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STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

CERVICAL CANCER — PART I EPIDEMIOLOGY, ETIOLOGY AND PATHOGENESIS

Cervical cancer is unique because it is potentially preventable by using a rather simple screening technique, the Papanicolaou (Pap) test. The Pap test is designed to detect lesions in the cervical epithelium that may antedate the development of invasive cancer by several years and, as such, is a central part of a strategy designed to prevent the development of invasive cancer. Yet, although rare in the West, cervical cancer is the leading gynecological cancer in the rest of the world where screening is inadequate or unavailable.

This first installment of a 3-part series on cervical cancer, reviews the epidemiology of this malignancy and its precursors, and discusses putative risk factors associated with its development.

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

Cervical cancer is a slow-growing malignancy with several precursor premalignant stages referred to collectively as cervical intraepithelial neoplasia (CIN), or cervical carcinoma *in situ* (CIS), or cervical dysplasia, that affect more than 2% of all women worldwide. In 1970, in order to classify CIN by severity, Barron and Richart proposed a change in the terminology (JNCI, 1970; 45(5):1025-30) by demonstrating that, although clinically similar, the natural history of mild and moderate dysplasia is significantly different from that of severe dysplasia and CIS. The authors suggested that the terms dysplasia and CIS be replaced with CIN Grades 1-3, with CIN 1 being mild dysplasia, CIN 2 moderate dysplasia, and CIN 3 severe dysplasia and CIS.

In 1988, the National Cancer Institute (NCI) recommended another change to this terminology (J Reproductive Med, 1992;37(5): 383-6), the Bethesda System, which incorporates the role of human papillomavirus (HPV) infection in the development of precursor lesions and invasive cancers, by introducing the terms low-grade squamous epithelial lesion (LSIL) and high-grade SIL (HSIL) which correlate with CIN 1, and CIN 2-3, respectively. Any HPV-related cytology is added to the diagnosis of LSIL or HSIL. Abnormalities that do not meet the criteria for SIL are denoted as atypical squamous cells of undetermined significance (ASCUS). Colposcopic evaluation of persistent atypical smears show that in about 20% of cases they are either HSIL or invasive cancer. Staging of CIN and cervical cancer is described in Exhibit 1.

EPIDEMIOLOGY

Cervical cancer is the second most common cancer in women worldwide, although it is much rarer in western Europe and North America (see Exhibit 2). Cervical cancer is a potentially preventable disease because of the availability and widespread use of the Pap test. In the last 50 years, screening using Pap has resulted in a 70% decline in the mortality from cervical cancer in the USA and in most Western countries. This is in contrast to many Third World countries where cervical cancer is the leading cause of cancer among women with approximately 500,000 new cases reported each year. About 80% of all cervical cancer cases occur in developing nations. Incidence and death rates are particularly high in Latin America, Africa, India and Eastern Europe. The highest incidence rates in the world are found in the Eastern European nations. Rates in Chile and Cuba are also high. Cervical cancer is the cause of 25% of all cancer-related deaths in Mexican women. The lowest incidence rates have been reported in Finland and Israel. However, there is evidence of a recent rise in cervical cancer incidence in younger women in several developed countries, among them the UK, New Zealand, and Finland.

Cervical cancer is particularly common in Africa. In Northern Africa, cervical cancer is the second most common cancer among women. The diagnosis is usually made in advanced stages, and mortality is high. Cervical cancer screening in a rural district hospital in Zimbabwe identified a high frequency of abnormal smears in a relatively young population. When data from 419 cervical smears performed on young women (47.2% were age 20 to 29 years and 62.6% had fewer than 3 children) as part of a routine post partum visit from 1994 to 1996 was analyzed, about 15.5% were indicative of CIN (see Exhibit 3) (Thistle PJ and Chirenje ZM, Central African J Medicine, 1997 Sep, 43(9):246-51). In contrast, in the USA, CIN is detected in about 1.2% of women of all ages screened in the USA.

USA Epidemiology

Cervical cancer is uncommon in the USA with an incidence of 14,500 new cases and 4,800 deaths in 1997. This low incidence is attributable to widespread use of the Pap test. In the USA, CIN or SIL are far more common than cervical cancer. Almost 600,000 women (1.2% of all tested) are diagnosed yearly with premalignant changes such as SIL or CIN of whom 200,000 are new cases of CIN Grade 3. If untreated, about 30%-70% of patients with CIN 3 will develop invasive carcinoma over a period of 10-12 years. The majority of cases of CIN 3 are diagnosed in patients 20-34 years-of-age with the peak age being between 20-29 years-of-age. The significance of peak age at diagnosis of CIN lies in its comparison to the peak age-adjusted incidence of invasive cervical carcinoma, which occurs in the late fourth and fifth decade of life. This difference in peak age may be attributable to a long latent period between the progression from preinvasive to invasive forms of cervical cancer. Of note, 5% of CIN 3 lesions will progress to invasive cancer in less than 3 years.

Cervical cancer usually occurs in the fifth or sixth decade of life at a mean age of 54 years (Van Nagell JR and Barber HRK, eds, Modern Concepts of Gynecological Oncology, Boston, John-Wright-PSG, 1982). Also, although the age-adjusted incidence of cervical cancer is different among white, black and Hispanic women, the difference of *in situ* disease between the three groups differs only slightly. This finding may reflect more access to therapy for diagnosis of *in situ* lesions rather than a proclivity for progression (Handbook of Gynecological Oncology, 2nd edition 1996:82-83).

RISK FACTORS

Putative risk factors include young age at first intercourse, multiple sexual partners, low socioeconomic status and HPV infection, but the extent to which these risks are important in the etiology of cervical cancer has been difficult to assess because of confounding factors. Other risk factors include oral contraceptive use and certain nutritional deficiencies and host factors such as histocompatibility types (Apple, etal, JNCI, 15 Mar 1995, 87 (6):427) and immunologic response, hormonal influences, and infections with other sexually transmitted agents such as *Chlamydia trachomatis*. Also, male factors become very important because the sexual behavior of the male consort may determine the degree of exposure of the female to infectious agents.

It has also been suggested that the risk of cervical cancer is increased in patients who are immunosuppressed as a consequence of renal-allograft transplantation or lymphoma (Obstetrics Gynecology 1986; 68:251-8; Acta Cytology 1983; 27:22-4; Acta Cytology 1987; 31:845-54). This observation supports the theory that cellular immunity to the viral infection may be a critical factor in determining the impact of HPV; inadequate host defenses possible contribute to the carcinogenic effects of the virus.

Sexually Transmitted Diseases

Numerous epidemiological studies have linked cervical cancer with sexually transmitted diseases. Case control studies demonstrate a fivefold risk for the development of cervical cancer among women with multiple pregnancies (more than 10), multiple sexual partners or a partner with multiple sexual partners. Additional risk factors include early sexual activity, HPV infection of the cervix, human immunodeficiency virus (HIV) infection, and smoking (NEJM, 1965; 273:235-9; American J Epidemiology, 1990; 131:945-57; Cancer Research 1976; 36:783-91).

The fact that the number of steady partners and frequent intercourse at early ages enhance risk support the hypotheses that there exists a vulnerable period during which repeated exposure of the cervix to an infectious agent leads to cervical cancer.

Human papillomavirus (HPV) infections have been established as the leading etiologic factor in the development of cervical cancer. Numerous studies have demonstrated a strong relationship between HPV, CIN and invasive carcinoma of the cervix. HPV DNA has been identified in more than 60 % of cervical cancers and HPV DNA transcripts and protein products have also been identified in invasive cervical carcinomas (PNAS USA 1986; 83:4680). The proportion of histologically-confirmed high-grade cervical lesions that are attributed to HPV infections is 80% and presence of HPV infection confers a 10-fold to 200-fold risk to develop CIN compared to controls. However, because development of full blown malignancy occurs about 20 years after HPV infection, this virus alone is not the cause of cervical cancer and, because in most cases, even infection with a high-risk HPV is self-limited, the term high-risk is discouraged in describing this infection.

Papillomaviruses are members of the *Papovaviridae* family; they are nonenveloped viruses whose genomes consist of double-stranded circular DNA containing approximately 8000 base pairs. The study of HPVs has been hampered by the lack of a cellular culture system suitable for virus propagation and, thus, many aspects of their development remain unknown. Nonetheless, molecular cloning, genomic reassociation kinetics and serological studies have resulted in the identification of at about 90 different genotypes of HPVs with about half of them infecting the genital tract. Although exhibiting extreme heterogeneity, all HPVs show the same overall genomic organization, encoding eight genes divided into early genes that are expressed before DNA replication, and late genes expressed after viral DNA replication has begun. The early genes are essential to the initiation and maintenance of cellular transformation.

Based on extensive epidemiological data HPVs are strongly associated with anogenital neoplams, including cervical dysplasia and cervical cancer (see Exhibit 4). The HPV genome is usually present in an episomal configuration in CIN and integrated in the human genome in invasive carcinoma (Cancer Research 1991; 51:5019s-5022s). Overall prevalence of HPV among 932 confirmed cervical cancer specimens from 22 countries was 92.9%. Mean patient age was 47.8 years, ranging from 33.9 years in the African region to 56.5 years in Southern Europe. HPV subtypes that are commonly associated with high grade CIN and invasive cervical cancer are 16, 18, 31 33, and 45 (J Virology 1985; 54:675). Studies indicate that nearly 90% of invasive cervical tumors harbor HPV DNA and HPV type 16 can be detected in approximately 50% of squamous cell carcinomas of the cervix (JNCI 1985; 87:796-802). HPV type 18 has been associated with poorly differentiated carcinomas, an increased incidence of lymph node involvement and a high rate of disease recurrence, whereas HPV type 16 has been associated with large cell keratinizing tumors and a lower recurrence rate (Gynecologic Oncology 1988; 267: 1988).

Recent research has shown that the E6 and E7 genes of HPV 16 and 18 encode for oncoproteins than can immortalize human keratinocytes and are critical for the malignant transformation of cells. This potential appears to be limited to high-risk HPV types because E6 or E7 from HPV 6 or 11 (low risk serotypes) are nonimmortalizing (PNAS USA 1989; 86:563-7). The E6 and E7 oncoproteins alter cell growth regulation by inactivating the products of tumor-suppressor genes p53 and pRb, respectively. This inactivation leads to the dysregulated entry of cells into the S phase. E6 inactivates the function of wild-type p53 by enhancing its degradation, resulting in insufficient intracellular levels of this tumor suppressor protein (Cancer Research 1991; Suppl:5019s-5022s). In some cervical cancers, p53 is inactivated by mutation and as such represents an additional component of the process of malignant transformation (PNAS USA 1991; 88:5523-7; Oncogene 1994; 9:205-10). The continued expression of E6 and E7 nucleoproteins appears to be necessary for maintenance of the neoplastic state (J Virology 63:4417-4421,1989).

In a case-control study, all women (aged 20-49 years) in Greater Copenhagen diagnosed with invasive cervical cancer (n=59) or CIS (n=586) from January 1985 to December 1986, identified from the Danish Cancer Registry were matched with an age-stratified control group (n=586) that was randomly selected from the study area by means of the Danish Central Population Register. Information on risk factors was collected using a self-administered questionnaire. The study, conducted by the Danish Cancer Society, Institute of Cancer Epidemiology (Copenhagen, Denmark), found that both invasive cervical

cancer or CIS were strongly associated with sexual and venereal factors, especially the lifetime number of sexual partners and age at first episode with genital warts (proxy measure for HPV). This finding supports the theory that HPV infection in the adolescent cervix is associated with a higher risk of cervical neoplasia compared with such an infection later in life. Results also suggested that parity, oral contraceptive use, and smoking may be important risk factors.

Exhibit I
Staging of Cervical Dysplasia and Cancer

Stage	Description
	Precancerous
CIN 1	Low-grade squamous epithelial lesion (LSIL); mild dysplasia
CIN 2	High-grade SIL (HSIL); moderate dysplasia
	Cancerous
CIN 3	High-grade SIL (HSIL); severe dysplasia/carcinoma *in situ* (CIS)
ASCUS	Atypical squamous cells of undetermined significance (ASCUS)
Stage I	Carcinoma confined to the cervix
Stage Ia	Microinvasive
Stage Ib	All other
Stage II	Local disease
Stage IIa	No parametrial involvement
Stage IIb	Parametrial involvement
Stage III	Regional disease
Stage IIIa	No extension to the pelvic wall
Stage IIIb	Extension to the pelvic wall
Stage IV	Metastatic disease
Stage IVa	Spread to adjacent organs (rectum or bladder)
Stage IVb	Spread to distant organ

A second case-control study identified all women with one lifetime sexual partner, based on the questionnaire information obtained in the first case-control study. To investigate the role of the "male factor", the women were invited to participate in the study together with their husbands. In all, 41 case couples and 90 control couples were enrolled. Data collection included a personal interview, blood samples, and penile swabs from the males. The most significant risk determinants of cervical neoplasia were a history of genital warts in the male and non-use of condoms, emphasizing the venereal nature of this disease and pointing to HPV as an important risk factor. Genital warts are usually associated with the low-risk HPVs (types 6 and 11) rather than with the high-risk HPV types. An explanation for the observed relationship between risk of cervical neoplasia and genital warts in the woman and/or in her male partner could be that they were more likely also to harbor the high-risk HPV types. However, only 2 case husbands and no control husbands had HPV DNA detected in the penile swabs (Kjaer SK, Apmis Supplementum, 1998, 80:1-41).

Estimated prevalence of genital infections with oncogenic types of HPV among Nordic women and associated risk estimates indicate that approximately 45% of all cervical cancers arising in the these countries are caused by such infections. This is equivalent to about 550 new cases in each year around 2000, or 1% of all cancers arising in these populations (Winther JF, etal, Apmis Supplementum, 1997, 76:120-31).

A hospital-based case-control study to investigate known and suspected risk factors for cervical cancer that included 214 cases of invasive cervical cancer and 203 controls, conducted by the Institut National d'Oncologie (INO) (Rabat, Morocco), found that HPV DNA was the central risk factor and accounted for the large majority of the cervical cancer cases. The study was based on a structured questionnaire. Polymerase chain reaction (PCR) was used to detect the presence of HPV DNA and HPV type distribution with probes for 30 HPV types. The adjusted odds ratio for any HPV was 61.6% and the corresponding HPV attributable fraction was 92%. Among cases of cervical cancer, HPV 16 was the most common type (67.7%), followed by HPV 18. The HPV type-specific prevalence was similar for squamous cell carcinomas and adenocarcinomas. Other risk factors identified were sexual intercourse with multiple partners before the age of 20, low socioeconomic status, use of oral contraceptives for 5 or more years, and high parity. Screening is rare in this population but offered substantial protection against cervical cancer. In Morocco, cervical cancer is a late sequel of a viral infection with certain HPV types (Chaouki N, etal, Int'l J Cancer, 9 Feb 1998, 75(4):546-54).

DNA sequence variations have also been identified in different ethnic groups. Phylogenetic studies have identified five major branches for HPV 16 and indicated that viral diversity seems associated with ethnic characteristics of the populations. In a study of viral sequences among cervical tumors from the Mexican population, the existence of variants of HPV types 16, 18, and 45 was observed. One variant, found in more than half of HPV-16 positive tumors, seems to exhibit a more aggressive behavior. In HPV-18 positive tumors, in addition to the prototype, two variants were detected in nearly a fourth of the samples. Finally, all HPV-45 positive tumors showed a new variant

not yet reported in the literature. Some of these variants were found to be associated with specific histologic types of cervical cancer, suggesting the participation of these variants in its genesis or aggressivity (Lizano M and Garcia-Carranca A, Gaceta Medica de Mexico, 1997, 133 Suppl 1:43-8; Lizano M, etal, JNCI, 20 Aug 1997, 89(16):1227-1231).

Genomic variation of HPV type 16 is directly linked to risk for high-grade cervical intraepithelial neoplasia. Epidemiologic studies have demonstrated strong and consistent associations between detection of HPV type 16 DNA and the risk of CIN and cervical cancer. However, HPV 16 is also the most common type of HPV in the normal population, and only a minority of women with HPV 16 infection develop cervical cancer. Studies of genomic heterogeneity in HPV 16 have demonstrated the presence of multiple variant forms in all human populations examined to date. It is conceivable that the natural variants of HPV 16 in a given population may not have the same biologic behavior.

A study conducted at the Department of Epidemiology, School of Public Health, University of Washington (Seattle, WA) was designed to determine the association between natural variants of HPV 16 and the risk of biopsy-confirmed CIN 2 or 3. Prospective studies were conducted among women attending a university and women visiting a clinic for sexually-transmitted diseases. Subjects were eligible for inclusion in this investigation if the initial cytologic findings did not reveal CIN 2-3 and HPV 16 DNA was detected by means of a PCR-based method in one or more cervical or vulvovaginal samples. Eligible subjects were followed every 4 months with cervical Pap smears and colposcopic examinations. Women were referred for biopsy if cytology or colposcopy suggested CIN 2-3.

Two groups of HPV 16 variants, prototype-like and nonprototype-like, were determined by means of single-strand conformation polymorphism (SSCP) analysis of PCR products from the noncoding region of the viral genome. Representative SSCP patterns from HPV 16 variants were further characterized by direct DNA sequencing of the PCR products. Prototype-like variants accounted for 79% of the HPV 16 detected in university students and 86% of the virus detected in patients presenting to the sexually-transmitted diseases clinic. CIN 2-3 was confirmed by biopsy in nine of 57 HPV 16-positive women attending the university and in 10 of 66 HPV 16-positive women presenting to the sexually-transmitted disease clinics. Among university students, those with HPV 16 nonprototype-like variants were 6.5 times more likely to develop CIN 2-3 than those with prototype-like variants. A similar association was observed among women presenting to the sexually-transmitted diseases clinic who were 4.5 more likely. This study suggests that the risk of developing CIN 2-3 is not the same with all variants of HPV 16 and that nonprototype-like variants confer a greater risk compared with prototype-like variants. The important genomic differences underlying this increased risk of CIN 2-3 remain to be determined (Xi LF, etal, JNCI, 4 Jun 1997, 89(11):796-802).

The prevalence of HPV in the population at large varies from about 10% of all women over 40 years of age in the USA and Western Europe, to as high as 20% in countries like Thailand, the Philippines, Brazil, or Colombia. It is estimated that over 6 million American women, and probably as many males, harbor HPV infections. In the USA, prevalence of HPV infection in asymptomatic, healthy males is estimated at 7%. Usually, such infections in males are subclinical. In one study of male sexual partners of HPV-infected females, 77% were infected with HPV and, in 87% of cases, the viral types found in the men were identical to those in their female partners.

Other infections that may contribute to the development of CIN and cervical cancer include other viral infections, bacterial vaginosis or nonspecific vaginitis, and cervicitis. Bacterial vaginosis is an infection involving both aerobes and anaerobes. Bacteria isolated from vaginal secretions of infected patients include *Gardnerella vaginalis* as well as various *Bacteroides, Peptostreptococcus,* and *Mobiluncus* species. Bacterial vaginosis affects sexually active women. The common presenting symptom is a loose, often scanty, and usually nonirritating vaginal discharge which is frequently accompanied by a "fishy" odor. The most prevalent type, *G. vaginalis coccobacilli,* act synergistically with anaerobes to produce the amines responsible for the characteristic "fishy" odor associated with this infection but do not produce clinical disease if present alone. The role of curved anaerobic rods such as *Mobiluncus curtisii* is currently under investigation. Differential diagnosis includes microscopic evidence of clue cells (vaginal epithelial cells studded with tiny coccobacilli) in the discharge, an elevated vaginal pH of 5.0 or higher, and a positive whiff test.

The usual manifestation of acute cervicitis is an increased mucoid or purulent cervical discharge and cervical erythema and inflammation around the cervical os. Increased cervical discharge is also seen in pregnancy and in some patients who use oral contraceptives or contraceptive intrauterine devices (IUDs). However, this discharge is generally mucoid rather than purulent and does not contain abnormally large numbers of polymorphonuclear leukocytes (PMNs).

Etiologic agents of acute cervicitis include herpes simplex virus (HSV), recovered from the cervix of 80% of women with primary herpes genitalis. This type of cervicitis is often accompanied by a mucoid discharge. It may not be associated with lesions of the external genitalia, but cervical ulcerations and necrosis may be present.

Cervicitis of gonococcal or chlamydial origin is usually accompanied by a purulent or mucopurulent discharge. Analysis reveals large numbers of PMNs and gram-negative diplococci in about 50% of women with gonorrhea. Other gram-negative diplococci, present in normal vaginal secretions, may result in misleading smears. About 50% of women with gonorrhea also have chlamydial infection. Gonococci or chlamydiae are isolated from 60-90% women

Exhibit 2
Worldwide Crude Incidence and Mortality of Cervical Cancer in 1997

Country	Incidence		Mortality	
	(#)	Rate*	(#)	Rate*
Belgium	412	7.9	118	2.3
Denmark	571	21.4	157	5.9
France	4,077	13.6	612	2.0
Germany	12,067	28.2	1,746	4.1
Greece	439	8.2	90	1.7
Ireland	161	9.0	64	3.6
Italy	3,925	13.3	319	1.1
Luxembourg	19	8.7	5	2.5
The Netherlands	766	9.7	218	2.8
Portugal	1,015	19.8	148	2.9
Spain	1,642	8.2	409	2.0
United Kingdom	4,720	15.8	1,470	4.9
Total EEC	29,814	16.5	5,354	3.0
Austria	595	14.4	134	3.2
Finland	180	6.9	47	1.8
Iceland	19	14.0	4	3.0
Malta	13	6.6	3	1.4
Norway	311	14.0	109	4.9
Sweden	561	12.4	119	2.6
Switzerland	462	12.6	110	3.0
Total non-EEC	2,133	12.2	457	2.6
Bulgaria	799	18.1	222	5.0
Czechoslovakia	1,221	23.0	357	6.7
Hungary	754	14.5	406	7.8
Poland	4,569	23.0	1,836	9.2
Romania	2,170	19.8	1,342	12.2
Yugoslavia	1,059	16.4	303	4.7
Total Eastern Europe**	10,651	20.4	3,043	5.8
Total Europe**	42,524	17.0	12,150	4.9
Total former USSR	24,101	16.0	6,886	4.6
Argentina	2,247	12.4	978	5.4
Australia	1,183	12.8	300	3.2
Chile	2,198	29.9	628	8.5
Costa Rica	323	18.5	220	12.6
Cuba	1,098	20.0	349	6.4
Hong Kong	620	19.8	177	5.7
Israel	111	4.0	43	1.6
Japan	10,066	15.7	1,385	2.2
New Zealand	278	15.4	98	5.4
Singapore	258	14.9	127	7.3
Uruguay	253	15.5	98	6.0
Total Others	18,636	9.4	5,325	2.7

— *continued on next page*

whose sexual partners are infected with gonococcal or chlamydial urethritis. Chlamydia is associated with a form of cervicitis characterized by erosion, edema, and hypertrophy about the cervical os, accompanied by a purulent discharge. The lesion is generally red and commonly bleeds when abraded during clinical examination. Chlamydiae are isolated from 50-90% of sexually active patients. After treatment, this hypertrophic cervicitis usually resolves to a simple cervicitis.

In addition to HPV, other viruses implicated in cervical cancer include HIV, Epstein-Barr virus and herpes simplex II (HSV 2) that may interact with HPV. It has also been shown that infection by AAV inhibits HPV-induced oncogenicity. Investigators from the University of Arkansas (Little Rock, AR) and Penn State University College of Medicine (Hershey, PA), in a presentation during the 1998 meeting of the Society of Gynecologic Oncology (SGO98), reported that adeno-associated virus (AAV) regulates HPV phenotypes, HPVs can serve as complete helpers for AAV and, in return, AAV affects the level of HPV replication and the degree of cellular differentiation within the epithelium.

Cervical cancer has been designated an AIDS-defining illness because in HIV+ patients, prevalence of HPV is 5 times that of the general population. Because the disease presents at a later stage in HIV+ patients when it is less responsive to treatment, close attention to timely Pap smears and appropriate follow-up is important in this population. A study designed to determine the prevalence of CIN among HIV+ women from the southeastern USA, relative to a control group, found a significantly increased risk for cervical dysplasia in HIV+ women. Demographic, medical, and cytopathologic data were collected on 89 HIV+ women being cared for at the Duke Adult Infectious Disease Clinic (Durham, NC) and were compared with that of 100 HIV- obstetric patients who delivered at Duke and with published reports from other regions of the USA and abroad. CIN was present in 43 (49%) of 87 HIV+ women compared with 23% of the 100 HIV- patients. Two of the HIV+ patients were diagnosed with invasive cancer. Comparison of these patients with those from other geographic regions revealed similar odds ratios for the presence of CIN in HIV+ patients compared with HIV- ones (Drapkin AL, etal, Southern Med J, 1997 Sep, 90(9):893-6).

Socioeconomic Factors

Cervical cancer may be generally categorized as a disease determined by sexual habits and socioeconomic factors in both underdeveloped and developed countries. Numerous epidemiologic studies of cervical cancer have shown strong associations with religious, marital and sexual patterns. For instance, the age-adjusted cervical cancer incidence and mortally rate of Hispanic women living in the USA is greater than women of other ethnic groups. Interviews with 803 Latinas (533 immigrants and 270 USA-born) and 422 Anglo women, revealed that those born in the USA had similar attitudes towards cervical cancer screening. However, among immigrant Hispanic women,

United States	14,500	10.6	4,800	3.5
Canada	1,315	8.9	390	2.6
Total North America	17,299	11.4	5,190	3.4
Triad (Europe**, Japan, N. America)	69,889	15.0	18,725	4.0

**Per 100,000 women*
***Excluding the former USSR*

a smaller portion had a Pap smear in the last three years. It is believed that immigrant women are less likely to seek cervical cancer screening because they associate this malignancy with sexual activity and the possibility of having the disease implies immoral behavior (Hubbell FA, etal, Arch Intern Med, 11 Nov 1996, 156:2353-8).

A retrospective study analyzed data extracted from the 1989-1991 Orange County (CA) Health Surveys which included information on female genital tract screening, also found a link between cervical cancer screening and socioeconomic status. Variables analyzed included history and frequency of Pap smears, race, age, household income, occupation and medical insurance status. Among 1,414 adult female residents who participated in the survey, 79% were screened for cervical cancer at least once every three years. Factors that most strongly correlated with cervical cancer screening were level of education, insurance status, and annual household income greater than the lowest quartile ($30,000). In the lowest income quartile there was no difference in the frequency of Pap smears irrespective of insurance status or whether the subject was a single parent. The frequency of Pap smears was directly related to patient age. Younger respondents (18-29 years old) were less likely to have been screened compared to older participants, 4% versus 17%. Other positive factors included professional occupations and being Caucasian. Factors that remained independent predictors for screening were household income, professional occupations, and race. Insurance status was not an independent predictor (Brewster WR, etal, SGO98).

In a study examining socioeconomic differences in invasive cervical cancer in Spain and Colombia, two countries that differ substantially both in cervical cancer incidence and economic development, pointed to higher HPV DNA prevalence and lower use of preventive care among those of lower socioeconomic status. Data were derived from two case-control studies carried out in Spain and Colombia involving 373 case subjects, 387 controls and 425 husbands, interviewed with a structured questionnaire. Exfoliated cells were obtained from cervical or penile scrapes and tested for human HPV DNA. Relative to better educated women, women with low educational levels in both countries reported fewer Pap smears and had a higher prevalence of HPV DNA. The prevalence ratio of HPV DNA across educational strata was twofold in Spain and fourfold in Colombia. In both countries, husbands of poorly educated women reported higher use of prostitutes than husbands of better educated women. In Colombia, 30% of husbands of poorly educated women harbored HPV DNA, compared with 10% of husbands of better educated women (Amer J Public Health, Nov 1996, 86(11):1532-8).

PATHOGENESIS

Carcinoma of the cervix uteri originates at the squamocolumnar junction in the endocervical canal or on the cervix. Changes that progress to cervical cancer range from low to high-grade SIL or CIN 1,2, and 3, reflecting increasingly abnormal maturation of the epithelium. These premalignant lesions may persist, regress, or progress to an invasive malignancy. However, in about 10% of patients, lesions progress from *in situ* to invasive cancer in less than one year.

As it becomes invasive, the tumor breaks through the basement membrane, invading the cervical stroma. Eventually, it may manifest as ulceration, exophytic tumor, or extensive infiltration of underlying tissue of the bladder or rectum. HSIL (CIN 2-3) is more likely to persist or progress and spontaneous regressesion is rare, while LSIL (CIN 1) often regresses without treatment. The average time for progression of CIN 3 to invasive cancer is 10-15 years, depending on mean age at diagnosis.

The majority of cervical cancer is squamous cell carcinoma (95%) with the remaining cases being either adenocarcinoma (3%) of adenosquamous carcinoma (2%).

Next issue: *Screening, molecular markers, diagnosis, staging, and prognosis of cervical cancer.*

SPECIAL REVIEW

OVERVIEW OF ONCOLOGY TRENDS — PART II COSTS ASSOCIATED WITH ADVANCED CANCER TREATMENT

A number of new drug approvals and indication expansions in the oncology field are changing the economics of advanced cancer treatment by providing:

- expensive first-line treatments
- second- third- and fourth-line salvage approaches using novel high-priced drugs
- off-label use of approved high-priced drugs
- multimodality therapies
- high-dose chemotherapy including use of hematopoietic support
- use of new high-priced agents in supportive care

COSTS OF CHEMOTHERAPEUTICS IN ADVANCED DISEASE

One of the most jarring changes in the oncology field has been the high cost of chemotherapeutics (see Exhibit 5). In many cases, use of newly-approved drugs has raised the cost of therapy by an order of magnitude. Take the case of costs associated with treatment of metastatic breast cancer. In a study conducted by Kaiser Permanente (Oakland, CA), of the three most commonly administered treatment regimens, Taxol, CMF and CAF, acquisition cost of Taxol was $9,469, compared with $3,225 for CAF and $782 for CMF. Other services including physician, nursing, and pharmacist salaries and benefits, and other non-labor costs per visit per course, were $407, $210, and $229 for initial visits, respectively. After adjusting for the total number of visits per course and including other medication costs such as antiemetics and colony stimulating factors, the total average cost per course of Taxol was $11,504, CAF $4,599 and CMF $1,934 (Bull SA, etal, ASCO98, Abs. 1632:424a).

However, despite the high costs of new drugs, they remain marginally effective, usually prolonging life by several months but rarely providing long-lasting remissions. In some parts of the developed world, even minor life extensions achievable with second-, third-, and fourth-line treatments has justified use of very expensive procedures. This is particularly true in the USA where the major goal of multilevel chemotherapy in advanced, refractory disease has been to prolong life.

A case in point is the approval and immediate widespread demand for trastuzumab (Herceptin; Genentech) as first-line therapy in combination with standard chemotherapy and as second- or third-line therapy for the treatment of a particularly aggressive breast cancer type characterized by the overexpression of HER2/neu. Much is being made about this drug, not because it is a particularly effective treatment for late-stage breast cancer, but because it belongs to a novel class of anticancer drugs that target only malignant cells and, therefore, do not cause the debilitating side effects of standard chemotherapy. Herceptin does cause a slew of side effects such as pain, fever, chills, nausea and vomiting, headache and weakness, but these are mild and usually subside after the first infusion. However, because, best results with Herceptin are achievable when it is administered in combination with other chemotherapeutics, its milder side effects profile becomes less relevant. Actually, Herceptin in combination therapy in advanced breast cancer appears to significantly increase the risk of life-threatening congestive heart failure. Currently, it is expected that Herceptin will be used as a first-line therapy, in combination with paclitaxel, to treat HER/neu-expressing tumors. In this scenario, drug therapy alone is expected to cost upward of $20,000 per regimen. Use of Herceptin in combination chemotherapy increases the disease-free interval by about 56% (see Exhibit 6) which translates into several months, but patients progress nevertheless.

Exhibit 3
Rates of Abnormal Cervical Smears in Young African Women

Smear Status	Smears (#)	Smears (%)
Normal	173	41.3
Abnormal	246	58.7
Inflammation	158	64.2
Abnormal cytology	65	26.4
Low-grade SIL (CIN 1)	50	76.9
High-grade squamous intraepithelial lesions (CIN 2/3 and CIS)	15	23.1
Other	23	9.3

PHARMACOECONOMICS

One way to justify the high cost of chemotherapy is by showing cost-effectiveness. However, this is a difficult task in advanced cancer where costs associated with most treatments are staggering and life extensions limited.

Some pharmacoeconomic evaluations are straightforward, especially between regimens with comparable outcomes. Investigators at the Center for Health Outcomes and Economics (East Brunswick, NJ), a Division of Bristol-Myers Squibb, and their collaborators, performed a meta-analysis of available clinical trials to estimate the clinical effectiveness of two common combination therapies, Taxol/carboplatin and vinorelbine/cisplatin in the treatment of nsclc. Despite the significantly lower AWP of vinorelbine, the total cost of these regimens was $19,322 and $20,790, respectively. Treatment of nsclc with the vinorelbine/cisplatin regimen resulted in an incremental cost of $1,468, or 7% more than the Taxol/carboplatin regimen. Equivalency in effectiveness was assumed because there was no statistically significant difference between the total response rates of either regimen. A review of the modeling analysis indicates that the key drivers in the lower treatment cost with the Taxol/carboplatin regimen were lower administration and adverse event management costs (Lappas PT, etal, ASCO98, Abs. 1897:493a).

NCI, in collaboration with the American Society of Clinical Oncology (ASCO), are attempting to take a proactive approach to pharmacoeconomic evaluation of oncology preparations, by initiating the economic analysis during the clinical trial period. A workshop sponsored in 1996 by ASCO resulted in the publication of a workbook that describes procedures to perform economic studies together with clinical ones.

As described in Exhibit 7, there are four separate classes of expenditures associated with the management of cancer patients. All of these are variable and depend on the patient's socioeconomic environment except for the cost of branded products, from anticancer drugs to those required for supportive care, that tend to be priced similarly.

Exhibit 4
Genital/Mucosal Human Papillomaviruses (HPVs)

HPV Subtypes	Degree of Risk	Involvement in Cervical Cancer
HPV 6	Low-risk	Almost never found in cervical cancer; associated with benign tumors (papillomas, condylomata or warts)
HPV 11	Low-risk	Almost never found in cervical cancer
HPV 16	High-risk; reproducibly induces immortalization of keratinocytes	Most common type found in 50% of cases based on analysis of 981 cervical cancer specimens from 22 countries; primarily associated with squamous cell carcinoma
HPV 18	High-risk	Predominantly associated with adenocarcinomas and adenosquamous carcinomas; found in 13.7% of all cases of cervical cancer and in 56% of adenocacinomas and adenosquamous carcinomas
HPV 31	High-risk	Found in 5.3% of cases of cervical cancer
HPV 45	High-risk	Found in 8.4% of cases of cervical cancer
Other HPV	Intermediate risk	Another 20 genital/mucosal HPV subtypes have been identified that may be implicated in cervical cancer

Individualized Treatment

One of the problems in using of pharmacoeconomics to establish standard therapy is the fact that no patient is alike and no treatment is predictable enough on an individualized basis. Actually, determination of optimal treatment in the future may be based on obtaining a detailed profile of a patient's cancer by performing a battery of diagnostic and prognostic tests including *in vivo* imaging procedures to fine tune tumor staging, and elaborate *in vitro* tests to identify relevant markers to tailor the treatment to the cancer. Undoubtedly, this will result in higher costs but may prove pharmacoeconomically sounder by significantly improving outcomes.

Costs Associated with Screening Programs

Although in many cases screening costs are rather low per patient as is the case with PSA screening in prostate cancer, mammography in breast cancer and Pap smear tests in cervical cancer, the cost per life saved maybe staggering because of the large number of individuals screened. So, despite the fact that relatively low-cost Pap tests have been shown to save lives, they are not used outside the developed word because of socioeconomic and logistical considerations. Again, economics has conspired to undo a critical medical advance with a powerful public health component that could prevent millions of women from contracting a deadly disease. The gap in screening and prevention programs will more likely become wider when new tests, such as those identifying individuals at risk for certain cancers because of inherited and other genetic factors, become widespread.

A case in point involves the BRCA1 and BRCA2 genes involved in hereditary breast and ovarian cancer. Investigators at the Herbert Irving Comprehensive Cancer Center at Columbia University (New York, NY) used the ability to genetically screen for these genes in at risk populations to estimate the cost-effectiveness of prevention programs. One group of individuals at high risk for breast cancer are Ashkenazi Jewish women. In this population incidence of BRCA1 and BRCA2 gene-positive women is estimated at 2.5% and the associated risk at 56% for breast cancer and 16% for ovarian cancer. It has been shown that prophylactic mastectomy performed on BRCA1 and BRCA2 gene-positive Ashkenazis would increase their survival by up to 6 years.

Investigators used a Markov model to estimate the cost-effectiveness of screening for these genes among Ashkenazi Jewish women. The cost of testing assumed that all positive results would be repeated and that the sensitivity and specificity of a single test would be .98 and .99, respectively. Medicare payment data was used to estimate the costs of surveillance, prophylactic oophorectomy, prophylactic bilateral mastectomy, or both (see Exhibit 8), and Surveillance, Epidemiology, and End-Results (SEER) data was used to estimate survival. According to this model, based on the assumption that bilateral prophylactic oophorectomy reduces ovarian cancer risk by 50% and that prophylactic mastectomy reduces breast cancer risk by 90%, genetic screening would prolong the average survival of an Ashkenazi Jewish woman by 17.8 days with combined surgeries and by 2.3 days with surveillance alone. This compares favorably to routine cervical and breast cancer screening that each saves ≤10 days. At $2,400 per test (for full sequence analysis), costs per life-year saved would be $61,829 for surgery versus $487,402 for surveillance. Using a test for the three known Ashkenazi-specific mutations at $450 lowers the costs per life-year saved significantly to $21,907 and $179,402, respectively. Investigators concluded that genetic screening in this high-risk population could significantly increase average survival and, depending on costs and screening/treatment strategies, could be cost-effective by the standards of accepted cancer screening tests (Grann VR, etal, ASC98, Abs. 2102:548a).

COSTS OF CHEMOTHERAPEUTICS IN ADVANCED DISEASE IN THE DEVELOPING WORLD

The high cost of novel drugs has in effect precluded their use in most countries of limited resources, creating a multi-tiered marketplace, not only in the developing world, but also among the haves and have-nots within many other countries in the developed world.

A very poignant example of the current tiered nature of oncology care comes from the Ukraine where, if the state-of-the-art in cancer treatment were to be made widely available, the cost of drugs would exceed the country's total annual healthcare budget. Although, as of 1996, according to its constitution, citizens of the Ukraine have the right of free-of-charge medical care, economic considerations prevent them from realizing this entitlement. The healthcare budget of the Ukraine, one of the largest states (population=51.1 million) formed after the break-up of the USSR, was $355 million ($7 per person) in 1997 and comprises 2.4% of all national expenditures. Cancer incidence in Ukraine is relatively low, 138,000-140,000 cases per year (270-275 cases per 100,000 population), but mortality at 100,000-102,000 patients per year (196-198 cases per 100,000) is high. This high death rate is probably attributable to inadequate early detection, prevention, and treatment programs.

Exhibit 5
Costs of Novel Chemotherapeutics in the USA

Agent (Brand Name; Supplier)	AWP per Cycle ($)
Paclitaxel (Taxol; Bristol-Myers Squibb)	1,950-2,700
Docetaxel (Taxotere; Rhône-Poulenc Rorer)	3,350-4,400
Gemcitabine (Gemzar; Eli Lilly)	712
Irinotecan (CPT-11, Camptosar; Pharmacia & Upjohn)	3,973-4,696
Topotecan (Hycamtin; SmithKline Beecham)	2,250
Vinorelbine (Navelbine; Glaxo Wellcome)	1,100
Rituximab (Rituxan, MabThera; IDEC Pharmaceuticals)	2,666 (about 10,000 per regimen)
Trastuzumab (Herceptin; Genentech)	9, 900 per regimen

Note: *Treatment regimens range from 3 to 7 cycles, depending on patient tolerance, response, health status, etc. On the average probably about 4 cycles are delivered.*

Exhibit 6
Treatment Outcomes with Herceptin

Treatment	Enrolled Patients (#)	Time to Progression (months)	Response Rate (%)	Overall Severe Adverse Effects (%)
Standard Chemotherapy	234	5.5	36.2	66
Standard Chemotherapy + Herceptin	235	8.6	62.0	69
Doxorubicin + Cyclophosphamide	145	6.5	42.1	71
Doxorubicin + Cyclophosphamide + Herceptin	146	9.0	64.9	68
Paclitaxel	89	4.2	25.0	59
Paclitaxel + Herceptin	89	7.1	57.3	70

Source: Slamon D, etal, ASCO98, Abs. 377:98a

Expenditures for oncology drugs (cytostatics, hormones and supportive care) averages between $15-$20 per primary cancer patient per year. Standard chemotherapy alone for the treatment of tumors considered curable by cytostatics, makes up 5% of the whole annual health care budget. Therefore, the new cancer therapy standards are unattainable in the Ukraine. Using novel chemotherapeutics for only four of their key indications would result in over 5 times the current oncology drug budget for all cancers treated by standard chemotherapy (see Exhibit 9). When taking every cost into account, including palliative and supportive care (e.g., antiemetic therapy would cost more than $5 million), as well as provisions for diagnostic workups and noncytostatic treatment, the total outlay would exceed the annual health budget.

Because most of these expensive treatments are aimed at advanced disease, their high prices have not created much of a response. Extending a very ill person's life by a few months is a very low priority in countries lacking the resources to provide even rudimentary healthcare. Just as in the case of the new AIDS drugs, novel therapies for advanced cancer may become unattainable for those outside the few privileged. However, developments in oncology are hurtling towards breakthrough treatments that may cure advanced cancer, prevent disease progression in those diagnosed with early-stage disease, cure early cancer and even prevent cancer all together. In such a case, unavailability of treatment because of economic considerations will raise serious ethical issues.

MEETING COVERAGE

RECENT DEVELOPMENTS IN ONCOLOGY APPLICATIONS OF NUCLEAR MEDICINE

FROM THE 45TH ANNUAL MEETING OF THE SOCIETY OF NUCLEAR MEDICINE (SNM) TORONTO, ONTARIO, CANADA, JUNE 7-11, 1998

Probably no other specialty in medicine has had more ups and downs than the field of nuclear medicine. This discipline has continually gone through cycles ranging from highly in-favor to out-of-favor, from a very important aid to the practice of medicine to of little or limited importance. During SNM98 it became obvious that nuclear medicine is once again in an upswing and one of the bright spots relates to its role in the management of cancer. This article summarizes some key clinical results presented at SNM98 and was prepared with the collaboration of Ron Kovach, a member of FUTURE ONCOLOGY'S editorial board.

A NEW DEFINITION FOR AN ESTABLISHED DISCIPLINE

According to Henry N. Wagner, Jr., MD, of Johns Hopkins University (Baltimore, MD), "nuclear medicine is the medical specialty concerned with global and regional *in vivo* chemistry and physiology and *in vivo* whole-body imaging; or molecular nuclear medicine, closely aligned with pharmacology and, increasingly, with genetics." This description represents a significant broadening of the role of nuclear medicine as compared to its old and now retired definition as a modality that accomplishes visualization of previously invisible organs by means of radioactive tracers. Furthermore, according to Wagner, nuclear medicine views disease as abnormalities in one or more of the four major domains of living organisms:

- structure
- viability (including bioenergetics)
- function
- communication

What became evident from the SNM meeting was that nuclear medicine represents a holistic approach to medicine because, by its very nature, it takes into consideration the whole body. Unlike the so-called holistic approach of alternative medicine, nuclear medicine follows a proven pathway characteristic of traditional medicine and good science. The number of potential applications for this medical specialty is without equal.

The Role of Nuclear Medicine in Oncology

Oncology was the topic of one-third of all presentations at SNM98, an indication of the importance of nuclear medicine in this field. In cancer, nuclear medicine is used:

- to establish diagnosis, staging and disease prognosis
- to help make treatment decisions and plan treatment strategy (image-guided therapy), including prediction of outcomes
- to monitor treatment
- as a therapeutic modality
- to evaluate neoplastic and normal tissue histogenesis and communication.

Expanding Role for Positron Emission Tomography (PET) in Oncology

PET imaging, with its sensitivity at the nanomolar and picomolar range, has proven a valuable research tool. Now, however, PET imaging is moving into the clinic and may evolve into one of the most flexible disease management tools in oncology. In a concession to PET's importance in clinical medicine, the NIH which in the past only used PET in research, has started a clinical program to define where and how PET should be used in patient care.

IN VIVO IMAGING WITH F-FLUORODEOXYGLUCOSE (FDG) AND PET

Use of fluorine-18 (^{18}F) deoxyglucose (FDG), one of the primary positron emitters used alone or in combination with other tracers in PET, has expanded rapidly in the last few years (see FO, pp 340-42 and 164-65). Issues surrounding PET-FDG were the topic of 117 presentations (out of a total of 1,199) at SNM98, 21 involving lung cancer, 13 colon cancer, 11 breast cancer, 10 head and neck cancer, 8 brain cancer, 6 thyroid cancer, 7 melanoma, as well as 41 other tumors (see Exhibit 10). A prevailing theme among these presentations was the superiority of the PET-FDG combination when compared to other imaging modalities including conventional x-ray, CT scanning (often considered the "gold standard" for the diagnosis of many types of cancers), MR, and such nuclear imaging modalities as single-photon emission computed tomography (SPECT) and radioimmunoscintigraphy, among others.

During SNM98, in presentation after presentation, PET-FDG was deemed superior to almost all other modalities as first-line evaluation of high-risk cancer patients. Also, the procedure fulfilled the requirement of practicing smart medicine by optimizing patient care in a cost-effective manner. Although some variation in disease detection in certain specific sites was encountered when dedicated PET-FDG scanning was compared with the less expensive dual-detector coincidence scanning, in most clinical cases described at SNM98, PET-FDG:

- produced the most accurate staging information while causing the least patient discomfort
- eliminated unnecessary procedures
- saved considerable time and money by replacing several conventional approaches with one easy-to-perform procedure

Starting in 1995, the FDA required that all preparers of FDG either for in-house use or commercial distribution, submit an ANDA and comply with all GMPs. Subsequently, in 1997, regulation of PET radiopharmaceuticals was transferred to state boards of pharmacy and medicine and suppliers must now comply with USP standards. Users of FDG imaging have a number of options regarding sources of FDG.

Exhibit 7
Costs Associated with the Management of Cancer

Type of Expenditure	Description	Comments
Direct medical costs	Costs directly associated with patient care, including drugs and supplies, professional fees, labor	Direct costs may vary somewhat from site to site depending on treatment protocols
Diagnostic, prognostic, staging and monitoring procedures	Costs associated in profiling the disease; because of major developments, these procedures are accounting for an increasingly larger piece of the pie	These procedures require expensive *in vivo* imaging installations and sophisticated laboratory tests, often unattainable in many world regions
Therapeutic procedures	Costs associated with surgery, radiation therapy, chemotherapy, bone marrow transplantation, etc.	Different standard therapies are used in different countries depending on economic considerations
Drugs	Costs of anticancer drugs and adjuncts are used in the treatment of mostly advanced cancer	Costs of novel drugs preclude their use in the developing world
Anticancer preparations	Costs are determined by disease stage and protocols; newer standard therapies in advanced disease, based on expensive drugs, may result in somewhat better response rates, but disease-free survival remains unchanged	In the USA, approved drugs are rapidly adopted into widespread use; this is not true in most other world regions with some exceptions; however, chemotherapy using generic preparations is practiced worldwide
Adjuncts	Costs associated with preparations to combat complications of cancer and its treatment, such as hematopoietic factors, antiemetics, bisphosphonates, analgesics, etc.	Introduction of novel drugs in this area has resulted in significant treatment cost increases but has not impacted availability of treatment because of lower priced less effective alternatives
Supplies	Supplies range from sophisticated infusion pumps to standard hospital supplies	Supply costs vary significantly between countries
Labor costs, professional fees and services	Professional fees are for general practitioners, oncologists, surgeons and specialists and labor costs cover nursing, rehabilitation, hospice care, etc.	Professional fees and labor costs vary significantly between countries and are rarely the limiting factor in providing access to treatment in the developed world
Direct nonmedical	Nonmedical costs include transportation, special nutrition, living aids, etc.	Nonmedical costs such as transportation to specialized centers may be prohibitive and a barrier to proper care
Indirect costs	Indirect costs involve lost wages to disability, morbidity, or death	Indirect costs vary significantly between countries; interestingly, although lost wages may represent a much lower value in the developing world, such losses may be devastating to a family because of lack of support systems after the loss of the breadwinner
Intangible costs	Intangible costs reflect loss of family life, pain and suffering, depression, etc.	Intangible costs are similar all around the world

Those with cyclotron installations may manufacture their own and supply others within a certain radius from the producing site. In August 1998, Syncor International (Woodland Hills, CA) signed a five-year, exclusive agreement with Massachusetts General Hospital (MGH; Boston, MA) to distribute the latter's FDG which the hospital has been producing in-house for the past 9 years. As part of the agreement, Syncor assumes responsibility of the transport of the radiopharmaceutical in shielded containers, and all paperwork. Syncor will also promote FDG use via educational and promotional programs and by cosponsoring with MGH training seminars for professionals.

PET-FDG in Detecting Bone Metastases in Advanced Solid Tumors

In a comparison of 44 patients with known and advanced carcinoma of the thyroid, lung, or prostate, using both conventional planar radionuclide bone (RNB) scintigraphy and PET-FDG to determine the detection rates for bone metastasis, PET-FDG proved to be the superior detection system. PET-FDG identified a total of 205 lesions of which 96 were attributable to metastasis, in contrast to the 109 lesions revealed by RNB of which 46 were attributable to metastasis. After comparisons were made with the reference methods used in the study, diagnosis was correct in 199 lesions (97%) with PET-FDG and in 87 lesions (80.5%) with RNB (Schirrmeister H, etal, SNM98, Abs. 444:113-4P).

PET-FDG in Diagnosing Lung Cancer

A common problem in patients found to have solitary pulmonary nodules is differentiation of benign from malignant lesions. The importance of this distinction is underlined by the fact that more than 25,000 documented thoracotomies are performed each year in the USA on patients whose lesions prove to be benign. Conversely, more than 30,000 thoracotomies are performed each year

Exhibit 8
Cost Effectiveness of Prophylactic Treatment for Inherited Breast and Ovarian Cancer

Treatment options	Days of life added	Incremental cost/life-year using full sequence analysis ($2,400 per procedure)	Incremental cost/ life-year testing only for certain mutations ($450 per procedure)
Combined Surgery	17.8	61,829	21,907
Mastectomy	14.3	80,435	30,471
Oophorectomy	5.3	204,968	71,034
Surveillance	2.3	487,402	179,402

on patients in whom the disease has already spread to the point that a thoracotomy is of little or no use and the patient should be treated with radiation and/or chemotherapy.

In a prospective multi-institutional study, ^{18}F-FDG was used with dual-detector PET to differentiate benign from malignant lung lesions as well as for tumor staging. The study included 103 patients with pulmonary lesions (≥1 cm) detected by chest x-ray or CT, and 26 controls who were imaged by PET-FDG. Two experts were asked to interpret the scans with no other data provided and their findings were compared to the surgical pathology. The FDG studies were 95% sensitive (87/91) and 75% specific (9/12) in identifying proven malignant lesions, and were accurate in 25/26 normal controls. PET-FDG was a sensitive and specific means of diagnosing malignancy in patients with pulmonary lesions and, as a side benefit, this approach also had the potential to be more cost effective.

Despite the adequate performance of the dual-detector system, in a similar study using FDG with a full ring PET scanner, the dedicated PET proved to be the superior modality. In this study, all 20 patients with lung cancer were correctly diagnosed by both systems. But, 2 of 8 patients with node metastasis were missed by the dual-detector system as compared to a 100% accuracy of the dedicated PET (Weber W, etal, SNM98, Abs. 1129:257P).

In yet another study comparing PET-FDG with CT scanning in preoperative staging of lung cancer patients to determine the likelihood of lymph node involvement, the value of PET-FDG proved superior to CT (see Exhibit 11). The likelihood ratio to detect lymph node involvement by dedicated PET-FDG was 13.7:1 compared to 1.6:1 for CT (Gupta NC, etal, SNM98, Abs. 310:80P).

PET-FDG in Diagnosing Nasopharyngeal Carcinomas (NPC)

In a study from Taiwan comparing the diagnostic effectiveness of PET-FDG to CT for suspected recurrence of nasopharyngeal carcinomas (NPC), again PET-FDG proved the superior modality although CT is considered the "gold standard". Thirty-six patients who had undergone radiotherapy (RT) for a minimum of 7 weeks for NPC were included in the study. Among 11 patients found to have recurrent NPC verified by biopsies, the results of PET≥FDG and CT scanning performed 4 months after the completion of RT, are summarized in Exhibit 12. PET-FDG was not only more reliable than CT for the detection of recurrent NPC, but it had an additional benefit of being very reliable in distinguishing cancer recurrence from benign lesions in NPC patients with previous RT (Kao CH, SNM98, Abs. 1125:256P).

PET-FDG in the Management of Colorectal Cancer

PET-FDG has proven more sensitive to CT scanning and/or conventional battery of tests including endoscopy and CEA-based scanning, in the management of colorectal cancer. For instance, PET-FDG is proving to be a very helpful tool in helping surgeons distinguish between benign and malignant colorectal lesions. Nearly all cases classified as malignant by PET-FDG were accurately diagnosed, preventing surgeons from operating for benign conditions. However, PET-FDG was not as reliable in lesions <0.6 cm in size (Akhurst T, etal, SNM98, Abs. 526:134P).

In the diagnosis of recurrent colorectal cancer, PET-FDG has been shown to be superior to CT scanning which is also considered the "gold standard" for detecting recurrent colon cancer, or radioimmunodiagnosis. According to various comparisons of PET-FDG and CT in the evaluation of recurrent colorectal cancer, PET-FDG was consistently more sensitive than CT (see Exhibit 13). In a series of 36 colorectal cancer cases involving suspected metastases, use of PET-FDG was instrumental in changing patient management in 39% of cases (Schröder O, etal, SNM98, Abs. 529:134P).

A German study compared the efficacy of diagnosing the recurrence of colon cancer by PET-FDG and immunoscintigraphy using CEA-Scan, a Tc-99m-labeled anti-CEA monoclonal antibody (MAb) developed by Immunomedics (Morris Plains, NJ). Twenty patients with a history of colorectal carcinoma were examined by CEA-Scan immunoscintigraphy and PET. The most common diagnoses that lead to check for recurrent cancer were elevated serum CEA (12 cases) and CT-detected lesions (5 cases). All patients were administered CEA-Scan. Planar and SPECT imaging were performed 6 hours after IV administration of CEA-Scan. In contrast, PET-FDG imaging was performed 45 minutes after injection of 5-10 mCi ^{18}F-FDG. All findings were confirmed by surgery and histologic examination. All local recurrences (5 cases) of colorectal cancer were identified by both procedures. However, PET-FDG identified liver metastases in 6 patients,

CEA-Scan, in only one. Lymph node metastases were identified in 2 patients by PET-FDG as well as bone metastases in one patient which were not identified by CEA-Scan. Results of this study indicate that although PET-FDG and CEA-scan are suitable for diagnosing colorectal cancer recurrence, PET-FDG is superior in diagnosing liver, lung, and lymph node involvement (Willkomm P, etal, SNM98, Abs. 595:151P). Although this was a small study, if the results hold, it appears that immunoscintigraphy may be confined to those institutions that cannot afford the purchase of a PET system.

Interestingly, PET-FDG was even more sensitive and specific than *in vitro* tests using tumor markers such as CEA and CA19-9. Among 45 cases of colorectal cancer (34 confirmed recurrences and 11 normal), CEA correctly identified 31/45 (69%) with 24 true-positive and 7 true-negative, for a sensitivity and specificity of 71%, and 64%, respectively. CA19-9 correctly identified 25/45 (57.8%) with 19 true-positive and 7 true-negative, for a sensitivity and specificity of 54% and 78%, respectively. PET-FDG, however, correctly identified 42/45 (93.3%) with 34 true-positive, 8 true-negative and no false-positive, for a sensitivity and specificity of 100% and 73%, respectively. More to the point, although PET-FDG correctly identified 26/28 cases of elevated CEA and 20/21 cases of elevated CA19-9, it also identified 16/17 and 22/23 malignant lesions in patients with normal CEA and CA19-9, respectively (Bender H, etal, SNM98, Abs. 531:135P).

PET-FDG in Gastric Cancer

A study from Memorial Sloan-Kettering Cancer Center (New York, NY), demonstrated advantages and some disadvantages of PET-FDG in the detection of metastatic gastric cancer. Currently available modalities including CT, ultrasound and MR, are unsatisfactory in the detection of metastatic gastric cancer, especially lymph node metastases and peritoneal spread.

Among 18 patients with a history of gastric cancer, PET-FDG identified 9 out of 10 with primary tumors, as confirmed by histology and/or surgical findings. The one false negative (FN) occurred in a poorly-controlled diabetic (blood sugar > 400 at the time of the study). However, although PET-FDG was highly sensitive in detecting primary gastric cancer, it was of limited value in detecting perigastric lymphadenopathy and peritoneal spread. Seven patients with prior gastrectomy were true negative (TN) in the region of the stomach. However, for intra-abdominal lymph node involvement, PET-FDG was true positive (TP) in 3, FN in 4, and TN in 16, yielding a sensitivity of only 43% and accuracy of 83%. Also, PET-FDG only detected 3 out of 7 perigastric lymph node metastases (Yeung HWD, etal, SNM98, Abs. 532:135P).

Exhibit 9
Costs Associated with Chemotherapy for Advanced Cancer in the Ukraine

Cancer Type	Patients/year	Regimen	Cost per case[1] ($)	Total costs ($)
		Conventional Care		
Breast cancer (adjuvant)	9,000	CMF	270	2,430,000
Breast cancer (adjuvant)	4,000	Tamoxifen (5 years)	420	1,680,000
Colon cancer (adjuvant)	3,000	5-FU + levamisol	200	600,000
Ovarian cancer	4,000	CP	470	1,880,000
Testicular cancer	500	BEP	416	208,000
Hodgkin's disease (HD)	1,000	COPP	450	450,000
Non-Hodgkin's lymphoma (NHL)	3,000	CHOP	612	1,836,000
Prostate cancer	3,000	Flutamide (1 year)	1,550	4,650,000
Small cell lung cancer (sclc)	5,000	CAV/EP	743	3,715,000
All	32,500			17,449,000
		New Standard Care		
Melanoma (adjuvant)	300	Intron A	25,000	7,500,000
Ovarian cancer	4,000	Taxol + carboplatin	13,500	54,000,000
Breast cancer (neoadjuvant)	2,500	Taxol	10,000	25,000,000
Hodgkin's disease	1,000	BEACOPP	1,884	1,884,000
Total	7,800			88,384,000

[1] Excluding supportive care

Key: BEP-bleomycin, etoposide and cisplatin, CAV-cyclophosphamide, doxorubicin, vincristine, CHOP-cyclophosphamide, doxorubicin, vincristine and prednisone CMF-cyclophosphamide, methotrexate and 5-FU, COPP-cyclophosphamide, vincristine, prednisone and procarbazine, EP-etoposide

Source: Shparik J, etal, ASCO98, Abs. 1644:427a

Exhibit 10
Sampling of Clinical Studies Involving PET-FDG

Application	Results	References
	Advanced Solid Tumors	
Detection of bone metastases in advanced carcinoma of the thyroid, lung, or prostate	When compared to conventional planar radionuclide bone scintigraphy, PET-FDG proved superior (see text)	Schirrmeister H, etal, U Hospital of Ulm (Germany), SNM98, Abs. 444:113P
	Ovarian Cancer	
Suspected recurrent serous ovarian cancer	PET-FDG is the most accurate diagnostic procedure when compared to CT, ultrasound, or planar and SPECT immuno-scintigraphy with Tc-99m-labeled anti-CA-125 MAb B43.13; 61 lesions were detected by PET-FDG, compared to 11 by CT and 19 by immunoscintigraphy; PET-FDG was decisive on patient management in >50% of cases	Baum RP, etal, U Frankfurt/Main Medical Center (Germany), SNM98, Abs. 253:66P
Recurrent ovarian cancer	Overall, PET-FDG demonstrated a sensitivity of 92.3%, a specificity of 84.6% and an accuracy of 89.7% in detecting recurrent ovarian cancer	Smith GT, etal, U Tennessee Medical Center (Knoxville, TN), SNM98, Abs. 1096:249P
	Cervical cancer	
Newly-diagnosed or recurrent cervical cancer	PET-FDG detected 19/21 (90%) of newly-diagnosed or recurrent tumors and is promising for the detection of untreated cervical cancer	Sugawara Y, etal, U Michigan Medical Center (Ann Arbor, MI), SNM98, Abs. 254:66P
	Breast cancer	
Detection of bone metastases in advanced breast cancer	PET-FDG sensitivity was 11/12 (91.7%) and specificity was 41/42 (97.6%)	Suzuki Y, etal, Tokai U Medical School (Isehara, Japan) and HIMEDIC Imaging Center at Lake Yamanaka (Yamanashi, Japan), SNM98, Abs. 578:147P
	Germ cell tumors	
Staging/restaging of germ cell tumors	Of 79 scans in 72 patients, PET-FDG was accurate in 89.9% of cases and gave an FN result in 10.1% of cases, all mature teratomas	Lang O, etal, Katharinen Hospital (Stuttgard, Germany), SNM98, Abs. 255:66P
Prognosis before high-dose chemotherapy	Residual tumor viability, detected by PET-FDG after induction chemotherapy, is predictive and may improve patient selection	Dohmen BM, etal, Eberhard-Karls U (Tuebingen, Germany), SNM98, Abs. 256:67P
	GI cancer	
Pancreatic ductal adenocarcinoma	PET-FDG is more accurate (90%) in detecting pancreatic ductal adenocarcinoma compared to CT (76%) and was instrumental in changing patient management in 32% of cases	Delbeke D, etal, Vanderbilt U Medical Center (Nashville, TN), SNM98, Abs. 313:81P
Recurrent colorectal cancer	PET-FDG detected recurrent tumors with high sensitivity and specificity; it identified true positives in 70% of patients with negative CT scans	Valk PE, etal, Northern California PET Imaging Center (Sacramento, CA), SNM98, Abs. 530:135P
	Melanoma	
Staging of patients with metastatic melanoma	In whole body imaging studies, PET-FDG had a higher predictive value for metastatic melanoma when compared with CT scanning and, except for the detection of brain metastases, a single whole-body PET-FDG scan can replace the standard battery of imaging tests performed in high-risk melanoma patients	Hoh CK, etal, Ahmanson Biochemical Imaging Center, UCLA School of Medicine, and St. John's Medical Center (Los Angeles, CA), SNM98, Abs. 366:94P; Baum RP, etal, Abs. 365:94P; Steinert HC, etal, University Hospital of (Zürich, Switzerland), Abs. 367:94P
	Head and neck cancer	
Evaluation of recurrence of head and neck cancer	Sequential PET-FDG proved to be highly accurate in the detection of recurrent cancer of the head and neck; whole body PET-FDG imaging is more accurate than CT/MR in diagnosing local and regional recurrence	Lowe VI, etal, St. Louis U Health Sciences Center (St. Louis, MO), SNM98, Abs. 478:122P; Abella-Columna, etal, Northern CA PET Imaging Center and UC Davis Medical Center (Sacramento, CA) and Stanford U and the Palo Alto VANC, SNM98, Abs. 479:122P
Preoperative lymph node staging	PET-FDG sensitivity was 100% and specificity was 96.5% compared to 71.4% and 50% for CT and 94.4 and 58.4% for MR, respectively	Müller-Berg M, etal, Eberhard-Karis U, SNM98, Abs. 480:122-23P

— continued on next page

Thyroid cancer		
Thyroid nodules	The sensitivity of PET-FDG in distinguishing malignant from benign nodules was 100% and the specificity is 94%	Reimer SE, etal, U Hospitals of Cleveland (OH), SNM98, Abs. 482:123P
Residual thyroid cancer	PET-FDG detects residual thyroid cancers in high risk patients with negative I-131 whole-body scans and is superior to Tl-201	Seabold JE, etal, U Iowa Hospices and Clinics (Iowa City, IA), Good Samaritan PET Center (Phoenix, AZ), and West Virginia U PET Center (Morgantown, WV), SNM98, Abs. 483:123P
Lymphoma		
Evaluation of tissue viability to establish residual or recurrent masses in Hodgkin's disease (HD)	PET-FDG proved to be a highly sensitive technique in evaluating residual or recurrent tumors in HD	Dittmann H, etal, Eberhard-Karis U, SNM98, Abs. 581:147P
Prognosis of intensive chemotherapy in high-grade non-Hodgkin's lymphoma (NHL)	Whole-body PET-FDG identified those NHL patients who will respond to treatment	Jerusalem G, etal, U Hospital (Liege, Belgium), SNM98, Abs. 580:147P
Lung cancer		
Detection of pulmonary lesions and lymph node metastases	PET-FDG exhibited higher sensitivity in detecting both lymph node metastases (87.5% versus 25%) and pulmonary lesions (92.3% versus 84.6%) than Tc-99m-tetrofosmin/SPECT	Tatsumi M, etal, Osaka U Medical School (Japan), SNM98, Abs. 165:44P
Detection of primary lung nodules	Dual-detector PET-FDG exhibited a sensitivity of 100% and a specificity of 66.6% in identifying malignant lesions	Abdel-Davem HM, etal, St. Vincent's Hospital (New York, NY) and New York Medical College (Valhalla, NY), SNM98, Abs. 425:109P
Laryngeal cancer		
Early-stage (T1-T2) laryngeal cancer	PET-FDG identifies early-stage laryngeal cancer and is helpful in following the disease after therapy	Lowe VI, etal, St. Louis U Health Sciences Center (St. Louis, MO), SNM98, Abs. 477:122P
CNS cancer		
Detection of recurrent brain tumors	PET-FDG had lower sensitivity than 1-[C-11]aminocyclobutanecarboxylic (ACBC) acid and PET (67% versus 95%)	Hubner KF, etal, U Tennessee Medical Center (Knoxville, TN), SNM98, Abs. 197:52P
Sarcoma		
Untreated osteosarcoma	PET-FDG effectively detects osteosarcomas, with pediatric tumors being significantly more FDG-avid	Myers MT, etal, U Hospitals of Cleveland and Case Reserve U (Cleveland, OH), SNM98, Abs. 370:95P
Assessment of tumor response	PET-FDG can assess tumor response to treatment	Eary JF, etal, U Washington (Seattle, WA), SNM98, Abs. 371:95P

PET-FDG in High-risk Melanoma

PET-FDG may prove particularly attractive in the evaluation of high-risk melanoma patients. Currently, these patients undergo a battery of tests including brain MR, chest x-ray, CT of the thorax, abdomen and pelvis, ultrasound of the abdomen, high resolution sonography of lymph nodes and skeletal scintigraphy. Whole-body PET-FDG using a dedicated PET scanner, may replace all of these except the brain MR, as a front-line procedure for patient staging.

Among 52 patients with primary disease and 48 suspected recurrences, PET-FDG was 100% accurate in detecting metastases in those diagnosed with a primary tumor compared with conventional imaging that detected none. Also, in patients with suspected recurrence, 121 lesions were detected, 111 (92%) by PET-FDG and 69% by conventional imaging. Results were confirmed by histology. There was some variation in the imaging results in different sites with PET-FDG yielding a higher sensitivity in identifying cervical metastases (100% versus 67%) and abdominal metastases (100% versus 27%). CT scanning proved superior in discovering lung metastases (87% versus 70%). Therefore, one whole-body PET-FDG approach may be all that is needed for melanoma staging, that can be performed in a few hours rather than over several days. In another study, of 202 histologically-confirmed metastases, whole-body PET-FDG using a dedicated PET system identified 186 lesions compared to 120 by conventional imaging. The sensitivity of PET-FDG was 70% and specificity 75% compared with 62% and 27%, respectively, for conventional imaging (Hoh CK, etal, SNM98, Abs. 366:94P; Baum RP, etal, SNM98, Abs. 365:94P; Steinert HC, etal, SNM98, Abs. 367:94P).

PET-FDG in Lymphoma

Whole-body PET-FDG is proving very effective in evaluating tissue viability of residual/recurrent masses in Hodgkin's disease (HD) to distinguishing malignant metastases from scar tissue. Among 30 patients with HD, overall sensitivity was 100% and specificity was 86% (Dittmann H, etal, SNM98, Abs. 581:147P).

Exhibit 11
Comparison of PET-FDG and CT Scanning in Patients with Suspected Lung Cancer

Modality	Sensitivity (%)	Specificity (%)	Accuracy (%)	Likelihood Ratio
PET-FDG	95	91	94	13.7:1
CT	63	60	61	1.6:1

Whole-body PET-FDG was also effective in predicting response to intensive chemotherapy in patients with high-grade non-Hodgkin's lymphoma (NHL). Such prognostic information may be of value to those patients who will not benefit from intensive chemotherapy and may be candidates for alternative treatments. Among 20 patients with NHL, all 13 with a normal PET-FDG after two or three chemotherapy cycles achieved CR while there were only 2 CR among seven with active sites, and only 1/7 with a CR remained disease-free for at least 30 months. In contrast 11/13 patients with negative PET-FDG scans at the time of chemotherapy were disease-free 8 to 36 months later (Jerusalem T, etal, SNM98, Abs. 580:147P).

Exhibit 12
Comparison of PET-FDG and CT Scanning in the Diagnosis of Recurrent Nasopharyngeal Carcinomas

Modality	Sensitivity (%)	Specificity (%)	Accuracy (%)
PET-FDG	100	96	97
CT	72	88	83

PET-FDG Imaging in Assessing Responses to Gene Therapy

PET-FDG may also play a significant role in monitoring the results of gene therapy by *in vivo* imaging of gene expression and viral delivery of genes. In a study conducted at the University of Pennsylvania (Philadelphia, PA), PET-FDG imaging was incorporated in the assessment of responses to gene therapy in patients with high grade gliomas. Twenty-eight PET scans were performed on 10 patients with histologically proven glioblastoma or anaplastic astrocytoma, treated by suicide gene therapy involving static intratumoral injection of recombinant adenovirus vector with HSV-tk gene, followed by IV administration of ganciclovir. A second round of treatment was administered 8 days later, followed by a series of PET-FDG scans. It was concluded that PET-FDG showed great specificity in distinguishing active tumors from non-neoplastic inflammation (Hustinx R, etal, SNM98, Abs. 1121:255P).

EQUIPMENT UPDATE

FDG imaging is accomplished either using a dedicated PET scanner or a dual-detector coincidence imaging system which is a hybrid system with imaging quality somewhere between SPECT and dedicated PET. Despite the favorable results from clinical studies using FDG with either PET or a dual-detector system, the majority of hospitals in the USA do not have either technology and, thus, lack the superior capabilities of these diagnostic systems. According to Dr. Wagner, "both PET and hybrid, dual-detector coincidence systems are still considered by most insurance carriers to be elitist tools that should be limited to academic medical centers and, therefore, reimbursement goes wanting." It is only within the past year that Medicare agreed to provide reimbursement for certain PET studies for suspected lung cancer, solitary pulmonary nodules, and suspected brain cancer. The jury is still out on the position of managed care companies regarding reimbursement of these modalities. In addition, initial installation cost of these systems remains a problem for most institutions. Costs of dual-detector coincidence systems range from $750,000 to $1.2 million and dedicated PET systems cost between $2.5 million to $5.0 million.

All and all, unlike the clinical presentations, the instrumentation featured by the manufacturers at SNM98 did not represent new and earthshaking technological breakthroughs. PET and dual-detector systems have been shown for a number of years at this meeting. What was new was the enthusiasm for the new life being enjoyed again in the field of nuclear medicine, which is expected to translate into increased equipment sales. Next year's meeting in Los Angeles, CA should be interesting, if for nothing else, to see if the new highs can be sustained.

Dual-detector Coincidence Imaging

Depending on the isotope used and the tissue under consideration, photon attenuation produces significant artifacts in coincidence imaging, which is often a major drawback for this technology when compared to dedicated PET. Generally, however, dual-detector systems are sufficiently sensitive and specific to provide an effective means of diagnosing certain malignancies (Baehre M, SNM98, Abs. 422:108P). A multicenter prospective study demonstrated that the sensitivity of PET-FDG using a dual-detector system was 95% and the specificity 75% in identifying malignant pulmonary lesions (Weber W, etal, SNM98, Abs. 423:108P). In another study the dual-detector system identified 84% of lesions >1 cm that were detected by a dedicated PET scanner.

Favorable clinical results and the considerable price advantage of dual-detector systems over PET has spurred research in improving these systems. Investigators from UGM Medical (Philadelphia, PA) and ADAC Laboratories (Milpitas, CA) demonstrated the importance of single-transmission attenuation correction for dual-detector coincidence imaging in reducing artifacts, in improving sensitivity and localization, and in quantification of FDG studies in lung cancer (Shao L, etal, SNM98, Abs. 138:37P). In the study by Weber (*ibid*), use of an attenuation correction device supplied by ADAC, produced more favorable results with dual-detector imaging compared with those obtained using a dedicated PET system.

Dedicated PET Mammography Scanners

In an attempt to find a suitable replacement for conventional mammography, a technology with many shortcomings, investigators at the University of Pennsylvania designed and constructed a dedicated PET scanner for breast imaging using two curve-plate NaI(TI) detectors (Freifeld R, etal, SNM98, Abs. 778:171P).

Investigators at McGill University (Montreal, Canada) constructed a dedicated positron emission mammography (PEM) system by integrating two pixilated planar bismuth gallium oxide (BGO) detectors in a standard mammography system. These detectors, operated in coincidence, collect emission data which is processed, analyzed and displayed live. In 12 patients, PEM-FDG exhibited a specificity of 100%, a sensitivity of 63%, and an accuracy of 83.3%. Improvements in this system are being undertaken to reduce the current 25% FN rate (Murphy K, etal, SNM98, Abs. 575:146P).

Manufacturers Round-up

ADAC Laboratories introduced its new dedicated PET system, CPET ranging in price from $1.2 million to $1.5 million, depending on add ons. The company also supplies the Vertex Molecular Coincidence Detection (MCD) gamma camera used in dual-detector coincidence scanning.

Elscint (Rockleigh, New Jersey), a subsidiary of Elbit (Haifa, Israel) showed off its new MagiCam dual-head, variable-angle digital camera, the first release of ELGEMS (Haifa, Israel), the joint venture between Elscint and GE Medical Systems (GEMS; Waukesha, WI). This company that assumed all nuclear medicine-related technologies and products from both companies, began operations in April 1997. In September 1998, Elscint agreed to sell its global CT business to Picker International (Highland Heights, OH) for $275 million and, in October 1998, agreed to sell its nuclear medicine and MR business to GEMS for $100 million. Elscint and GEMS plan to continue ELGEMS. The feature instrument from GEMS was the Millennium VG, a dual-detector system.

The Nuclear Medicine Products Division (Aliso Viejo, CA) of Hitachi Medical Corporation of America (Tarrytown, NY) also featured a dual-detector system, the Spectra Digital V250DSP.

Siemens Medical Systems (Iselin, NJ) supplies both full ring PET systems (ECAT, high resolution brain PET ECAT HRRT, and EXACT) and dual-detector systems, such as E.CAM and several extensions of this line, resulting from a joint marketing and development agreement with Toshiba America Medical Systems (TAMS; Tustin, CA). E.CAM is a dual-detector, variable-angle gamma camera, which allows performance of whole body PET and general imaging procedures. E.CAM's features include a modular system design and software-programmable detectors for easy, cost-effective expansion; 90-degree image capability for enhanced cardiac throughput; coincidence-capable detectors and works-in-progress 511 keV coincidence imaging; a complete selection of collimators including pinhole; robotics which ensure greater patient comfort and technologist efficiency; and an image processor with the ability to meet connectivity and networking requirements.

Exhibit 13
Sensitivity of PET-FDG and CT in the Detection of Recurrent Colorectal Cancer

Metastasis Site	PET Sensitivity (%)		CT sensitivity (%)	
	Study A	Study B	Study A	Study B
Liver	95	100	84	86
Pelvis	97		68	
Abdominal and retro-peritoneal	85	100	50	38
Lungs	94	100	94	88
Peritoneal carcinosis		100		38
Local recurrence		100		100
Other	100		33	
Total	93		69	

Study A-Valk PE, etal, SNM98, Abs. 530:135P
Study B-Schröder O, etal, SNM98, Abs. 529:134P

Toshiba offers a full-line of nuclear medicine products, featuring single head, dual fixed head and dual variable head gamma cameras. Additional systems include the GCA-7100A digital gamma camera with a rectangular detector and the GCA-7200A/UI digital gamma camera with fixed dual opposing rectangular detectors. These systems have the ability to perform SPECT, offering dynamic and static acquisition in one touch. All Toshiba gamma cameras are combined with SUN Microsystems' UltraSPARC work-station which is equipped with a 64-bit processor and high-speed accelerator.

In October 1998, Toshiba was awarded a one-year contract that may be extended up to a total of five years, from the Defense Logistics Agency Support Center Philadelphia (DSCP), to supply nuclear medicine imaging systems to military hospitals worldwide. Under the contract, Department of Defense facilities, as well as other federal hospitals, can purchase nuclear medicine systems directly from Toshiba.

The highlight of the Picker International booth was its gammaPET system. With the use of a triple head, this system can reduce imaging time to about one-half of a dual-head system. Picker also supplies the PRISM 2000 XP PCD coincidence imaging system.

Market Outlook

The equipment segment of the nuclear medicine market represents only a fraction of the worldwide revenues posted by such modalities such as MR, CT and x-ray, estimated at about $110 million compared to billions of dollars. However, it is hoped that new applications in the clinic will eventually translate into new equipment installations.

ECONOMIC ISSUES

Despite the high cost of the initial installation of a dedicated PET, use of this modality may, in the long run, prove cost-effective by, generally, improving patient management and resulting in significant cost-savings by eliminating unnecessary procedures. The consensus that the less expensive MCD cameras perform comparably to the more expensive dedicated PET systems, will undoubtedly also help to expand use of this approach. At this juncture, it appears that lack of a center's ability to perform PET-FDG in evaluating oncology patients may be considered poor quality care. Currently, the fees for a whole-body PET-FDG range from $1,300 reimbursed by Medicare to $2,800 for private pay.

Economic Efficacy

A new term, economic efficacy, has been added to medical jargon that reflects the cost effectiveness of a technology, procedure, or treatment. For medical companies, proving "economic efficacy" of their technology may become just as important to their marketing efforts as proving technical efficacy to the FDA is to the commercialization of the technology. The concept of economic efficacy is expected to gain increasing importance in the USA and around the world as nations struggle to provide the most cost-effective care while being inundated with new technologies carrying higher and higher price tags. Several papers at SNM98 centered on the theme of economic efficacy of nuclear medicine procedures and, in most use of PET was particularly cost-effective not only in managing cancer patients but also those with coronary artery disease (Merhige ME, etal, SNM98, Abs. 350:90P).

Swiss investigators analyzed the clinical and economic effects of whole-body PET-FDG on the surgical management of patients with newly diagnosed non-small cell lung cancer (nsclc). Treatment records of 107 consecutive patients were reviewed. All patients were thought to have operable disease on the basis of physical examinations, routine clinical laboratory tests, chest x-ray, and contrast enhanced CT scans. Whole-body PET was performed prospectively and any changes in the surgical management as compared to the usual hospital routine, that resulted from PET findings, and any cost savings based on true cost calculations, were registered.

Seven patients were removed from the study because final histopathologic diagnosis revealed a tumor other than nsclc. Of the remaining 100 patients, thoracic surgery was canceled in 10 patients and 4 underwent only minimal surgery because of changes in diagnosis resulting from the PET studies. In 4 other patients, surgery was done palliatively to lessen pain and prevent complications and resection of the tumor and metastases was performed in 3 patients. In one patient, PET showed a false positive result.

The total cost for whole-body PET scans was 100 x SFR1,280=SFR128,000 ($95,232). The costs for examinations undertaken to confirm metastasis were SFR20,260. Based on average costs of SFR25,000 for thoracotomy and SFR10,000 for explorative surgery, SFR310,000 was saved because of changes in the surgical management of patients. In this particular case PET evaluations resulted in fewer invasive procedures and a savings-to-cost ratio of more than 2:1 (Steinert FC, etal, SNM98, Abs. 309:P80).

In a similar situation, distinguishing malignant from benign thyroid nodules saves considerable moneys and spares patients unnecessary discomfort. Using PET-FDG scanning, costing $1,700 per scan, about $6,470 was saved per patient presenting with a thyroid nodule. The savings are so significant because the yield of malignant lesions at surgery is 30% (Reimer SE, etal, SNM98, Abs. 482:123P).

Whole-body PET-FDG also improves the management of patients with recurrent melanoma and improves life expectancy by 3 months by accurately identifying those who would benefit from chemotherapy or surgery at an additional $779 per patient based on an average cost of PET-FDG at $1,200 per scan. The incremental cost effectiveness ratio (ICER) was $3,000-$8,000 with PET-FDG (Gambhir SS, etal, SNM98, Abs. 368:94-95P).

Smart Medicine

Another term often heard at SNM98 was "smart medicine." A term of the managed care age it loosely appears to mean efficient and economical medicine as a result of taking into consideration all known data and options before initiating a diagnostic and/or treatment procedure. For example, a study was conducted to test the assumption that distant skeletal metastasis are rare in breast cancer patients in the absence of lesions in the thorax. In examining over 1,000 bone scans performed at Beth Israel Medical Center (New York, NY) covering a 7-year period, 59 scans from patients with bone metastasis from breast carcinoma were identified. The majority of the cases involved at least one focus in the thorax. There was no case in which a distant metastasis was found in the absence of an existing thoracic metastasis. The investigators concluded that in breast cancer patients with a normal thorax on bone scan, abnormalities outside the thorax require firm documentation before metastatic disease is assumed. In this example, smart medicine provides a relatively accurate means of selecting patients thus eliminating unnecessary testing and/or treatment procedures (Goldfarb CR, etal, SNM98, Abs. 446:114P).

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Smart medicine is by no means cheap medicine. Actually, in many cases, practicing of smart medicine may require access to highly sophisticated equipment and resources to perform a multimodality diagnostic work-up before designing a treatment plan better tailored to manage the disease. Although the initial costs of this approach may be high, it results in significant long-term savings by eliminating unnecessary procedures and/or optimizing treatment for a favorable outcome.

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PUBLISHER AND EDITOR:	**Katie Siafaca, MS**
ASSISTANT EDITOR:	**Angelika Gerth**
CIRCULATION:	**Noyan Aynechi**
DATABASE MANAGER:	**Feisal Yamani**
DESIGN & PRODUCTION:	**Jill Burch**
WEBMASTER:	**Jose A. Ferran**

NEW MEDICINE, INC. MAILING ADDRESS:

P.O. Box 909
Lake Forest, California 92630
Tel: 949. 830. 0448 ■ Fax: 949. 830. 0887
e-mail: info@newmedinc.com
www:http://www.newmedinc.com

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