# Biomedical Engineering for Global Health

# Lecture One



### **Overview of Lecture 1**

Course Overview:
 Course organization
 Four questions we will answer
 Course project

Technology assessment – The big picture

World health: an introduction

## **Course Organization**

### Syllabus

### Website:

http://www.owInet.rice.edu/~bioe301/kortum /class/

BIOE 301 Roadmap



### **Four Questions**

What are the problems in healthcare today?

Who pays to solve problems in healthcare?

How can we use science and technology to solve healthcare problems?

Once developed, how do new healthcare technologies move from lab to bedside?

## **Your Situation**

- You have just been diagnosed with advanced cancer
  - Your physician tells you that with standard treatment, there is only a 15% chance that you will survive 5 years.
  - She informs you that she is testing a new therapy which may increase your chance of surviving 5 years by more than 40%.
  - The new therapy has extremely painful side effects and there is limited scientific evidence that it works.
  - The new therapy costs \$150,000 and your insurance company refuses to pay for it.
- What do you do?

## Technology Assessment

What is it?

Why do we need it?

Example

Bone marrow transplants for breast cancer

### Technology Assessment: Overview

### The disease:

- Breast Cancer
- The technology:
  - High dose chemotherapy (HDCT) with autologous stem cell support (ASCS)
  - \$80,000-\$150,000, high morbidity, initially high mortality

### The assessment:

- 1980s: Small clinical trials promising
- Many patients demanded treatment even though there was very little evidence that it worked
- What happened next?

## The Disease

#### Breast Cancer

- 211,240 new cases of breast cancer will be diagnosed in the U.S. in 2005
- Over 2.3 million women living in the U.S. who have been diagnosed with & treated for breast cancer
- 2<sup>nd</sup> leading cause of cancer death among women in the U.S.
- Incidence and mortality rates vs. time

Figure 4. Female Breast Cancer Incidence Rates\* by Race and Ethnicity, SEER, 1973-1998



Data source: NCI Surveillance, Epidemiology, and End Results Program, 2001.



\*Rates are age-adjusted to the 2000 US standard population.

tinformation is included for all states except Connecticut, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, and Vermont.

Data source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2005.

American Cancer Society, Surveillance Research, 2005



# **Breast Cancer Staging**

Stage	Definition	5 yr survival
Stage 0	Cancer cells are located within a duct and have not invaded the surrounding fatty breast tissue	100%
Stage I	The tumor is 2 cm or less in diameter and has not spread to lymph nodes or distant sites.	98%
Stage II	The cancer has spread to 1-3 lymph nodes close to the breast but not to distant sites	76-88%
Stage III (High risk)	The cancer has spread to 4-9 lymph nodes close to the breast but not to distant sites	49-56%
Stage IV (Metastatic)	Cancer has spread to distant organs such as bone, liver or lung or to lymph nodes far from the breast.	16%

### **Treatments for Breast Cancer**

#### Surgery

- Lumpectomy
- Mastectomy
- Used to remove small tumors

#### Chemotherapy

- May be used to shrink larger tumors so that they can be removed surgically
- May be used following surgery to reduce risk of recurrence
- May be used to treat stage IV breast cancer
- e.g. cyclophosphamide with doxorubicin or epirubicin

#### Radiation Therapy

May be used following surgery to reduce risk of recurrence

#### Hormone Therapy

- May be used to shrink larger estrogen positive tumors so that they can be removed surgically
- May be used following surgery to reduce risk of recurrence
- e.g. Tamoxifen an anti-estrogen drug

# The Technology

High dose chemotherapy (HDCT) with autologous stem cell support (ASCS) How does chemo work? How does high dose chemo work? Why do we need ASCS? Bone marrow transplants What are they? How were they developed?

# Chemotherapy

#### How does it work?

- Chemotherapy drugs given IV or by mouth
- They travel through the bloodstream to reach cancer cells in most parts of the body
- Interfere with ability of cell to divide
- Cancer cells cannot repair damage caused by chemotherapy drugs so they die
- Rapidly dividing normal cells may also be affected by chemo drugs but they can repair this damage

#### Possible Side effects

- Temporary: Nausea and vomiting, loss of appetite, hair loss, mouth sores, low blood cell count (infection, bleeding, fatigue)
- Permanent: Premature menopause and infertility

# High Dose Chemotherapy

#### Dose of chemotherapy

- Balance between goal of completely destroying all cancer cells & causing too much damage to normal cells
- Dose comparison studies of chemo in metastatic breast cancer show high dose is associated with high response rate

#### High dose chemotherapy (HDCT)

- Wipe out cancer cells with extremely high doses of chemotherapy
- Such doses also destroy bone marrow, including stem cells that eventually mature into cells of the blood and immune system
- Patients receiving HDCT must undergo a transplant to restore the bone marrow cells

### **Bone Marrow Transplants**

Components of blood

- Plasma
- Cells
  - Red blood cells
  - White blood cells
  - Platelets
  - Cells are produced in the bone marrow from pluripotent hematopoeitic stem cells

Lab expts: a single stem cell can yield the half-trillion blood cells of an entire mouse



### History of Bone Marrow Transplants

- Conceived in a dog kennel in Cooperstown, NY during the 1950s
  - RBCs could be successfully transfused from compatible donor to needy recipient
  - Marrow cells could not: Body identified them as foreign invaders and destroyed them
  - Hiroshima one reason that radiation was so deadly because it destroyed the bone-marrow cells of its victims – hemorrhage, infection
  - Need: ability to restore bone marrow

### History of Bone Marrow Transplants

#### E. Donnal Thomas

- Grew up in Texas, attended Harvard Med School
- Treated leukemia patients with chemotherapy
- Believed that providing new, healthy bone marrow cells was essential to curing leukemia
- Tested various transplant techniques in dogs
- Tested them in patients with late stage leukemia
- Every patient who underwent transplantation died during the procedure of shortly thereafter. After 4 years stopped human trials.
- "Things were pretty grim."

### **History of Bone Marrow Transplants**

#### E. Donnal Thomas

- 8 years later, identified genetic markers on WBCs of histocompatibility
- Enabled close matching of donor and recipient
- Led to successful results in dogs
- Resumed human trials
- Led to successful treatment for leukemia
- Received the Nobel Prize in 1990



http://research.medne t.ucla.edu/images/nob el\_med.gif



### **Bone Marrow Transplants: Leukemia**

- Courtney Stevens
  - High school sophomore with leukemia
  - Treated with a bone marrow transplant
- "It was a complete nightmare. For days, I'd be on all fours and just retch and retch."
- "I looked like a lobster, and thought I had bugs crawling on me. I'd hit myself and scream."
- " I was in that sterile bubble, and forgot what skin against skin felt like. That was lost. I just wanted to hold on to my mom or dad, like a two-year-old, and I couldn't"
- "I had terrible diarrhea, a blistering rash all over my body, and jaundice. I was the color of an egg yolk."

http://www.jeromegroopman.com/bmt.html

### Bone Marrow Transplants: Breast CA

- Chemotherapy is often ineffective for Stage IV breast cancer
- Would higher doses of chemotherapy be more effective?
- Requires bone marrow transplant
- Can do autologous transplant (use patient's own bone marrow)
- HDCT + BMT:
  - Harvest stem cells from patient
  - Give HDCT
  - Perform autologus stem cell transplant (ASCT)
- Expensive, high morbidity and mortality

### Bone Marrow Transplants: Breast CA

#### Tamar Lowenstein

- 39 yo lawyer with widely metastatic breast cancer
- Treated with HDCT and bone marrow transplant
- Peripheral blood stem cell transplantation

### "It's getting worse every hour."

Lips were so blistered that speaking was painful

Chemical burn throughout her entire GI tract

"I wish I hadn't done it. It was a mistake."

Could not eat for 5 weeks. Weight dropped 46 lbs Tumor did respond to therapy

http://www.jeromegroopman.com/bmt.html

### PBSC Transplantation with Apheresis

#### Where are stem cells?

- Most stem cells are found in the bone marrow,
- Some, called peripheral blood stem cells (PBSCs), can be found in blood

#### Apheresis:

- Patient given medication to increase the # of stem cells released into the bloodstream
- Blood is removed through a central venous catheter
- Blood goes through machine that removes stem cells
- Blood is returned to patient and collected cells stored

# "The Equipment"



### "The Centrifuge"

http://www.caridianbct.com/cps/rde/xchg/caridianbct/hs.xsl/Products\_124\_ENU\_HTML.htm

Blood components are separated by centrifugal force.

Packed Red Blood Cell Layer

**Plasma Layer** 

Buffy Coat Layer Containing Progenitor Cells



**Stem Cell Collection Port** 

## Clinical Trials of HDCT + BMT

#### **1980-1990**:

- Phase II Trials with historical controls
- Pts with metastatic breast cancer treated with HDC+BMT
  - 40% improvement in 3-yr survival compared to historical controls treated with standard chemo
  - Increased adverse effects: high mortality (0-22%) and morbidity
  - Increased cost: \$160,000 (now \$60,000)
  - Selection bias??
    - Only included patients that responded to initial standarddose chemotherapy
    - Prospects better for treating responsive disease

#### 1991: 60 Minutes

Aired piece decrying Aetna's decision to deny coverage for HDCT+BMT for breast CA

**1993**:

- Nelene Fox (38 yo mother of 3) sued HealthNet for failure to provide coverage for HDC+BMT
- HealthNet paid for a relative of its CEO to receive HDC+BMT, but denied coverage to Fox and others
- Fox's family raised \$210k for the transplant
- Fox died of breast cancer before the verdict
- Fox's family was awarded \$89M, largest jury verdict against an HMO at the time
- Received wide publicity

### **1993**:

Massachusetts legislature mandated benefit law for HDC+BMT

**1994**:

- Insurers approve 77% of breast cancer patient requests for HDC+BMT clinical trial participation
- Approval is highly arbitrary, even for similar patients covered by the same insurer
- 9 of 12 large insurers surveyed say threat of litigation was a major factor in their decision to provide coverage

#### **1995**:

- Small (90 pts), short randomized trial by Bezwoda showed survival benefit for HDCT+BMT for metastatic breast cancer
- More than 80% of American physicians believe that women with metastatic breast cancer should be treated with HDCT+BMT

#### ■ 1990s:

- More than 41,000 patients underwent HDCT+BMT for breast cancer despite a paucity of clinical evidence regarding effectiveness
- Difficult to recruit patients to randomized Phase III clinical trials (took twice as long to complete as planned)

#### **1999**:

- American Society of Clinical Oncology Meeting
- Results of 5 randomized clinical trials reported
- Four studies showed no survival benefit with BMT; some showed it took longer for cancer to return
- One South African study showed survival benefit
  - 83% five year survival for BMT
  - 65% five year survival for controls
  - 100 months average disease free survival for BMT
  - 47.5 months average disease free survival for controls
- 1999 NY Times articles
  - Doubts Raised on a Breast Cancer Procedure By DENISE GRADY April 16, 1999, Friday
- NPR Story
  - <u>http://www.npr.org/templates/story/story.php</u> <u>?storyId=1049404</u>

# **RCT Results**

Study	# Pts Randomized	% survival	Disease-free survival
Stadtmauer	184	32% 3 year BMT	9.6 months BMT
Metastatic		38% 3 year control	9.0 months control
Lotz Metastatic	61	29.8% 5 year BMT 18.5% 5 year control	<ul><li>9% disease free at 5 yrs BMT</li><li>9% disease free at 5 yrs control</li></ul>
Peters	783	79% 3 year BMT	71% disease free at 3 yrs BMT
High Risk		79% 3 year control	64% disease free at 3 yrs control
Rodenhuis High Risk	885	75% 5 year BMT 73% 5 year control	65% disease free at 5 yrs BMT 59% disease free at 5 yrs control p=0.09*
Tallman	511	58% 6 year BMT	49% disease free at 6 yrs BMT
High Risk		62% 6 year control	47% disease free at 6 yrs control

### **RCT Results**



### **RCT Results**



### Why was only one study positive?

Team of scientists sent to audit trial results Study showed little evidence of randomization Records for many patients could not be found Many patients did not meet eligibility criteria Trial was not approved by the University's IRB No signed informed consents forms University conducted formal ethics inquiry Dr. Bezwoda admitted "serious breach of scientific honesty and integrity" University fired Dr. Bezwoda

## **Current Thinking**

Appears to be no survival benefit to HDCT+BMT

- 3 years
- 5 years
- There is a significant increase in disease free survival at 3 years with HDCT + BMT
- This increase disappears at 5 years
- Side effects are more common with HDCT+BMT, most are reversible
- Quality of life is lower at 6 months, but similar at 1 year

# **Technology Assessment**

- Biological Plausibility
  - Does the biology support the technology?
- Technical Feasibility
  - Safely and reliably deliver technology to patients?
- Clinical Trials
  - Sensitivity & specificity in a relevant population?
  - Disease-free survival & 5-year survival in a relevant population?
- Patient Outcomes
  - Does the technology improve the patient's health?
- Societal Outcomes
  - Cost and ethical implications of the technology?

Littenberg B. Technology Assessment in Medicine. Academic Med 67:424, 1992



What are the dangers of allowing political pressures to overwhelm science?

What is the proper forum to resolve controversies?

### Read More About It:

- Breast Cancer Facts and Figures:
  - http://www.cancer.org/downloads/STT/CAFF2 005BrF.pdf
- Dr. Groopman's article on BMT:
  - <u>http://www.jeromegroopman.com/bmt.html</u>
- Aetna announcement on coverage of BMT for breast cancer:
  - <u>http://www.aetna.com/cpb/data/CPBA0507.ht</u> <u>ml</u>

### Assessing Health

Individual Health vs. Population Health
 Pooled figures such as:

- Infant mortality rates
- Numbers of deaths and causes
- Immunization rates

## **Example of Health Data**

#### Estimated number of adults and children living with HIV, by region, 1990–2007







### **Questions about health data**

Why do we need it?
What data do we need?
Where do we get it?
How do we use it?

## World Health Organization

- Established by charter of the UN after World War II
- Headquartered in Geneva
- Mission:
  - Attainment by all peoples of the highest possible level of health"
- Website:
  - http://www.who.int/en/

### **Functions of the WHO**

### Services to governments:

- Epidemiologic intelligence
- International standardization of vaccines
- Reports of expert committees
- Data on world health problems
- Member countries must provide certain info in regular reports
  - Disease outbreaks
  - Health of population
  - Steps to improve health

### Uses for health measures

#### Identify emerging problems (early warning)

- Rubella during pregnancy
- Thalidomide during pregnancy
- AIDS → Kaposi's sarcoma, PCP
- Help determine public policy
  - Estimate impact of health problems
    - # people affected, ages, locations
  - Set funding priorities— Millenium Development Goals
  - Educate legislators
- Monitor progress toward goals

# Types of health data

#### Data on the population

- # of people
- Age, sex, ethnic origin, urbanization
- Vital statistics
  - Live births
  - Deaths (including infant deaths) by sex, age, cause

#### Health statistics

- Morbidity by type, severity and outcome
- Data on reportable diseases
- Tumor registries

#### Statistics about health services

- # and type of facilities
- # and qualifications of health personnel
- Services and utilization rates
- Costs and payment mechanisms

### Quantitative measures of health

#### Incidence

- Number of new cases of a disease in a population over a period of time
- Annual incidence rate

 $AnnualIncidenceRate = \frac{\# \text{ of new cases of a defined condition in a defined population in one year}}{\# \text{ in that population at mid - year of that same year}}$ 

### Quantitative measures of health

#### Prevalence

- Number of existing cases of a disease in a given population at a specific time
- Point prevalence

 $Po \text{ int } Pr evalence = \frac{\# \text{ of cases of a defined condition in a defined population at a point in time}}{\# \text{ in that population at same point in time}}$ 

### Quantitative measures of health

#### Mortality rate

- Mortality = Death
- Crude death rate, Infant, Neonatal, Post-neonatal, Maternal

### Mortality Rate MortalityRate = # of deaths in a defined population in a year # in that population at mid - year of the same year Infant mortality rate

 $InfantMortalityRate = \frac{\# \text{ of deaths under 1 yr of age in a defined population in a year}}{\# \text{ of live births in that population in same year}}$ 

## Burden of disease

#### Quality adjusted life year (QALY)

Measure of quality adjusted life years gained by an intervention

#### Disability adjusted life year (DALY)

- Years of disability free life lost
- Combines several elements
  - Levels of mortality by age
  - Levels of morbidity by age
  - Value of a year of life at specific ages

#### Examples:

- Stroke: 6 DALYs
- Car accidents: 9 DALYs
- Self inflicted injuries: 17 DALYs
- Violence: 9 DALYs
- Lower respiratory infections: 1 DALY
- HIV: 28 DALYs

# The study of global health

#### Epidemiology

- The study of the prevalence and spread of disease in a community
- Measures of health
  - Vary throughout the world
- Burden of disease
  - Varies throughout the world
- How can technology impact health and disease?
  - Varies throughout the world

#### We will examine in detail in BIOE 301

#### Leading causes of mortality among adults, worldwide, 2002

Mortality – adults aged 15–59			Mortality – adults aged 60 and over		
Rank	Cause	Deaths (000)	Rank	Cause	Deaths (000)
1	HIV/AIDS	2279	1	Ischaemic heart disease	5825
2	Ischaemic heart disease	1332	2	Cerebrovascular disease	4689
3	Tuberculosis	1036	3	Chronic obstructive pulmonary diseas	e 2399
4	Road traffic injuries	814	4	Lower respiratory infections	1396
5	Cerebrovascular disease	783	5	Trachea, bronchus, lung cancers	928
6	Self-inflicted injuries	672	6	Diabetes mellitus	754
7	Violence	473	7	Hypertensive heart disease	735
8	Cirrhosis of the liver	382	8	Stomach cancer	605
9	Lower respiratory infections	352	9	Tuberculosis	495
10	Chronic obstructive pulmonary diseas	se 343	10	Colon and rectum cancers	477

## Leading Causes of Infant Mortality in Developing Countries WHO Annual Report 2003

Cause	Numbers (000)	
Lower respiratory infections	1856	
Diarrhoeal diseases	1566	
Malaria	1098	
Measles	551	
HIV/AIDS	370	
Pertussis	301	
Tetanus	185	

# Your Risk of Major Diseases

http://www.yourdiseaserisk.wustl.edu/ind ex.htm

### Life Expectancy at Birth (2000)



#### Infant Mortality Rate (2002)



#### Gross National Income per Capita at PPP (2001)



#### Access to Safe Water (2000)



#### Internet Users (2002)



### **Questions We Will Consider**

- How do we bring new technologies from lab to bedside in a safe and affordable way?
- How should we invest limited financial and human resources to develop new medical technologies?

Will new technologies reduce health disparities or widen the gap between developed and developing countries?