Therapeutic Innovations in Lung Cancer

What Patients and their Caregivers Should Know

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LUNG CANCER RISKS

- Tobacco (inhaled carcinogens): cigarettes > cigars — 85 -87%
- Second-Hand Passive Smoke — 5 - 7%
- Other(s) — 5 - 7%
  - Radon (?)
  - Asbestos (co-factor)
  - Uranium
  - Therapeutic XRT
  - Marijuana
  - Beryllium
  - Air pollutants: diesel, pitch, tar, arsenic, nickel, chronium, cadmium
- Scar/Fibrosis — 1 - 2%

Cigarettes and Lung Cancer

GOOD NEWS

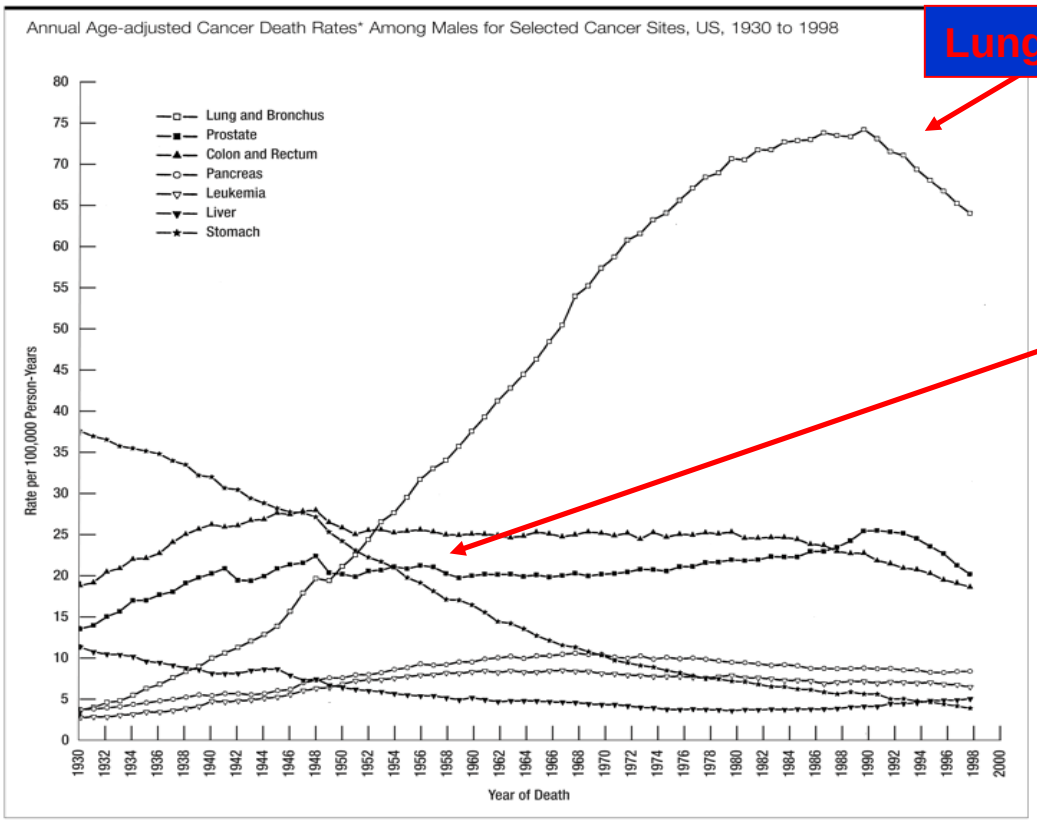
- Smoking rates have declined ~ 50% in US and Canada over past 50 years (50% → 25%)

BAD NEWS

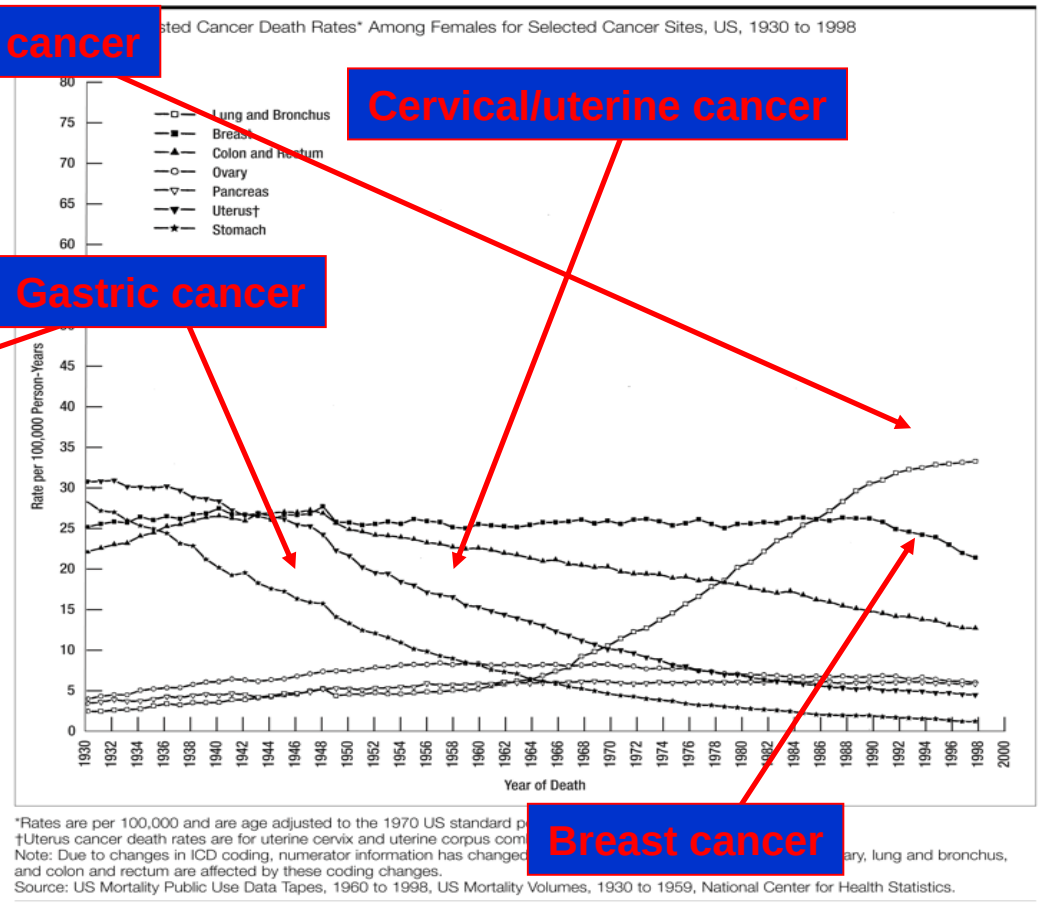
- ≥100,000,000 Americans/Canadians were ever smokers
- 3000 children each day start smoking; incidence rising
- Smokers avg. 5-7 yr reduction in life expectancy
- Only 1 in 10 quit attempts is successful
- Lung Ca risk declines with prolonged abstinence, but unlike CVD risk, never completely approximates general (non-smoking) population
- Former smokers: > 50% newly dx'd lung cancer

Cancer Death Rates (US)

Male



Female



Lung cancer

Cervical/uterine cancer

Gastric cancer

Breast cancer

LUNG CANCER

Presentation

- **Asymptomatic (accidental pick-up on CXR or CT)**
- **Local (cough, dyspnea, hoarseness, wheezing, pleurisy, chest pain, facial/neck swelling)**
- **Systemic (bone, brain, liver, adrenal, etc.)**
- **Paraneoplastic (tumoral, hormonal)**
  - **Decreased sodium (SIADH)**
  - **Increased calcium (increased PTH)**
  - **HPOA (hypertrophic pulmonary osteoarthropathy)**
  - **Cachexia (involuntary wt loss)**

NSCLC
PROGNOSTIC DETERMINANTS

- STAGE (Extent of disease)
- PERFORMANCE STATUS
- WEIGHT LOSS
- GENDER

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THERAPEUTIC DETERMINANTS

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THERAPEUTIC DETERMINANTS

- STAGE (Extent of disease)
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- WEIGHT LOSS
- HISTOLOGY (appearance under the microscope)

Frankly Speaking About Lung Cancer

LUNG CANCER STAGING (TNM)

T= Primary tumor size (T1-T4)

N= Lymph node involvement (N1-N3)

M= Distant metastasis (M0-M1)

Frankly Speaking About Lung Cancer

Stages of Non-Small Cell Lung Cancer

- **Stage I** — confined to lung tissue alone
- **Stage II** — lung tissue and lymph nodes in lung
- **Stage III** — lung tissue and lymph nodes outside of the lung (SCN)
- **Stage IV** — distant spread (liver, adrenal glands, bone, brain, other sites)

ECOG/ZUBROD PERFORMANCE STATUS SCALE

0. Asymptomatic; minimal symptoms; fully functional; maintaining ADLs
1. Symptomatic; able to carry out all ordinary tasks
2. Symptomatic; compromised; ≤ 50% waking hours in bed
3. Symptomatic; severely compromised; > 50% waking hours in bed
4. Symptomatic; bedridden; often moribund

LUNG CANCER: DIAGNOSIS

- SPUTUM CYTOLOGY: non-invasive; low-tech
- BRONCHOSCOPY (FOB): assesses airway
  indication: all central tumors; surgical candidate
- EBUS and EUA (endoscopic ultrasound through Bronchoscope or Endoscope (EGD)
- TRANSTHORACIC FNA: CXR or CT guided
  indication: peripheral lesions; 15% F (-)
- MEDIASTINOSCOPY: assess mediastinal nodes
  indication: surgical candidates
- VATS: less invasive than thoracotomy
  indication: small, visible, peripheral lesions
- NODE BIOPSY: supraclavicular, cervical nodes

HISTOLOGY – LUNG CANCER

- NON-SMALL CELL (NSCLC) — Total Inc

  - ADENOCARCINOMA — 40-50%
    - incidence rising especially in women;
    - peripheral location;
    - higher metastatic risk (chance of spread beyond the chest)
    - less tightly linked to cigarettes vs other cell types
    - BAC subtype: 2-4%, but growing

HISTOLOGY – LUNG CANCER

- NON-SMALL CELL (NSCLC) cont'd — Total Inc

  - SQUAMOUS — 20-30%
    - incidence declining;
    - central location;
    - decreased metastatic risk;
    - tighter smoking linkage (?unfiltered cigs)

  - LARGE cell — 5-10%
    - usually peripheral;
    - may be more aggressive

HISTOLOGY - LUNG CANCER

- SCLC (Small Cell)
  - APUD cells; specialized cells producing specialized proteins
  - central presentation;
  - highly aggressive 12-15%
  - presumed metastatic at dx
  - tightest smoking link;

- CARCINOID 1-3%
  - Morphologically similar to SCLC;
  - “blander” histology (appearance);
  - usually localized +/- endobronchial;
  - decreased metastatic risk

NON-SMALL CELL LUNG CANCER

Surgery

- Cornerstone of treatment
- Anatomic resection – key
- Node sampling/dissection: crucial
- Potential role – isolated metastases

NON-SMALL CELL LUNG CANCER

Radiation Therapy

- Surgically unresectable/medically inoperable
- Minimum dose ≥ 60 Gy [up to 74 Gy],
  - Usually 1.8-2 Gy/Fx, 6-7 weeks of Tx
- Other curative venues:
  - Adjuvant treatment after surgery (N_2): 50-55 Gy
  - Pre-op in locally advanced stage III/Pancoast: 45-54 Gy
- Palliative Role
  - Local (SVC syndrome; hemoptysis; post-obstructive pneumonia)
  - Brain
  - Bone
  - Spinal cord

NON-SMALL CELL LUNG CANCER

Radiation Therapy (cont'd)

- Research arena
  - 3-D conformal (IMRT)
  - Acceleration
  - Hyperfractionated
  - Stereotactic (Cyberknife)
  - Protons
  - PDT
  - Limiting toxicity (mucoprotectants)

NSCLC: STANDARD AGENTS

OLD (pre 1990)

- Cisplatin → Carboplatin
- Etoposide
- Vinblastine
- Ifosfamide
- Mitomycin-C

NEW (post 1990)

- Paclitaxel
- Docetaxel
- Gemcitabine
- Vinorelbine
- Irinotecan

LATEST (post 2000)

- Pemetrexed
- Gefitinib
- Bevacizumab
- Erlotinib

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NSCLC: NEW AGENTS (e.g)

- Antibodies targeting EGFR: Cetuximab
- New Angiogenesis Inhibitors: Axitinib, Vandetanib
- IGFR Monoclonal Antibodies: Figitumumab
- HSP 90 Inhibitors
- EML4/ALK inhibitors
- Obataclax in SCLC: triggers apoptosis (programmed cell death)

Customized (“Personalized”) Therapy

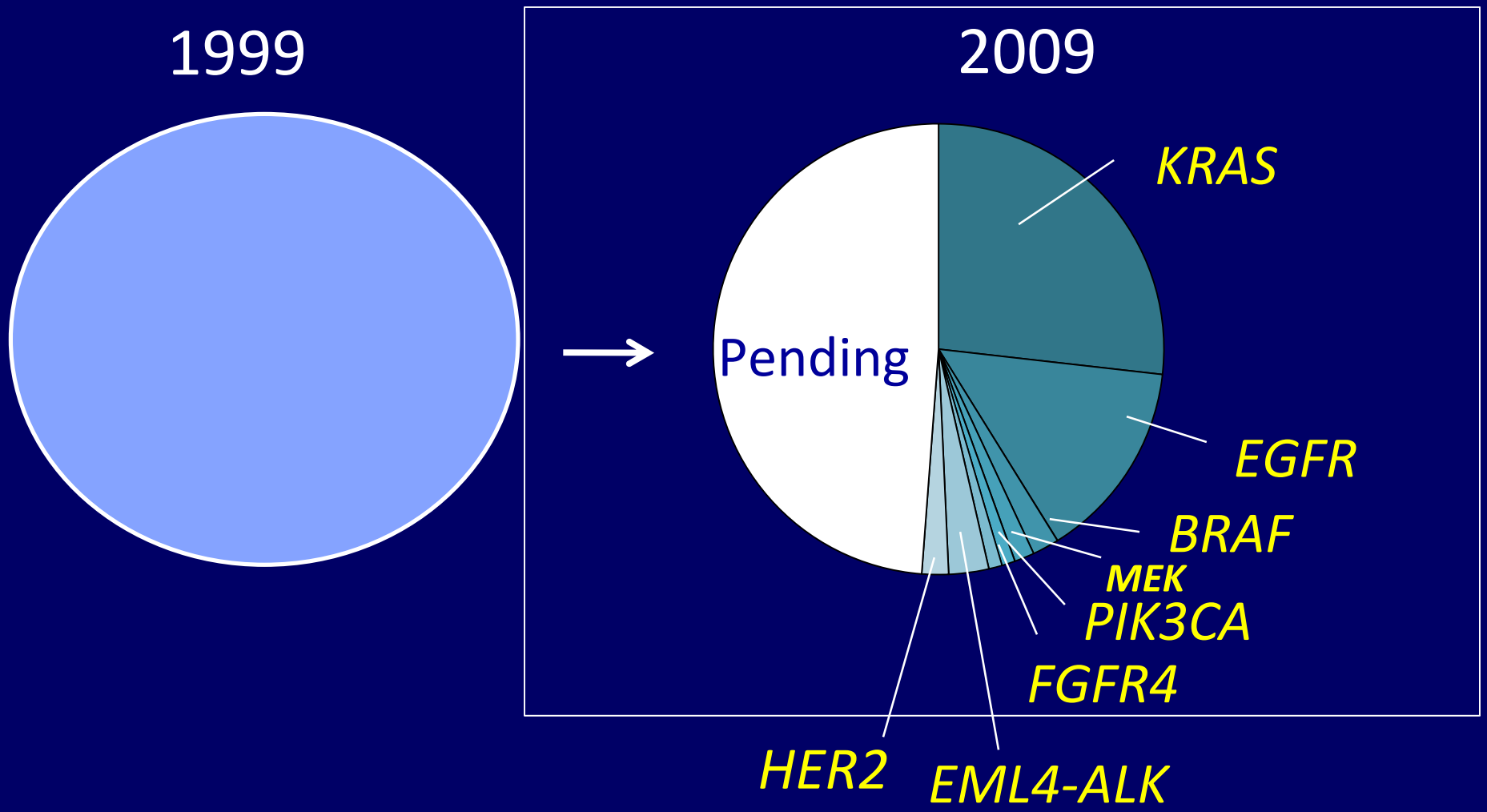
- Integrates combination of Tumor and Patient Characteristics into Therapeutic Decision-making
- Replaces our previous “One Size Fits All” approach
- NSCLC:
  - Paying attention to histology, as well as
  - Specific Markers

Customized ("Personalized") Therapy
NSCLC

- Histology,
  - Squamous (SqCC):
    - Gemcitabine superior to pemetrexed
    - Emerging MAbs targeting IGFR
  - Adenoca (AdC):
    - Pemetrexed, Bevacizumab use restricted to this histology
    - Higher relative response rate to erlotinib (EGFR TKIs) vs SqCC, though no obvious difference in survival advantage
- Specific Markers
    - EGFR mutation: Increasing use of Erlotinib first line
    - EML4/ALK: Emerging oral inhibitors

An Evolving View of Adenocarcinoma

Emergence of Molecular Markers



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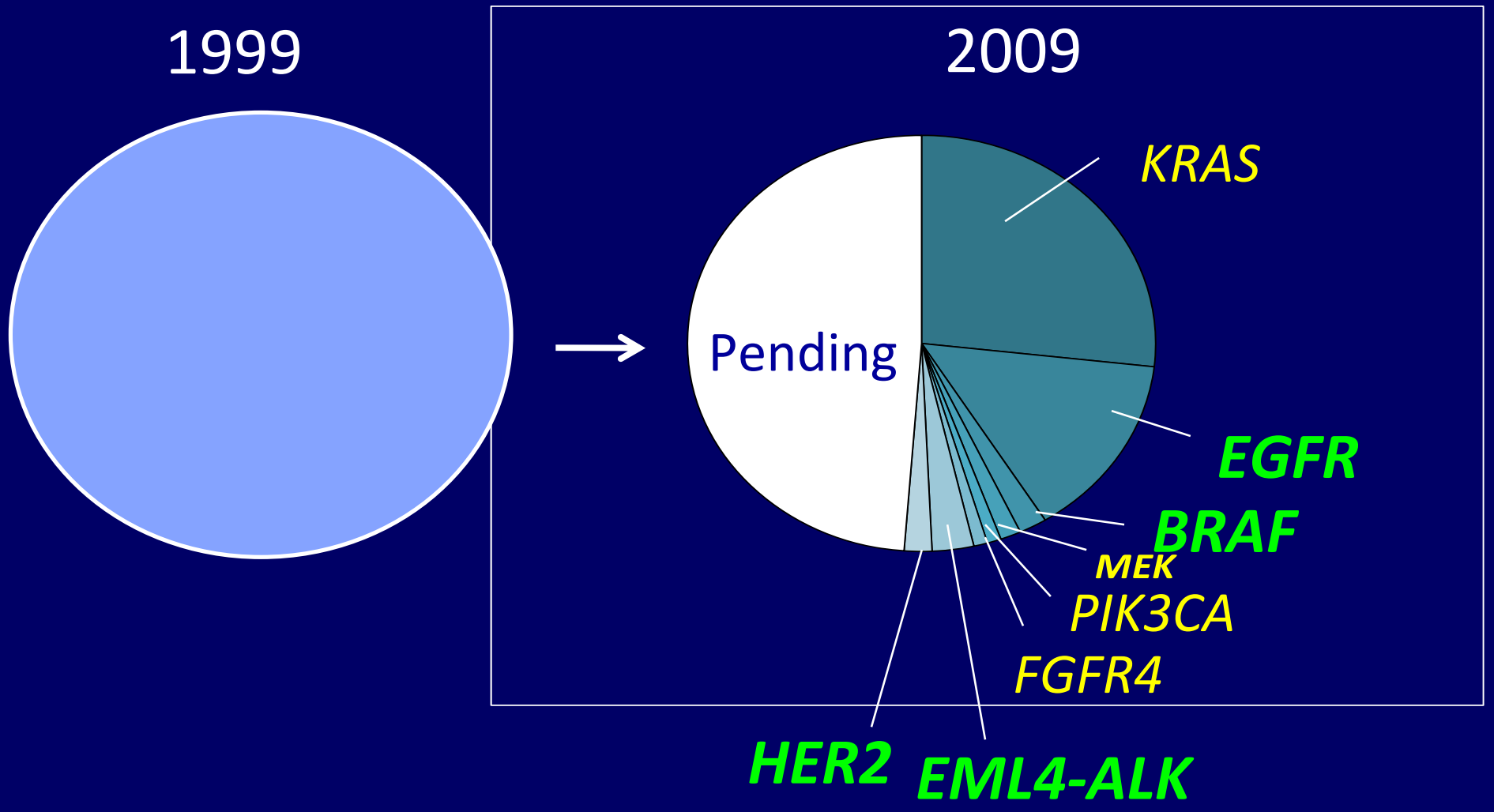

SCLC

- Chemotherapy: cornerstone of treatment
- Limited disease: concurrent chemoradiation
  – best hope of long-term survival
- Extensive disease: chemotherapy +/- radiation
- Surgery: limited role, reserved for very early stage SCLC (confined to chest without nodal invasion)
- PCI (Prophylactic Cranial Irradiation): eradication of occult, microscopic brain metastases before they grow clinically evident, established role in limited disease and emerging role in extensive disease

SCLC: STANDARD REGIMENS - 2000

TREATMENT-NAÏVE

- **Etoposide-Cisplatin (EP)**
- **Etoposide-Carboplatin (ECb)**
- **Irinotecan-Cisplatin (IP)**
- **Cyclophosphamide-Adriamycin-Vincristine (CAV)**

SALVAGE SETTING

- **Topotecan (IV or oral) or Irinotecan**
- **Paclitaxel**
- **Gemcitabine**

RESEARCH AGENDA SYMPTOM SUPPORT TOXICITY MANAGEMENT

- Nausea/Vomiting
- Appetite
- Diarrhea
- Mucositis (mouth sores; esophagitis)
- Fatigue
- Neuropathy (numbness and tingling)
- Psychosocial

CLINICAL TRIAL HIERARCHY

- PHASE I (EXPERIMENTAL)
  - New agent(s) or new combination of established agents
  - Establish top, safe dose (MTD ~ maximally tolerated dose) or optimal biologic dose
  - *May* require tumor biopsies or frequent blood draws (PKs)
  - Usually reserved for tumors for which no standard treatment exists or after "standard" treatments have been exhausted
- PHASE II
  - Systemic agent(s) applied to multiple patients with a specific disease type
  - Gauge side effects (toxicity); feasibility
  - Determine activity (response rate); freedom from progression; survival
- PHASE III
  - Randomized comparison of standard established treatment (control arm) vs. new(er) promising regimen (investigational arm)
  - Computerized coin toss (neither patient nor physician chooses)
  - Placebo controls used only if observation is standard

IMPEDIMENTS TO CLINICAL TRIALS

- TIME (labor-intensive)
- FUNDING (third party payer)
- PERCEPTION: physician; patient

WHAT PATIENTS (and CLINICIANS)SHOULD KNOW ABOUT CLINICAL TRIALS

1. Carefully conducted protocols mandate IRB approval, intensive monitoring, and close follow-up.
2. Informed consent is required.
3. Alternative options must be discussed. You cannot be coerced.
4. Total accrual is limited; statisticians oversee results/analysis.
5. Serious adverse events (AEs) are reported to IRB. Excessive AEs can result in a trial's early closure.
6. All clinical trials subject to FDA audit.
7. Enrollees on clinical trials do as well, if not better, than patients treated off protocol or empirically; costs are $\leq$ 10% higher than standard care.
8. You are not a guinea pig; you can opt out of clinical trial at will, without compromise to subsequent care.
9. Your physician may halt your participation if you are not benefiting, if superior therapies emerge, or if toxicity proves intolerable.

10 QUESTIONS to ASK YOUR HEALTH CARE TEAM

1. What are the most common side effects of my treatment?
2. What causes the side effects?
3. How can I prevent or minimize the side effects?
4. Do you have any printed material on the treatment?
5. Can I take other medicines while I am receiving treatment?
6. How will I know if my treatment is working?
7. Can I speak with someone on a one-to-one basis who has had a similar treatment experience?
8. What other options do I have regarding therapy?
9. Can I get financial assistance with medications or transportation?
10. How can I help other patients once I've completed my own treatment?

... SPIRIT Project

OTHER QUESTIONS

- Expectations of treatment
- What do we do if treatment doesn't work?
  What are the options?
- Can I stop treatment early?
  What are the consequences?

LUNG CANCER

Patient/Family Perspective

- Silence equals complicity (or denial)
- Articulate
- Advocate
- Ally