(2;8), t(8;14), t(8;22). These cells have mature B cell phenotype with surface Ig. CD10,19,20,21,22

Poor Prognostic Features
- Philadelphia positive (Ph+), t(9;22). This is a different fusion protein than that seen in Chronic Myelogenous Leukemia and it can be present w/o seeing the Philadelphia chromosome. Molecular studies to look for the bcr-abl fusion gene should be performed on all pts with ALL. It is present in 25% of adults.
- t(4;11)
- L3, Advanced age
- Mature B cell lineage
- High white blood cell count
- In adults Tcell is better than pre-B cell which is better than mature B cell.
- Slow time to complete remission

Treatment:
Whenever possible enroll these patients onto clinical trials. Since neutropenia is an expected consequence of the disease and the treatment these patients should be cared for by physicians/nurses with experience in acute leukemia and in centers equipped to give frequent transfusion and handle complications of the disease. There are three phases of treatment- Induction, CNS prophylaxis, and Maintenance
- Average treatment lasts from 1.5 to 3 years

Induction treatment:
Uses prednisone, vincristine, and an anthracycline. Some programs add L-asparaginase and/ or cyclophosphamide. The Complete response rate is between 60-90%
CNS prophylaxis:
Three standard approaches:
1. Cranial radiation and intrathecal methotrexate
2. High dose methotrexate and intrathecal methotrexate
3. Intrathecal methotrexate alone.

Maintenance:
There are three approaches. Bone marrow transplant is most appropriate for patients with a poor prognostic subtypes such as CD 10-, elevated WBC count, Ph + chromosome, t(4;11)

1. Short term intensive chemotherapy followed by long term treatment at a lower doses
2. Marrow ablative chemotherapy or chemoradiation therapy followed allogeneic stem cell rescue (alloBMT). The bone marrow for alloBMT is from a matched sibling donor. AlloBMT has the lowest rate of leukemia relapse but this is offset by the morbidity and mortality of the procedure from Graph Versus Host Disease (GVHD), Veno-Occlusive Disease (VOD), and interstitial pneumonitis.
3. High dose chemotherapy followed by autologous bone marrow transplants. These transplants use the patient’s own marrow. They have been less successful in ALL than in AML.

- L3 is treated differently than other types of ALL. Brief duration, intensive and rapidly cycling chemotherapy including multiple agents and CNS prophylaxis or treatment has achieved high cure rates. This B cell disease is treated similarly to small-noncleaved cell or Burkitt’s Lymphoma.

**Recurrent ALL:** These patients are unlikely to be cured by standard therapy and should be enrolled on clinical trial
Section 6

Acute myelogenous Leukemia

Incidence: 10,000 cases in 2001, 5,200 in men and 4,800 in women. 2.6/100,000 in all age groups, 16/100,000 in age greater than 75.

Etiology:
1. Ionizing radiation--- atomic bomb, nuclear power disasters, and therapeutic irradiation
2. Chemicals--- benzene, alkylating agents (associated with chromosome 5 and 7 abnormalities), chloramphenicol, topoisomerase I inhibitors (associated with the 11q23 translocation), arsenic, tobacco.
3. Genetic---Down syndrome, Fanconi syndrome, ataxia-telangiectasia, Klinefelters syndrome, congenital aneuploidy
4. Viral---HTLV-1 in association with acute T-cell leukemia

Classification

Diagnosis is made in the right clinical setting, with a bone marrow aspirate and biopsy. Histochemical stains, TdT determination (to sort AML from ALL), cell surface antigen determination, and chromosome analysis are done.

Blasts comprise 20% of nucleated marrow cells (excluding lymphocytes)
- The new WHO classification recognizes importance of cytogenetic abnormalities.
- The new classification recognizes the following:
  - AML with recurrent cytogenetic translocations [ t(8;21); t(15,17), inv 16, 11q23
  - AML with multilineage dysplasia

AML and MDS therapy related

FAB Classification

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Incidence</th>
<th>Morphology</th>
<th>Cytogenetics</th>
<th>Special Stains</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>3%</td>
<td>Very immature blasts&lt;br&gt;No maturation</td>
<td>Frequently complex</td>
<td>&lt; 3% peroxidase +&lt;br&gt;TdT +</td>
</tr>
<tr>
<td>M1</td>
<td>15-20%</td>
<td>No maturation&lt;br&gt;Auer rods absent</td>
<td>Non-specific</td>
<td>≥3% blasts are peroxidase +&lt;br&gt;PAS (-)</td>
</tr>
<tr>
<td>M2</td>
<td>25-30%</td>
<td>Myeloid maturation seen&lt;br&gt;Auer rods present</td>
<td>t(8;21) in 50%</td>
<td>Strongly peroxidase +&lt;br&gt;Non-specific esterase (-)</td>
</tr>
<tr>
<td>M3</td>
<td>10%</td>
<td>Promyelocytes &gt;30%&lt;br&gt;Auer rods abundant</td>
<td>t(15;17)</td>
<td>Strongly peroxidase +&lt;br&gt;Usually NSE (-)</td>
</tr>
<tr>
<td>M4</td>
<td>20-30%</td>
<td>Myelomonocytic appearance&lt;br&gt;20% marrow of monocytic lineage</td>
<td>Inv 16 (typical of M4eo type)</td>
<td>Peroxidase +&lt;br&gt;NSE (+)</td>
</tr>
<tr>
<td>M5</td>
<td>2-9%</td>
<td>&gt;80% non-erythroid are monocytic</td>
<td>Non-specific</td>
<td>Peroxidase (-)&lt;br&gt;NSE (+)</td>
</tr>
<tr>
<td>M6</td>
<td>3-5%</td>
<td>Erythroblasts &gt;50% nucleated cells&lt;br&gt;30% nonerythroid cells are blasts</td>
<td>Non-specific</td>
<td>Peroxidase +&lt;br&gt;PAS +&lt;br&gt;NSE –&lt;br&gt;Glycophorin +</td>
</tr>
<tr>
<td>M7</td>
<td>3-12%</td>
<td>Multinucleated blasts&lt;br&gt;Marrow fibrosis&lt;br&gt;“dry tap”</td>
<td>Non-specific</td>
<td>Peroxidase (-)&lt;br&gt;NSE +/-&lt;br&gt;Platelet glycoprotein +</td>
</tr>
</tbody>
</table>
**Clinical Features**

- Fatigue, fever, frequent infections, bleeding are common.
- Coagulopathy (DIC) is frequent in M3 (promyelocytic) AML, related to procoagulant and fibrinolytic properties of leukemic granules
- Extramedullary involvement (e.g. gingival hyperplasia, meningitis, leukemia cutis) is common in M4 & M5 AML
- Markedly elevated peripheral blast count (>50,000/uL) is associated with:
  - pulmonary leukostasis (respiratory failure, lung infiltrates, fever, pulmonary hemorrhage)
  - cerebrovascular leukostasis (stroke, hemorrhage, retinopathy)
- Hepatosplenomegaly

**Prognosis:**
Approximately 60 to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. More that 15% of adults with AML can be expected to survive 3 or more years and may be cured. Remission rates in adult AML are inversely related to age.

- Other Adverse Features:
  - Older age (> 55)
  - Karyotypic abnormalities involving chromosomes 5 and/or 7
  - Multidrug resistance phenotype
  - Secondary AML
    - Arising from myelodysplastic syndrome
    - Previous chemotherapy (alkylating agents, epidiphllotoxins)
  - Leukocytosis at diagnosis
  - Elevated LDH at diagnosis
  - CD 34 negative leukemic blasts

- Favorable Features
  - Younger age (<55)
  - Promyelocytic subtype (M3)
  - M4eo subtype
  - Karyotypic abnormalities: t(8;21), inv 16

**Therapy**
Patients go through two phases of treatment: Induction (to attain remission) and postremission (to maintain remission). Because only 5% of patients with AML develop CNS disease, prophylactic treatment is not indicated.

- Standard induction therapy with anthracycline + cytosine arabinoside remains the standard (idarubicin/daunorubicin x 3 days, cytarabine x 7 days)
  - Variations of dosing schedules (e.g. high-dose cytarabine) do not affect survival, though may be more toxic.
  - Complete remission rates approach of 70-80%, though only ~50% in older patients or those with secondary AML. However, relapse occurs in ½ of cases.
  - Newer therapies include topoisomerase 2 inhibitors (e.g. topotecan), which may have an improved response rate in secondary AML and MDS.

Myelosuppression is an anticipated consequence of both the leukemia and its treatment with chemotherapy. Prophylactic platelet transfusions should be given for a level of 10,000 per cubic millimeter. Colony stimulating factor (G-CSF) and GM-CSF) have been studied in an effort to shorten
the period of granulocytopenia associated with leukemia treatment. IF used, they are started after the chemotherapy has been completed. Empiric broad spectrum antimicrobial therapy is necessary for febrile neutropenic patients. Prophylactic oral antibiotics may be appropriate in patients with prolonged granulocytopenia. Norfloxacin and ciprofloxacin have been shown to decrease the incidence of gram-negative infection and time to first fever.

- Consolidation chemotherapy with high-dose cytarabine is standard (2-4 cycles)
  - Longer remission duration and event-free survival with consolidation
  - No evidence that more consolidation is better than less
  - Toxic for patients older than 60 years.
  - Cytarabine: cytopenias, cerebellar toxicity (when given in high-dose). Risk of cerebellar toxicity with high-dose cytarabine much higher in elderly patients.

- Bone marrow/Stem cell transplantation has unclear role in 1st CR
  - Overall survival is not different between groups receiving chemotherapy alone, autologous transplantation, or allogeneic transplantation
  - Allogeneic BMT associated with lower risk of relapse, but higher risk of toxicity (e.g graft vs host disease, infection). End result is no improvement in survival.
  - Allogeneic (related or unrelated) indicated for relapsed or secondary AML, as chemo alone not curative.
  - High-risk or intermediate risk subgroups should be considered for allogeneic BMT in 1st CR. Low risk group (patients with t(8,21) or inversion 16) can be treated only by induction and further consolidation.

  Allogeneic transplantation is associated with a decreased risk of relapse from leukemia but a higher rate of death due to graft versus host disease. Allogeneic transplantation is limited by the need for a human leukocyte antigen (HLA)-matched sibling donor and the increased mortality in people older than 50. The use of matched unrelated donors is being evaluated but it is associated with a very high mortality.

  Autologous transplantation has a disease free survival of 35% to 50% in patients with AML is first remission. Ongoing controversies include the optimum timing of the procedure, whether is should be preceded by consolidation chemotherapy and the role of ex vivo treatment of the graft with chemotherapy.

- Newer agents and approaches for AML
  - Topoisomerase 2 inhibitors (see above)
  - Immune therapy with anti-CD33 (mylotarg- a potent chemotherapy attached to anti-CD33 monoclonal antibodies, associated with 30% response rate in relapsed patients. Major side effects includes prolonged thrombocytopenia, prolonged neutropenia, and minority of patients developed veno-occlusive liver disease)
  - Farnesyl transferase inhibitors (investigational) Mini” allogeneic stem cell transplants – promising due to less regimen related toxicity. Implores ability to achieve graft vs leukemia effect.
  - Dendritic cell based vaccine therapy (investigational)

- Miscellaneous
1. No clinical studies to date indicate that growth factors (G-CSF or GM-CSF) contribute to relapse when given following cytoreductive therapy. They do shorten neutropenic period.

2. AML is a very heterogeneous disease, whose treatment needs to be carefully tailored to each individual scenario.

3. Treatment related AML with chromosome 5 or 7 abnormalities carry a poor prognosis and should be considered for palliative care alone in patients with poor performance status.

4. Acute promyelocytic Leukemia (APL)(M3) is the only subset treated differently. The subtype is characterized by t(15,17) translocation, PML/RARα (fusion of PML gene with retinoic acid receptor. All trans retinoic acid (ATRA) is used with anthracyclines for treatment of this subset. CR 1 is achieved in more than 90% of cases treated with ATRA and chemotherapy. Maintenance with ATRA and chemotherapy decreases the relapse rates ATRA may cause an ATRA syndrome (ARDS like). Arsenic trioxide is approved for ATRA refractory APL.
Section 7

**Multiple Myeloma** Malignancy of monoclonal plasma cells

**Incidence / Etiology**
- 14,600 new cases in the U.S. expected in 2002
- Second to lymphoma as the most common hematologic malignancy
- Males are affected more than females.
- Twice as common in African Americans
- Etiology is unknown

**Pathology/Pathogenesis**
- Multiple myeloma is a neoplastic proliferation of plasma cells throughout the bone marrow.
- Clinical problems result from involvement of bone and bone marrow, from inappropriate secretion of monoclonal proteins, and impaired immune function of residual plasma cells.
- Monoclonal proteins (M-proteins) are present in over 95% of patients. Their frequency is IgG > IgA > IgD > IgE. IgM monoclonal proteins occur in Waldenstrom’s macroglobulinemia and in some patients with non-Hodgkin’s lymphoma or chronic lymphocytic leukemia.
- Kappa or lambda light chains are produced in excess of 70% of patients.
- In “light Chain Myeloma”, the SPEP shows hypogammaglobulinemia and the M-protein (light chain) is only found in the urine. It tends to carry a poor prognosis.
- Production of M-proteins also occurs in some patients with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and amyloidosis

**Clinical Features**

*Monoclonal gammopathy of undetermined significance* (MGUS) describes patients who do not have myeloma, other lymphoplasmytic proliferate disorders, or amyloidosis. Common with advancing age. 30% of patients will develop a B cell malignancy within 15 years. (rate of 1.5% per year), MGUS may be associated with peripheral neuropathy. Bone marrow plasma cells are less than 10%, paraprotein level is usually less than 3 g/dl.

*Amyloidosis*: similar to MGUS but with deposition of amyloid fibrils in organs resulting in clinical manifestations of cardiomyopathy, nephrotic syndrome, hepatomegaly, neuropathy, macroglossia, and carpal tunnel syndrome. Diagnosis can be made by presence of the apple-green birefringence on polarized light examination of subcutaneous fat aspirates stained with congo red.

*POEMS syndrome*: polyneuropathy, organomegaly, endocrinopathy and/or edema, monoclonal protein and skin changes.

*Localized Plasmacytoma*: this is the “solid tumor” form of multiple myeloma. 9% of those with plasmacytomas of bone will develop multiple myeloma. 5 to 10% of those with extramedullary plasmacytomas will develop multiple myeloma.

*Smoldering myeloma*: asymptomatic patients with M-protein and marrow plasma cell levels compatible with myeloma.

*Multiple Myeloma* – see below
Chart 1
A. Multiple Myeloma

Major Criteria
I. Plasmacytoma on tissue biopsy
II. Bone marrow plasmacytosis with > 30% plasma cells
III. Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for G peaks or 2 g/dL for A peaks
   ≥ 1.0 g/24 h of k- or λ-light chain excretion on urine electrophoresis in the presence of amyloidosis

Minor Criteria
a. Bone marrow plasmacytosis 10% to 30% plasma cells
b. Monoclonal globulin spike present but less than the level defined above
c. Lytic bone lesions
d. Residual normal IgM <50 mg/dL, IgA < 100 mg/dL, or IgG <600 mg/dL
diagnosis is confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b, i.e.:
   1. I + b, I + c, I + d (I + a not sufficient)
   2. II + b, II + c, II + d
   3. III + a, III + c, III + d
   4. a + b + c, a + b + d

B. Indolent Myeloma (same as myeloma except)
I. No bone lesions or only limited bone lesions (≤ lytic lesions)
   no compression fractures
II. M-component levels: (a) IgG <7 g/dL; (b) IgA <5/dL
III. No symptoms or associated disease features, i.e.:
   a. Performance status >70%
   b. Hemoglobin >10 g/dL
   c. Serum calcium normal
   d. Serum creatinine <2 mg/dL
   e. No infections

C. Smoldering myeloma (Same as indolent myeloma except)
I. No bone lesions
II. Bone Marrow plasma cells ≤ 30%

D. Monoclonal Gammopathy of Unknown Significance
I. Monoclonal gammopathy
II. M-component level
   IgG ≤ 3.5 g/dL
   IgA ≤ 2 g/dL
   BJ protein ≤ 1 g/24 H
III. Bone marrow plasma cells < 10%
IV. No bone lesions
V. No symptoms

IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; BJ, Bence Jones light chain

Frank Multiple Myeloma
The clinical course is characterized by bone destruction, hypercalcemia, nerve root and spinal cord compression, hypoproliferative anemia, renal failure, infections. Infection and renal failure are the most common causes of death. Most patients die in the chronic phase when chemotherapy is no longer effective. Some patients develop and acute terminal phase characterized by pancytopenia, fever, and extramedullary disease, rising LDH, rapidly progressive myeloma cell proliferation, immunoblastic transformation, and/or plasma cell leukemia.

**Chart 2.**

**Myeloma Staging System**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following:</td>
<td>&lt;0.6 (low)</td>
<td>0.6-1.2 (intermediate)</td>
<td>&gt;1.2 (high)</td>
</tr>
<tr>
<td>Hemoglobin value &gt;10 g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum calcium value normal (&lt;12 mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On roentgenogram, normal bone structure (scale 0) or solitary bone plasmacytoma only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low M-component production rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG value &lt;5 g/dL*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA value &lt;3 g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine light chain M-component on Electrophoresis &lt;4 g/24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclassification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A = relatively normal renal function (serum creatinine value ≤2 mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B = abnormal renal function (serum creatinine value ≥2 g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Examples**

- Stage IA: low cells mass with normal renal function
- Stage II B: high cell mass with normal renal function

**Interleukin –6**

- Is essential for the survival and growth of myeloma cells. It prevents spontaneous and dexamethasone- induced growth of myeloma cell.
- Activates osteoclasts and provokes bone resorption
Treatment

- Combination chemotherapy is used for “frank multiple myeloma”. The standard treatment is melphalan and prednisone. Combinations of other drugs including Vinca alkaloids, nitrosurea (BCNU) and anthracycline are active but no more effective than melphalan and prednisone. The regimen of vincristine, doxorubicin, and dexamethasone (VAD) did not prolong survival in a randomized trial. Its main advantage is it produces a rapid remission. The results of treatment with high dose glucocorticoid alone in patients with refractory disease, relapsed disease, or previously untreated patients are inferior to VAD.
- There is no role for maintenance chemotherapy. The M-protein reaches a plateau in most patients and may disappear in 20-30%. The continuation of chemotherapy for more than 4 to 6 months after the M-protein plateaus or disappears may increase the risk of secondary leukemia.
- Patients under the age of 65 could be treated with high dose therapy and autologous bone marrow transplantation since a randomized study showed this to be more effective than standard therapy. The disease is not cured, and relapse is seen after auto-SCT but survival at 5 years was superior.
- Thalidomide is established now for treatment of refractory or relapsed multiple myeloma with 30% of the patients achieving at least 50% reduction in paraprotein. Major side effects include fatigue, sleepiness, constipation and thromboembolic disease. Trials for using thalidomide in combination with dexamethasone as first line therapy are being done.

Supportive Care

Infection – because of impaired humoral mediated immunity, patients are at high risk for infection with encapsulated organisms, S. pneumonia, and H. influenza.

Renal failure – may be due to secretion of light chains, hypercalcemia, nephrotoxic drugs, dehydration, and infection. Management consists of treating the underlying cause. Lambda light chains are more toxic to the kidneys than kappa light chains.

Bone destruction – Bisphosphates, analgesia, radiation therapy, internal fixation
- Bisphosphates are potent inhibitors of bone resorption and have been shown to decrease the incidence of skeletal events (pathologic fractures, pain, spinal cord compression, need for radiation therapy, hypercalcemia. Pamidronate is given intravenously over 90 minutes every 3 to 4 weeks for at least 3 years.

Hypercalcemia – treat the underlying myeloma and treat specifically the hypercalcemia (see Part I, Section 7)
References

Cancer Statistics


General


7. www.nci.nih.gov

8. www.uptodate.com

Oncologic Emergencies


Management of Nausea


Sexuality and Gonadal Function


Hematopoietic Growth Factors


Breast Cancer


Colon Cancer


**Lung Cancer**


**Prostate Cancer**


**Testicular Cancer**


**Ovarian Cancer**


Head and Neck


Gastrointestinal Tumors


Aids Malignancies


Carcinoid tumors


Soft Tissue Sarcoma


Renal Cell Carcinoma

Carcinoma of Unknown Primary


Non-Hodgkin’s Lymphomas


Acute Myelogenous Leukemia


Multiple Myeloma


Appendix I

Karnofsky Performance Status Scales

<table>
<thead>
<tr>
<th>STATUS</th>
<th>SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no complaints</td>
<td>100</td>
</tr>
<tr>
<td>Able to carry on normal activities. Minor signs/symptoms</td>
<td>90</td>
</tr>
<tr>
<td>Normal activity with effort</td>
<td>80</td>
</tr>
<tr>
<td>Cares for self. Unable to carry on normal activity or to do active work.</td>
<td>70</td>
</tr>
<tr>
<td>Requires occasional assistance but able to care for most of needs.</td>
<td>60</td>
</tr>
<tr>
<td>Requires considerable assistance and frequent medical care.</td>
<td>50</td>
</tr>
<tr>
<td>Disabled. Requires special care and assistance.</td>
<td>40</td>
</tr>
<tr>
<td>Severely disabled. Hospitalization indicated though death not imminent.</td>
<td>30</td>
</tr>
<tr>
<td>Very sick. Hospitalization necessary. Active treatment necessary.</td>
<td>20</td>
</tr>
<tr>
<td>Moribund</td>
<td>10</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
</tr>
</tbody>
</table>

ECOG Performance Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Symptoms</td>
<td>0</td>
</tr>
<tr>
<td>Minimal symptoms</td>
<td>1</td>
</tr>
<tr>
<td>More than minimal symptom and up &gt; 50% by the time</td>
<td>2</td>
</tr>
<tr>
<td>Up less than 50% of the time</td>
<td>3</td>
</tr>
<tr>
<td>Bed Bound</td>
<td>4</td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
</tr>
</tbody>
</table>

LEGAL DEPARTMENT
General Information

Location: 6001 East Wing  
Hours: 8:00 a.m. — 5:00 p.m., Monday to Friday  
Telephone: 966-3041  
Fax: 966-6285

Ben Gilbert  
Director of Legal Affairs  
Sissy Holloman  
Attorney  
Kathryn Chappell  
Director of Risk Management

Activities of the Legal Department

1. To administer the daily operations of the Self-Insurance Program, under the overall direction and supervision of the Liability Insurance Trust Fund Council.
2. To investigate promptly serious incidents and claims so that information is gathered to aid in settlement negotiations of meritorious claims or in the defense of non-meritorious claims.
3. To respond to medical-legal questions regarding patient care issues (i.e. Do Not Resuscitate orders, ethical dilemmas with treatments, etc.)
4. To compile incident data to be used in quality assurance and loss prevention activities.

Professional Liability Coverage

As members of UNC Hospitals’ Housestaff, you are covered for professional liability while performing approved residency activities, including off-site residency rotations. Moonlighting is excluded from coverage. Professional liability coverage is provided to residents as a benefit of employment. Coverage is provided on an occurrence basis. This means that a resident is covered for anything that occurs within the course and scope of his or her employment as a resident, even if a claim or a lawsuit is brought for that occurrence after the resident has left the Hospitals’ employment. Coverage is triggered by an occurrence rather than a claim.

Professional liability coverage is provided by the UNC Liability Insurance Trust Fund which is administered by the Legal Department of UNC Hospitals. The limit of liability for each occurrence is in excess of $1 million.

Covered Persons’ Responsibility Regarding Identification of Incidents

It is the responsibility of all members of Housestaff to report to the Legal Department as soon as practical any adverse patient care occurrence and to cooperate in the investigation and resolution of any claim. The reporting of an incident may be accomplished by:

1. Completing a “Patient Incident Report” form. These forms are located at all Nursing stations. They are printed in red and noted as being the property of the Legal Department of IINC Hospitals. They should not be copied.
2. Placing a telephone call directly to the Legal Department (6-3041). This is the preferred method for reporting serious incidents, patient claims, and attorney contacts.
3. Writing a confidential letter to the Risk Manager or Hospital Attorney. No copies should be made of the letter.
   Any adverse patient occurrence, any potential claim, or any dissatisfied patient/family should
be reported to the Legal Department. All communications with the Legal Department are considered confidential. Although the actual incident report should not be shared with others, it is entirely appropriate to notify supervisors of the occurrence and the circumstances surrounding the incident.

By reporting an incident you are protecting yourself and others from frivolous claims, providing the opportunity to gather data and maximize all defenses to claims, providing data for use in quality assurance and providing an avenue for justifiable claims to be handled fairly and expeditiously.

**Good Risk Management Practices**

1. Know the hospitals’ and your specific department or service’s policies and procedures that govern your practice. Your failure to follow the applicable policies and procedures can be evidence of negligence.

2. Listen to your patients - communicate effectively. If you ignore their concerns or if they perceive you as callous, your chances of being sued increase dramatically. Patients seldom sue people they like.

3. Do not offer patients unrealistic expectations. Choose your words carefully - do not make false promises.

4. Comply with the Hospitals’ incident reporting to guarantee early intervention and resolution of problems.

5. Learn to recognize patient and family behavior that suggests a litigious propensity. Involve Risk Management, Patient Relations and Social Service with these persons early in hospitalization.

6. When in doubt, always err on the side of caution and always draw upon the expertise of others.

7. Treat each of your patients in the same way as you would like yourself or your family treated. Think of how you would react if you were in the patient’s position.

8. Document patient records as if all of your notes some day will be read by jurors in a court of law. Your notes should create a favorable impression about your level of practice.

9. When an incident occurs or there is an unusual event or unfortunate result in patient’s care, the event should be recorded in the medical record. Be objective in charting what occurred, without drawing conclusions or assigning faulty. Be sure to include actions taken to correct the problem.
APPENDIX 4
CODING AND DOCUMENTATION

As of May 2003, the Mandatory Teaching Physician and Evaluation and Management Services Coding and Documentation course will be offered monthly. The Compliance Office will announce the courses.

When billing based on time, Medicare requires only "a minimal" amount of one of the three areas: history, exam or medical decision making be documented in addition to the content of the counseling or coordination of care. For all carriers, only counseling may be included when billing E&M services in the outpatient setting. Inpatient services may include a combination of counseling and coordination of care--the total provided over the course of the day.

Following are three common scenarios for teaching physicians providing E/M services:

Scenario 1
The teaching physician personally performs all the required elements of an E/M service without a resident. In this scenario the resident may or may not have performed the E/M service independently.

- In the absence of a note by a resident, the teaching physician must document as he or she would document an E/M service in a non-teaching setting.
- Where a resident has written notes, the teaching physician's note may reference the resident's note. The teaching physician must document that he or she performed the critical or key portion(s) of the service and that he or she was directly involved in the management of the patient. For payment, the composite of the teaching physician's entry and the resident's entry together must support the medical necessity of the billed service and the level of the service billed by the teaching physician.

Scenario 2
The resident performs the elements required for an E/M service in the presence of, or jointly with the teaching physician and the resident documents the service. In this case, the teaching physician must document that he or she was present during the performance of the critical or key portion(s) of the service and that he or she was directly involved in the management of the patient. The teaching physician's note should reference the resident's note. For payment, the composite of the teaching physician's entry and the resident's entry together must support the medical necessity and the level of the service billed by the teaching physician.

Scenario 3
The resident performs some or all of the required elements of the service in the absence of the teaching physician and documents his/her service. The teaching physician independently performs the critical or key portion(s) of the service with or without the resident present and, as appropriate, discusses the case with the resident. In this instance, the teaching physician must document that he or she personally saw the patient, personally performed critical or key portions of the service, and participated in the management of the patient. The teaching physician's note should reference the resident's note. For payment, the composite of the teaching physician's entry and the resident's entry together must support the medical necessity of the billed service and the level of the service billed by the teaching physician.

Following are examples of minimally acceptable documentation for each of these scenarios:

Scenario 1
Admitting Note:
"I performed a history and physical examination of the patient and discussed his management with the resident. I reviewed the resident's note and agree with the documented findings and plan of care."

Follow-up Visit:
"Hospital Day #3. I saw and evaluated the patient. I agree with the findings and the plan of care as documented in the resident's note."
"Hospital Day #5. I saw and examined the patient. I agree with the resident's note except the heart murmur is louder, so I will obtain an echo to evaluate." (NOTE: In this scenario if there are no resident notes, the teaching physician must document as he/she would document an E/M service in a non-teaching setting.)

**Scenario 2**
Initial or Follow-up Visit:
"I was present with resident during the history and exam. I discussed the case with the resident and agree with the findings and plan as documented in the resident's note."

Follow-up Visit:
"I saw the patient with the resident and agree with the resident's findings and plan."

**Scenario 3**
Initial Visit:
"I saw and evaluated the patient. I reviewed the resident's note and agree, except that picture is more consistent with pericarditis than myocardial ischemia. Will begin NSAIDs."

Initial or Follow-up Visit:
"I saw and evaluated the patient. Discussed with resident and agree with resident's findings and plan as documented in the resident's note." Follow-up Visit: "See resident's note for details. I saw and evaluated the patient and agree with the resident's finding and plans as written."

Follow-up Visit: "I saw and evaluated the patient. Agree with resident's note but lower extremities are weaker, now 3/5; MRI of L/S Spine today."

**Following are examples of unacceptable documentation:**
- "Agree with above." followed by legible countersignature or identity;
- "Rounded, Reviewed, Agree." followed by legible countersignature or identity;
- "Discussed with resident. Agree." followed by legible countersignature or identity;
- "Seen and agree." followed by legible countersignature or identity;
- "Patient seen and evaluated." followed by legible countersignature or identity; and
- A legible countersignature or identity alone.

Such documentation is not acceptable, because the documentation does not make it possible to determine whether the teaching physician was present, evaluated the patient, and/or had any involvement with the plan of care.
Documenting Time-based E&M Services

- If time spent counseling and/or coordinating care is more than 50% of encounter, bill based on time using the usual E&M code
- Count face-to-face time only for outpatient services
- Counseling only in the outpatient setting, no coordination of care, it is considered overhead
- Count total for the day of counseling, coordination of care and time on floor in care of the patient for inpatient
- Document amount of counseling time and total time spent on encounter including time spent in history & exam (or state that it was over 50% counseling) and describe counseling, coordination activities
- Only documentation of a minimal history, exam OR medical decision making is required
- For Medicare patients, only the personal teaching physician time may be counted
Choosing the E&M level when time is the controlling factor

<table>
<thead>
<tr>
<th>Outpatient Visits</th>
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</thead>
<tbody>
<tr>
<td>Established</td>
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<td>99211</td>
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<tr>
<td>99212</td>
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<td>99213</td>
</tr>
<tr>
<td>99214</td>
</tr>
<tr>
<td>99215</td>
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</tbody>
</table>

Use the Prolonged Services code (99354) in addition to the highest level of E&M code if time exceeds the stated amount by over 30 minutes.

<table>
<thead>
<tr>
<th>Inpatient Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial inpatient consult</td>
</tr>
<tr>
<td>99251</td>
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<td>99253</td>
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<td>99254</td>
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