Management of Cancer in Older People 2
Series Editor: Riccardo A. Audisio

Stuart M. Lichtman
Riccardo A. Audisio *Editors*

Management of Gynecological Cancers in Older Women

Springer

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Preface

The aging of the population has resulted in the recognition that all of the subspecialties of oncology will be primarily concerned with the care of older patients. While there is not one precise definition of the age of "geriatric" patients, it is clear that the aging of our society has necessitated a focus on the older segment of the population. It has long been recognized that the most significant risk factor for the development of cancer is aging. This together with the epidemiologic shift has resulted in a marked increase in the number of older patients with cancer. This will markedly increase the cancer burden [1]. Cancer compromises the life expectancy as well as the active life expectancy of older individuals. Cancer and cancer treatment may appear as one of the prime causes of disability in older individuals, not only of mortality.

The traditional ways in which cancer is studied, i.e., clinical trials focusing on younger, healthier patients, has left us with a void in the available data to manage the older patients in an evidenced-based fashion. Not only do these trials often fail to establish the validity of cancer treatment in the elderly, but they also fail to provide information related to the long-term complications of the treatment including decline in function [2]. In the 1988 American Society of Clinical Oncology (ASCO) Presidential Address, Dr. B.J. Kennedy encouraged the study of aging and cancer [3]. He stated, " … Our society need not ration how we will treat our disadvantaged members, but should continue to seek those preventive and positive measures that can shorten our later period of morbidity. A very major cancer load will persist well into the twenty-first century, even if the attempts at prevention are eventually a total success. There is a developing knowledge on aging. Care of the older person needs to be part of medical education and oncology education. Research will help attain a desirable quality of life with aging and a reduced morbidity." We were pointed in the right direction, but these goals have proven to be somewhat elusive.

Since that time, studies of older cancer patients have revealed a significant amount of important clinical information. This has included the degree and severity of comorbidity and its effect on treatment, the role of polypharmacy, and the various social and financial problems facing older patients with cancer. The under-representation of older patients in clinical trials has been amply documented [4]. The adverse outcomes

of inadequate dosing and supportive care in both curative and palliative treatments have been demonstrated in a number of treatment settings. Even when clinical trials are available, barriers to participation of older patients have been shown to be primarily due to physician reluctance due to fear of toxicity, limited expectation of benefit, or agism. A number of important strides have been made in the evaluation of older patients through various methodologies of geriatric assessment. The comprehensive geriatric assessment (CGA) developed by geriatricians is a multidisciplinary evaluation of the older patient encompassing a number of important clinical domains [5]. Researchers in this area have shown that traditional oncology measures of performance are not adequate in older patients and that geriatric-specific measures (i.e., ADL, IADL) have a much greater predictive value [6]. Recent advances in geriatric oncology patient assessment were made by the publication of two important trials [7, 8]. These need to be validated in prospective trials but appear to be predictive and easy to administer.

There has been major interest shown in geriatric oncology by some oncology professional societies and organizations. In 1995, the Cancer and Leukemia Group B organized a Cancer in the Elderly Committee [9]. This has led to a number of completed and published studies in barriers to participation, supportive care, and cancer therapeutics. The newly formed Alliance (CALGB and NCCTG) will strengthen this committee. The Gynecologic Oncology Group has recently formed an Elderly Taskforce and has initiated a clinical trial in ovarian cancer. ASCO has sponsored a clinical practice forum in 2000, "Cancer Care in the Older Patient," as part of their Curriculum series and has incorporated geriatrics in the ASCO University program. The annual meeting has included a number of Education Sessions, Clinical Science Symposia, and oral presentations emphasizing Geriatric Oncology including a Geriatric Oncology track. The International Society of Geriatric Oncology (SIOG) with its headquarters in Switzerland has implemented a number of taskforces to evaluate the current literature and make treatment recommendations. Its annual meeting is a forum for updates and discussions about moving the field forward. The National Comprehensive Cancer Network (NCCN) has published practice guidelines for Senior Adult Oncology. The Cancer and Aging Research Group have been particularly productive in the development of geriatric assessment. A major milestone is the *Journal of Geriatric Oncology*, Elsevier Publ., which began publication in 2010.

Despite all of the changes that have taken place in the past few years there is still much that needs to be done. There needs to be improvement in the assessment of the older patient to allow clinicians to appropriate treatment decisions. An easily administered, predictable measure is critical. Practical treatment questions include whether adjuvant therapy is appropriate based on potential benefit of treatment versus predicted survival; what is the best palliative regimen; when is best supportive care appropriate. Clinical trial participation needs to be encouraged. Clinical trial design, statistical analysis, and trials reporting need to incorporate the specific needs of older patients and provide practical information for the clinician. Endpoints need to be practical to the elderly, i.e., maintenance of independence, avoiding functional decline, and time without symptoms. The publication of large trials in which older

patients have participated should give age-associated data. This is now lacking [10]. When prospective investigations are not appropriate, feasible, or ethical, there is a case for conducting good quality observational studies; these can provide reliable answers to the numerous questions regarding the management of older cancer patients.

The appropriate care of older women with gynecological cancer is of critical importance. Aging is an associated increased risk of gynecological cancer with the exception of cervical cancer. Treatment of these disorders often requires multimodality therapy which requires an integrated team approach. Older women, many of whom have significant comorbidity, are at increased risk of toxicity and undertreatment. It is imperative for clinicians to be acquainted with the various aspects of management and how they apply to older women. This book has been published to address these needs. It can be used as a reference for residents and fellows as well as experienced physicians in surgery, radiation oncology, and medical oncology.

The book covers a broad range of topics. There is an extensive review of geriatrics including background and epidemiology, basic science, geriatric assessment, and pharmacology. The genetics of gynecological cancer and the modalities of radiation and surgery are reviewed. The diseases covered are ovarian, endometrial, cervical, vulvar, and vaginal cancers as well as sarcomas. There are discussions for each entity including primary therapy and relapsed therapy. The quality of life of older patients is emphasized in the chapters on psychological issues, sexual medicine, end of life care, and the role of palliative surgery.

Society has evolved over of the past few decades in terms of how we view aging. Sixty-five years is, for the most part, not considered elderly. People are often very active into their seventies and eighties. Chronologic age should not be the sole parameter utilized in treatment decisions. Physicians caring for older women with gynecological malignancies need to be educated to these very important issues. Older patients need to be systematically evaluated to the degree necessary to make evidence-based decisions. In addition, studies in the basic sciences including the biology of aging need to be explored. As the older patients will become the majority of the patients that we evaluate and treat, they need to become the focus of our endeavors. Our elders deserve nothing less.

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Chapter 1
Background and Epidemiology

Nicole P.M. Ezendam, Lonneke V. van de Poll-Franse, and Jan-Willem Coebergh

Abstract Gynecological malignancies – cancer of the cervix, ovaries, uterus, vagina, vulva, and the fallopian tubes – affect many women each year: one in eight tumors among women is gynecologic. This chapter focuses on the four most common gynecological cancers: uterine, ovary, cervical, and vulvar cancer. To present the epidemiology of these gynecological cancers, the incidence, mortality, and survival in Europe and the United States are described. Moreover, this chapter provides information on important risk factors of these cancers, comorbidities that might affect treatment and mortality, and elements of cancer survivorship. Increasing numbers of patients survive gynecological cancer and (long-term) consequences of the cancer and its treatment become more apparent. As a result quality of life becomes a growing topic of attention.

Keywords Epidemiology • Cervical cancer • Ovarian cancer • Uterine cancer • Vaginal cancer • Gynecologic malignancies

Incidence and Mortality

Cancer of the Uterus

Uterine cancer is the most common gynecologic malignancy in Europe and the United States [1, 2] with about 17–23 new patients per 100,000 women in Europe and the United States [1, 3]. However, the incidence is much lower in developing countries [4]. Incidence increases with advancing age, especially above the age

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of 40 (Fig. 1.1a–d). The median age for being diagnosed with uterine cancer is 61 years. Women have a 2.6 % lifetime risk of developing uterine cancer in the United States [3]. Fortunately, most cases are diagnosed at an early stage when surgery alone may be adequate for cure. Incidence has increased considerably in the Nordic countries in the past five decades, while incidence was already high around 1975 in the United States and decreased slightly (Fig. 1.2a, b). When we compare countries for their age-standardized incidence and mortality rates, large differences are observed in especially incidence, indicating that a decrease in incidence might be feasible in some countries (Fig. 1.5).

Ovarian Cancer

Ovarian cancer is the second most common gynecological cancer in Europe and the United States (14/100,000 women) [1], and its incidence increases with age especially after 40 (Fig. 1.1b). The median age for being diagnosed with ovarian cancer is 63 years. Women have a 1.4 % lifetime risk of developing ovarian cancer, and it is the most common cause of death among women with gynecologic cancer and the fifth leading cause of cancer death in all women [5]. Incidence has increased slightly between 1960 and 1990 and has decreased thereafter, while mortality increased until the 1975 in the Nordic countries and until 2,000 among women over 75 in the United States. Only recently there might be a starting trend of a decrease (Fig. 1.3). Figure 1.5 shows that there are large differences in both incidence and mortality between countries, leaving room for improvement by changing risk factors and health care.

Cervical Cancer

About 7 per 100,000 women are diagnosed with cervical cancer each year in Northern and Western Europe and Northern America [6]. The lifetime risk of developing cervical cancer for the United States women, based upon the national data from 2006 to 2008, is 0.68 % [3]. Unfortunately, in countries that do not have access to cervical cancer screening and prevention programs, cervical cancer remains the second most common type of cancer (17.8 per 100,000 women) and cause of cancer deaths (9.8 per 100,000) among all types of cancer in women [6]. Cervical cancer occurs at much younger age than the other gynecological cancers (Fig. 1.1c). The median age at diagnosis of cervical cancer in the United States from 2004 to 2008 was 48 years [3]. Both incidence and mortality have decreased among all age groups in the Nordic countries and the United States since about 1970 (Fig. 1.4), possibly partly as a result of large screening programs that have been implemented in developed countries in the 1960s. Moreover,

since human papilloma virus (HPV) infection is a necessary – although not sufficient – cause of cervical cancer, the implementation of vaccination programs might lead to a further decrease in cervical cancer incidence and mortality in the future [7]. Large differences in incidence and mortality exist between countries within Europe (Fig. 1.5).

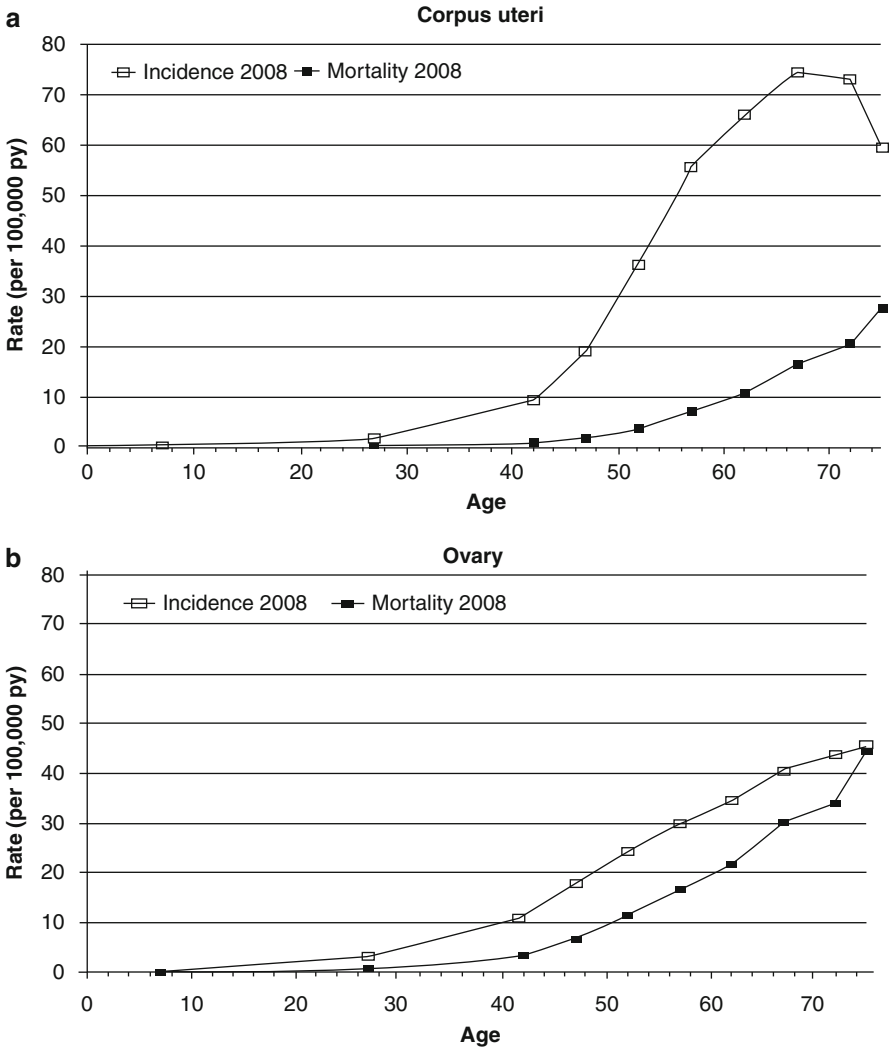

Fig. 1.1 (**a–d**) Incidence and mortality by age for patients with tumors of the corpus uteri, ovary, and cervix in 2008 in Europe and the USA combined and of the vulva between 2000 and 2008 in the United States (per 100,000 person-years) (*Source*: (**a–c**) GLOBOCAN; (**d**) SEER)

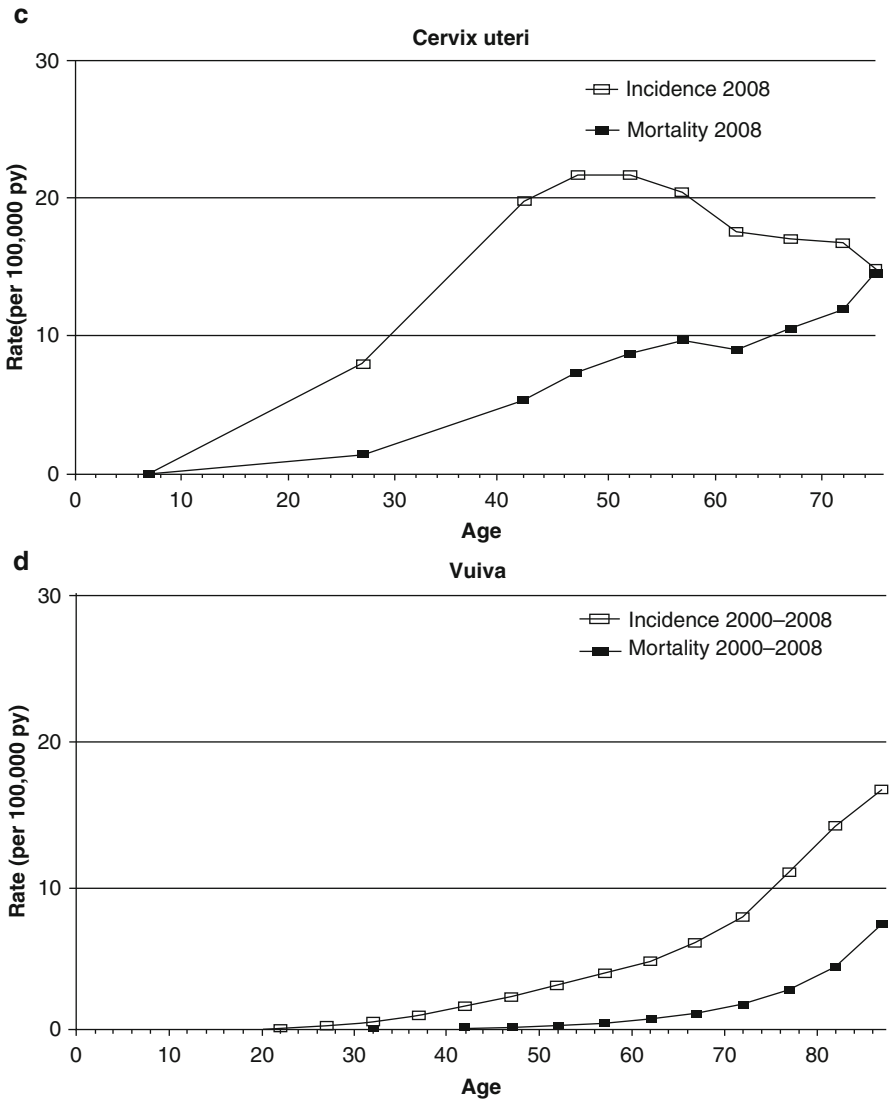

Fig. 1.1 (continued)

Vulvar Cancer

Vulvar cancer is a less common gynecological cancer. The age-adjusted incidence of vulvar cancer in the United States was 2.5 per 100,000 women [8]. The mean age at diagnosis is 65 years, but this is dropping due to an increase in incidence below the age of 40 [9]. Incidence and mortality have remained rather constant over the past few decades for women above 50 years in the United States (Fig. 1.6).

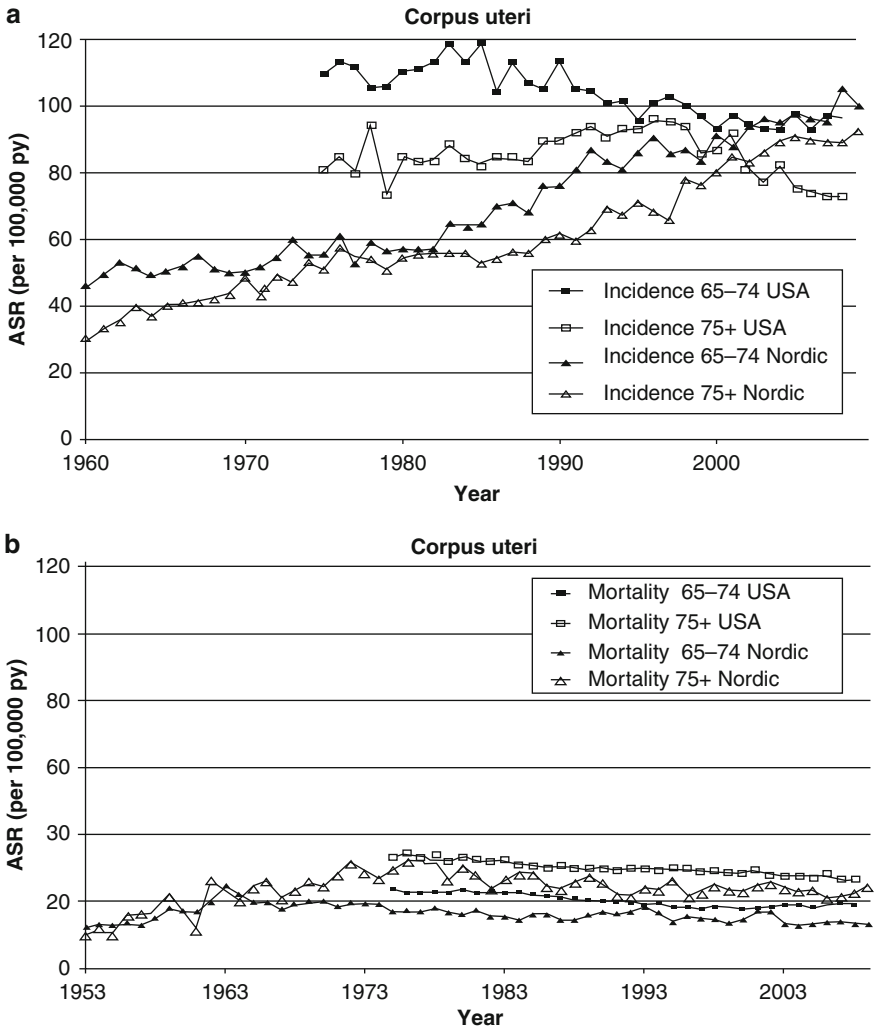

Fig. 1.2 (**a**, **b**) Trend in age-standardized incidence and mortality for tumors of the corpus uteri in the United States and in the Nordic countries [ASR (age-standardized rate) on the United States or European population per 100,000 person-years] (*Source*: SEER; NORDCAN)

Risk and Protective Factors for Gynecological Cancers

Cancer of the Uterus

Two types of endometrial carcinoma have been identified since the early 1980s. Type I is estrogen related and arises in women with obesity, hyperlipidemia, and signs of hyperestrogenism: anovulatory uterine bleeding, infertility, late onset of the

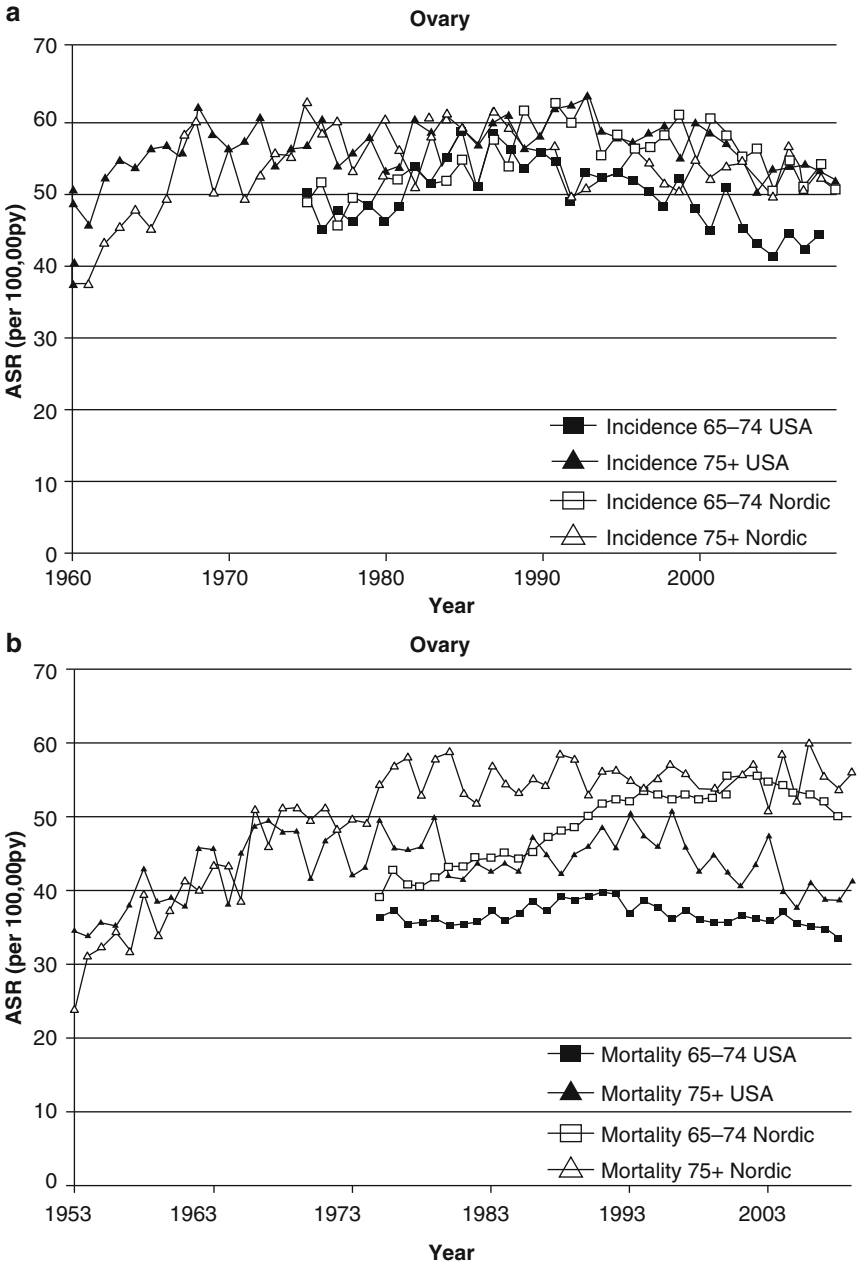

Fig. 1.3 (**a**, **b**) Trend in age-standardized incidence and mortality for tumors of the ovary in the United States and in the Nordic countries [ASR (age-standardized rate) on the United States or European population per 100,000 person-years] (*Source*: SEER, NORDCAN)

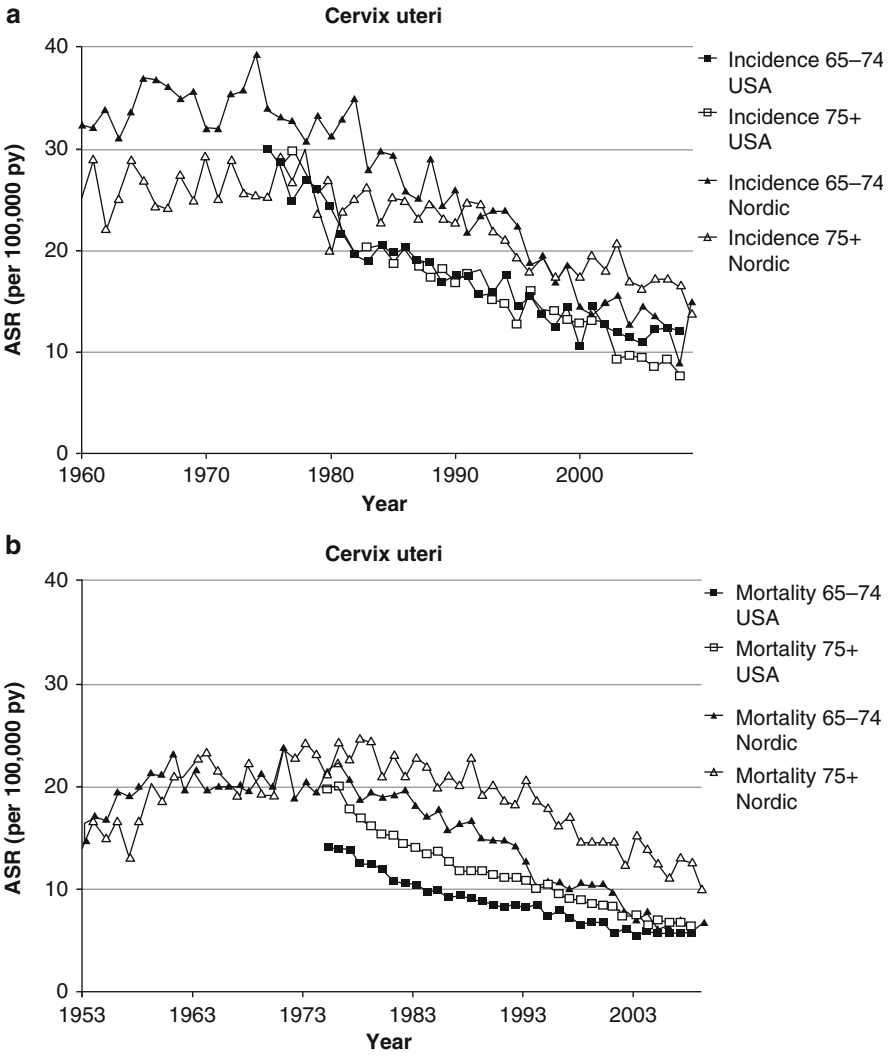

Fig. 1.4 (**a**, **b**) Trend in age-standardized incidence and mortality for tumors of the cervix uteri in the United States and in the Nordic countries [ASR (age-standardized rate) on the United States or European population per 100,000 person-years] (*Source*: SEER, NORDCAN)

menopause, and hyperplasia of the stroma of the ovaries and endometrium [10]. This type usually presents histologically as a low-grade tumor. About 80 % of women diagnosed with endometrial cancer have type I [11].

As type I endometrial cancer is related to (long-term) estrogen exposure, either from exogenous or endogenous sources, typical risk factors for this type are estrogen therapy [12], tamoxifen use in breast cancer patients [13], obesity [14], and nulliparity. Having had breast cancer appears to be associated with a higher risk of endometrial

cancer, but this seems to be largely explained by the coinciding risk factors obesity and nulliparity. Similarly, diabetes has also been identified as a risk factor for endometrial cancer, although obesity is an important confounding factor in this relation. Nevertheless, the independent association between diabetes and endometrial cancer has been shown and is heavily studied nowadays [15–17]. Women with the Lynch syndrome (hereditary nonpolyposis colorectal cancer) have an increased risk of endometrial cancer and other types of cancer (e.g., colon, ovarian, stomach cancer).

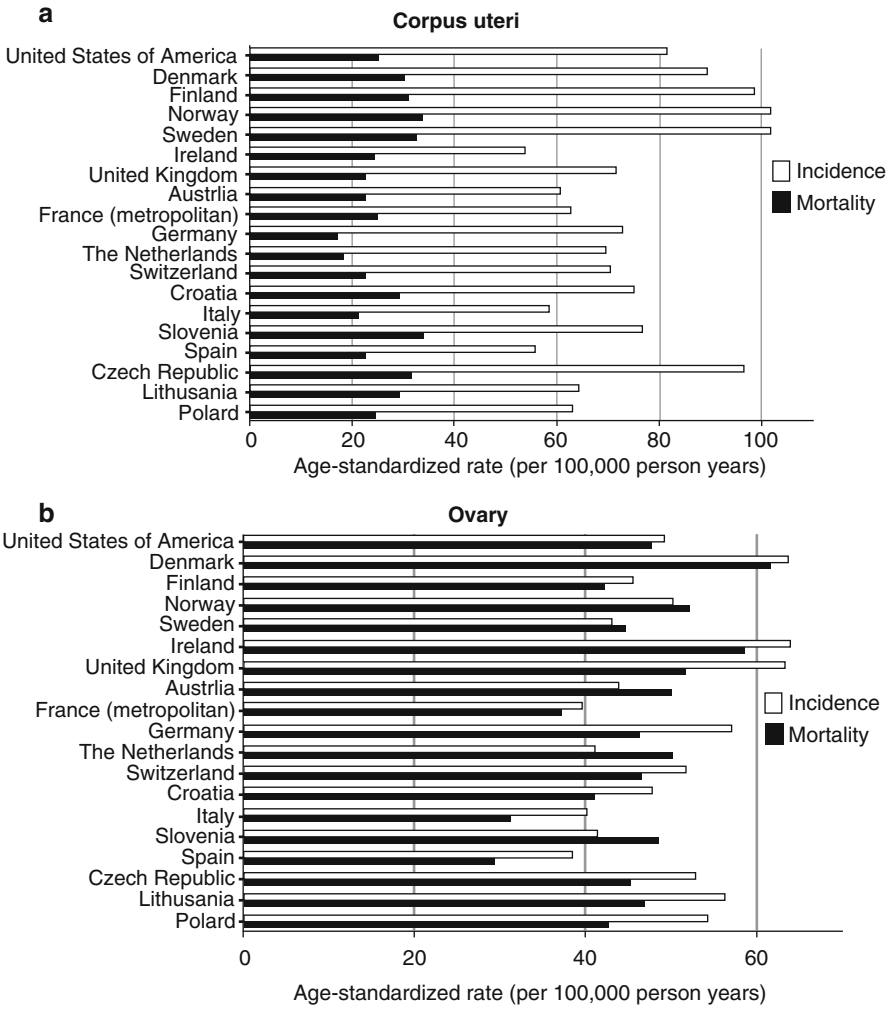

Fig. 1.5 (**a–c**) Country-specific incidence and mortality rates in 2008 for patients with tumors of the corpus uteri, ovary, and cervix age 70+ years [WSR (world-standardized rate); per 100,000 person-years] (*Source*: GLOBOCAN)

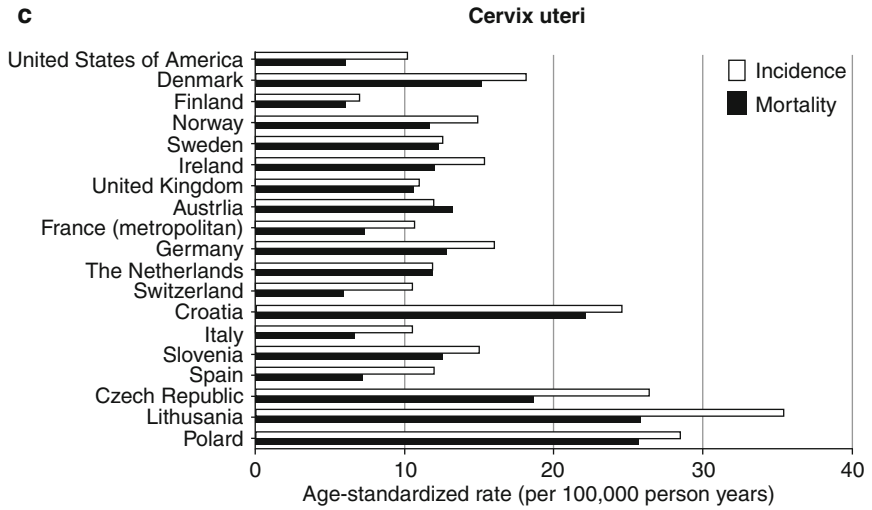

Fig. 1.5 (continued)

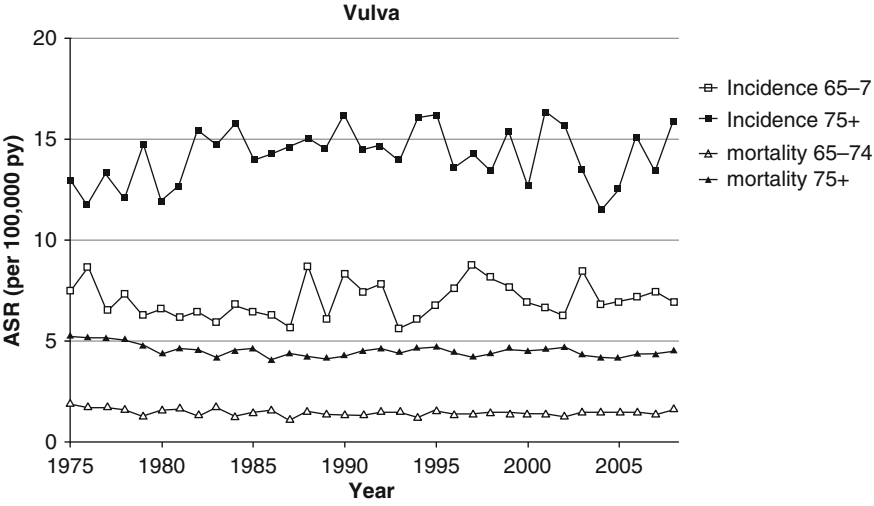

Fig. 1.6 Trend in age-standardized incidence and mortality in the USA for tumors of the vulva [ASR (age-standardized rate) on the United States population per 100,000 person-years] (*Source*: SEER)

The use of oral contraceptives (OC) decreases the risk of endometrial cancer, which is particularly marked for long-term users. This protective effect comes from the progestin that suppresses endometrial proliferation [18, 19].

Type II endometrial carcinoma arises in women who have no signs stated above, or these signs are not clearly defined. This type appears to be unrelated to estrogen

stimulation and often presents with higher grade tumors [10]. It often involves poor prognostic cell types, like clear cell or papillary serous tumors. About 20 % of women diagnosed with endometrial cancer have type II [11].

Ovarian Cancer

The causes of ovarian cancer are not very clear, but estrogen and progesterone play an important role in the carcinogenesis [20]. The hypothesis that suppression of ovulation reduces the risk of ovarian cancer is supported by the fact that the risk of ovarian cancer is increased among infertile women and reduced by OC use and multiparity. Also, late age of menopause is associated with increased risk of ovarian cancer [21–23]. The use of OCs reduces the risk of ovarian cancer. The reduction of ovarian cancer by oral OC is associated with duration of OC use and persists for more than 30 years after OC is ceased [24]. Hysterectomy and tubal ligation are also associated with a reduced ovarian cancer risk [25].

Atypical endometriosis has been positively associated with certain types of ovarian cancer [26], and this type of ovarian cancer appears to occur in younger and nulliparous patients [27]. Hereditary ovarian cancer syndromes (BRCA mutations, Lynch syndrome) account for 5–15 % of ovarian cancer cases [28, 29].

Cervical Cancer

Infection with the human papilloma virus (HPV) is the most important risk factor for cervical cancer [30]. Subtypes HPV 16 and 18 are considered high-risk types because they may cause cervical cancer in some women and are found in about 70 and 76 % of all cervical cancers in all world regions except Asia (in Western/Central Asia, 82 % of cervical cancer was HPV16/18 associated) [31]. As screening programs for (pre)cancer of the cervix have been implemented in many developed countries for years now, the incidence and mortality rates in these countries have decreased significantly [32, 33]. International and regional variation in age patterns of cervical lesions is likely attributable to differences in screening (age at initiation, frequency, follow-up) [34]. Cervical cancer has the highest incidence in undeveloped countries where no screening programs are present and in lower socioeconomic classes [35]. In the United States, nonwhite women have a higher incidence of cervical cancer [36]. With the introduction of HPV vaccination, the future of cervical cancer control may become a diversified strategy, one for non-vaccinated birth cohorts until 1995–2005 or so and another for vaccinated cohorts; it will take another 50 years before the non-vaccinated cohorts have passed the screening age [37].

Other risk factors that have been identified with cervical cancer are frequently related to HPV infection, such as young age at first sexual partner and multiple sexual

Table 1.1 Overview of risk factors for cervical, uterine, ovarian, and vulvar cancer

	Tumor			
Risk factor	Cervix	Corpus uteri	Ovary	Vulva
Smoking	+	–		+
Overweight/obesity		++	+?	
Fruit and vegetables	–			
HPV virus	++++			++
Immune deficiency	+?			+
Tamoxifen		++		
Hormones	+	++	++	
Physical activity		–		
Hyperlipidemia		+		
Infertility		+	+	
Nulliparity		++	+	
Late onset of the menopause		+	+	
Diabetes		+		
Lynch syndrome		++	+	
BRCA mutations			+++	
Oral contraceptives	+	–	–	
Young age of first sexual partner	++			
Multiple sexual partners	++			
Sexually transmitted disease	+			

+, Positive relation; –, negative relation; ?, insufficient proof

partners [38] and having had a sexually transmitted disease (genital herpes, Chlamydia). In contrast to endometrial or ovarian cancer, use of OC is associated with an increased risk of cervical cancer [39]. After taking HPV into account, smoking appears to be the most significant environmental risk factor for *squamous* cell cervical cancer [38, 39].

Vulvar Cancer

Vulvar carcinoma was typically observed among older aged, postmenopausal women. However, the mean age at diagnosis is decreasing [40], due to a change in risk factor prevalence. HPV has been shown to be responsible for 60 % of vulvar cancers [41] Due to a change in sexual behavior and an increased rate of HPV infection among younger women, increased incidence vulvar cancer has to be expected [9]. Other risk factors are smoking, an immunocompromised status, long-standing vulvar dystrophy, and a history of cervical cancer [42, 43].

A schematic overview of risk factors for cervical, uterine, ovarian, and vulvar cancer is provided in Table 1.1.

Comorbidity

Cancer treatment is often complicated by patients' comorbidities (chronic disabling conditions), and moreover, the prognosis is dependent of the number and kind of comorbidities [44]. A majority of the older patients suffer from one or more comorbidities, diabetes mellitus being most frequent. In Table 1.2 the number and most important comorbidities are stated per tumor and per age group. While a large proportion of the 55–69 year olds have already comorbidities, the number of comorbidities increases further with age. The pattern of comorbidity is to a certain extent also an indicator of the etiology of the tumor itself. Patients with cervical cancer experience COPD more often but have fewer other malignancies. Patients with uterine and vulvar cancer have more often diabetes (Table 1.2).

Survival

Relative survival represents cancer survival in the absence of other causes of death. Relative survival depends among others on tumor progression, comorbidity, and age (Fig. 1.7a–d). The 5-year survival for all ages is 79–84 % for uterine cancer, 42–43 % for ovarian cancer, 67–71 % for cervical cancer, and 76 % for vulvar cancer [45, 46]. Relative survival is considerably lower among older age groups (Fig. 1.8a–d). The 5-year relative survival of ovarian, cervical, and vulvar cancer has been constant over the past four decades, whereas the survival of uterine cancer has improved slightly. Relative survival is usually a bit higher in the USA according to SEER since these are often rates of whites and Medicare-insured people only. They would compare better with the rates in the northwest and continental Europe except the UK and Denmark.

Gynecological Cancer Survivors

As a result of the aging population and the increasing prevalence of a risk factor like obesity, the prevalence of endometrial cancer survivors is markedly increasing. The prevalence includes persons with active disease and those who are cured of their disease. The prevalence increase is most prominent among women aged 50–74 years. Since 2000, the 20-year prevalence in this group increased almost 40 % to 13,500 survivors in the Netherlands in 2010 (of about 16 million women) [48]. On January 1, 2008, in the United States there were approximately 573,300 women alive who had a history of cancer of the corpus uteri [46]. In comparison, currently more than 150 million women are living in the United States.

The prevalence of ovarian cancer survivors will increase only slightly, mostly due to the aging population and small improvements in survival, whereas the incidence is slightly decreasing in many countries. The prevalence increase is most prominent

Table 1.2 Percentage of the patients with comorbidity by age category for tumors of the corpus uteri, ovary, corpus cervix, and vulva between 2005 and 2010

	Corpus uteri			Ovary			Cervix			Vulva		
Age	55–69	70–79	80+	55–69	70–79	80+	55–69	70–79	80+	55–69	70–79	80+
N	744	370	194	335	243	109	93	72	32	59	52	56
No comorbidity (%)	59	37	29	59	40	31	54	44	25	41	54	25
One comorbidity (%)	29	32	32	31	32	35	29	36	41	41	25	45
Other malignancy (%)	25	28	17	33	23	26	11	15	[a]	29	[a]	20
Cardiovascular disease (%)	16	18	37	23	30	29	26	19	[a]	13	[a]	36
COPD (%)	6	6	5	8	5	0	22	15	[a]	13	[a]	0
Diabetes mellitus (%)	40	30	21	17	18	18	19	19	[a]	42	[a]	20
Cerebrovascular disease (%)	3	7	6	4	0	5	7	12	[a]	0	[a]	12
Two or more comorbidities (%)	12	31	38	10	28	34	17	19	34	19	21	30

Source: Eindhoven Cancer Registry

[a]No percentages for comorbidities presented in case of <20 cases per category (age group with one comorbidity)

among women aged 75+ years. Since 2000, the 20-year prevalence in this group increased about 33 % to almost 1,800 ovarian cancer survivors in the Netherlands in 2010 [48]. On January 1, 2008, in the United States there were approximately 177,578 women alive with a history of cancer of the ovary. Furthermore, on January 1, 2008, 243,884 women were alive who had a history of cancer of the cervix uteri [46]. Prevalence numbers for vulva cancer have not been reported.

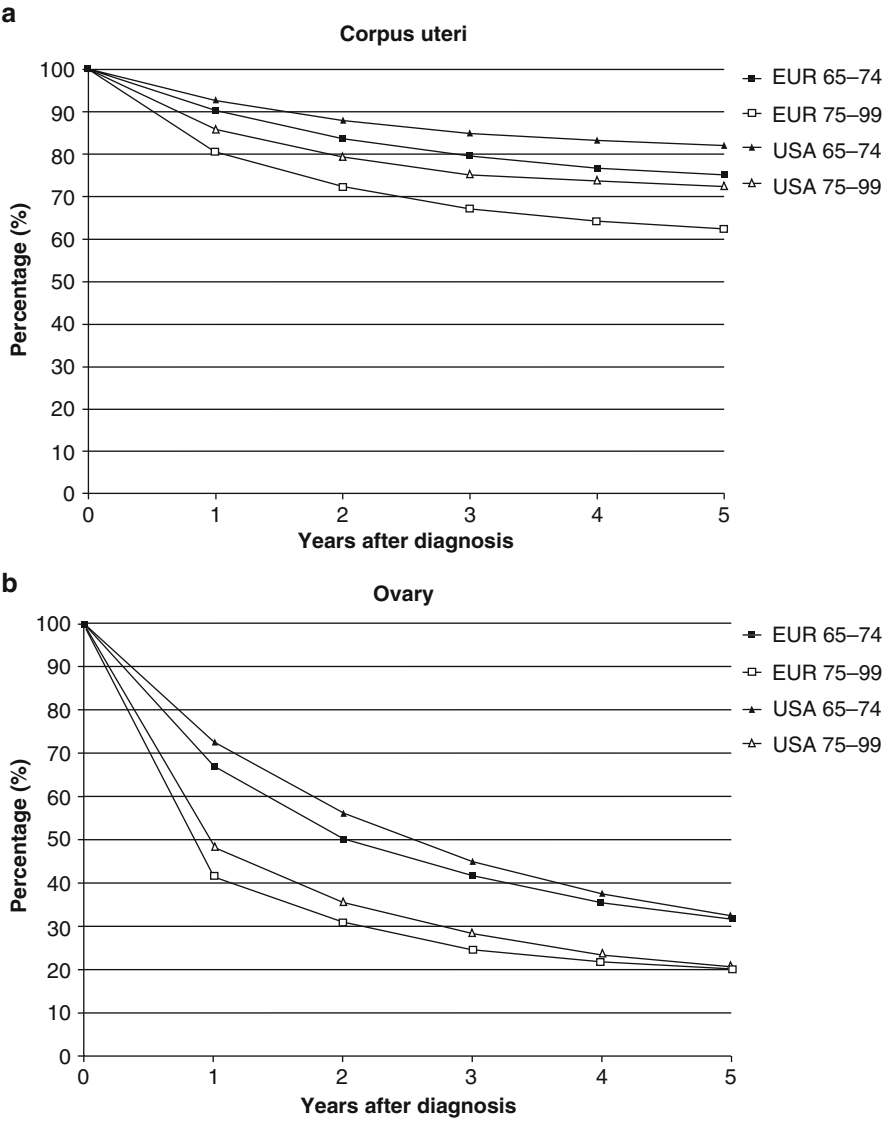

Fig. 1.7 (**a**–**d**) Relative survival according to age for patients with a tumor of the corpus uteri, ovary, cervix, and vulva in Europe (diagnosed between 1995 and 1999) and the USA (diagnosed between 1988 and 2007) (*Source*: (**a**–**c**) EUROCARE-4, SEER; (**d**) SEER)

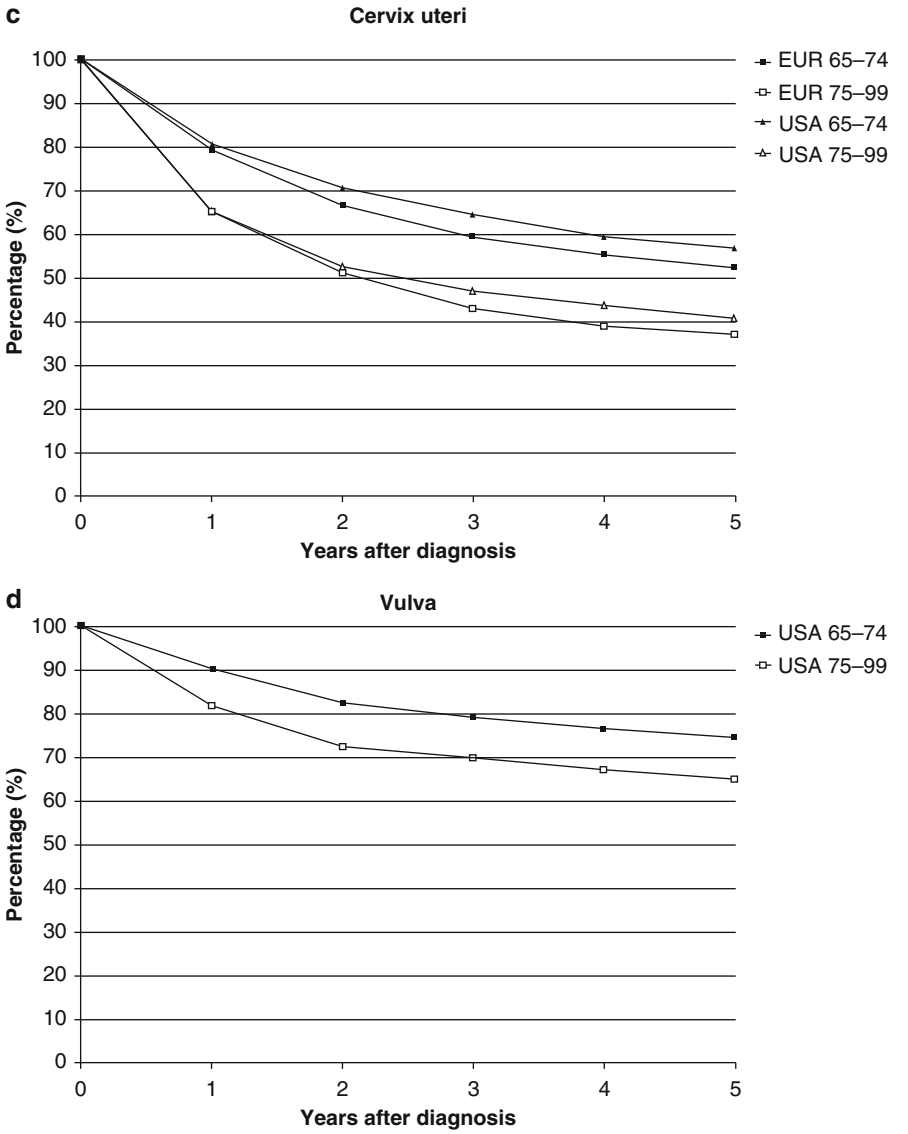

Fig. 1.7 (continued)

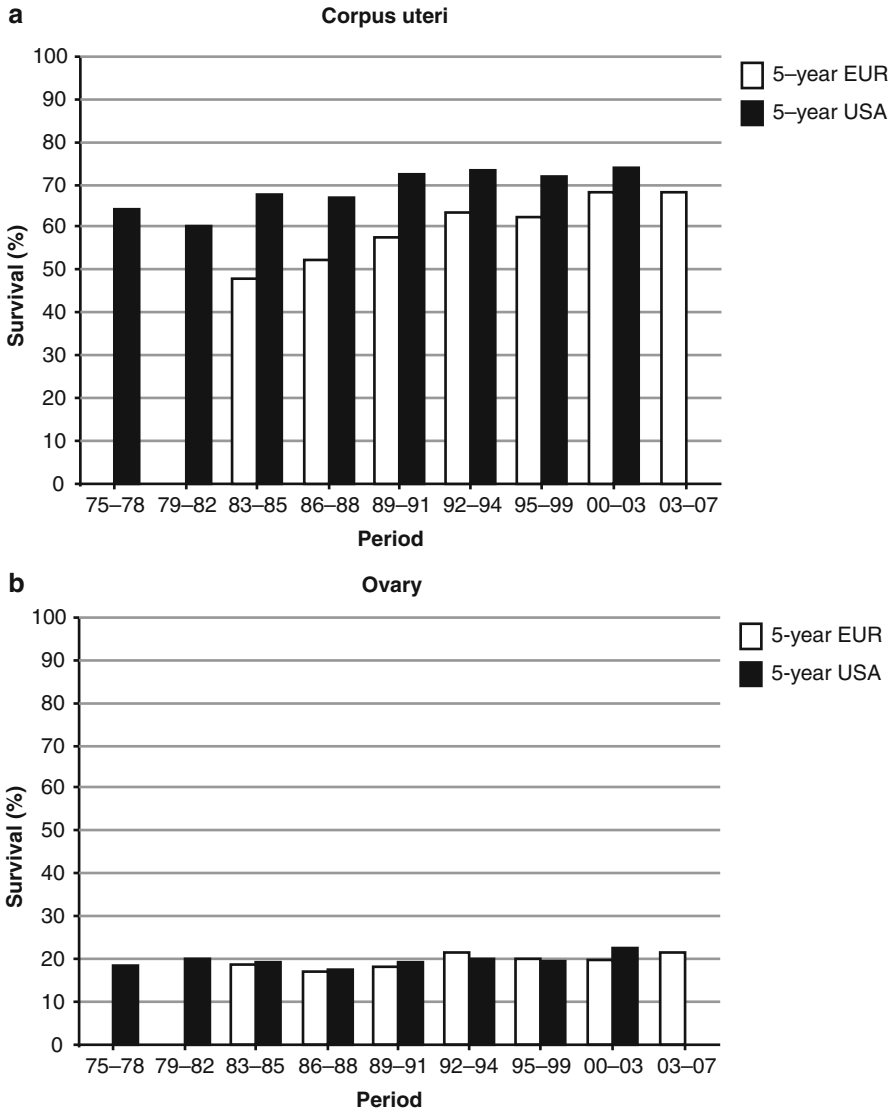

Fig. 1.8 (**a**–**d**) Trend in 5-year relative survival for patients aged 75 years and older with a tumor of the corpus uteri, ovary, cervix, and vulva in the Europe and the USA (Data: Europe 1983–1999 (Eurocare-4 [45]); Netherlands 1999–2007 (NKR [47]); USA 1975–2003 (SEER [46])) (*Source*: (**a**–**c**) EUROCARE-4, SEER; (**d**) SEER)

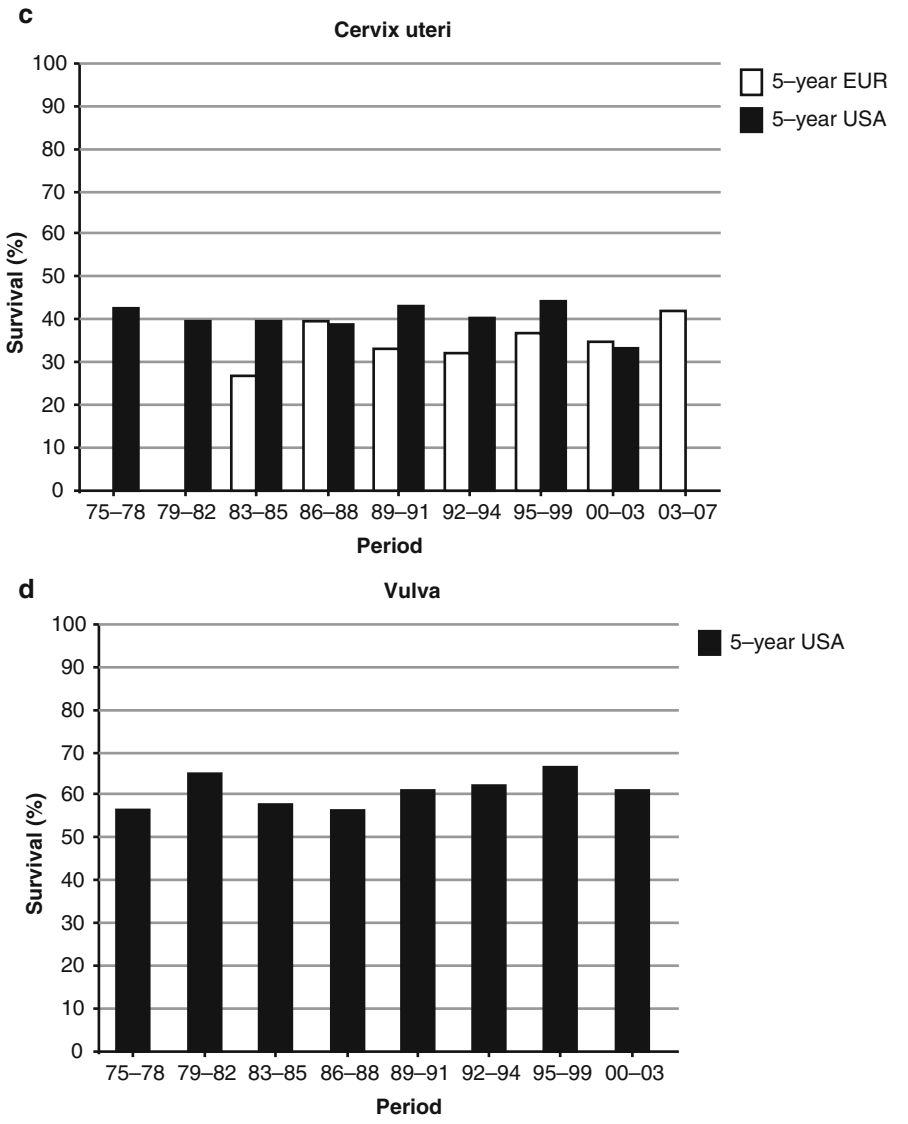

Fig. 1.8 (continued)

Data Sources

To describe the epidemiology of the gynecological cancer, various data sources are used mostly based on cancer registry data of countries of regions within countries.

- GLOBOCAN provides incidence and mortality data from the major cancer types at national level for all countries in the world. Estimates for 2008 are available and used for this chapter. The most important sources of information on cancer incidence are the successive volumes of Cancer Incidence in Five Continents CI5. Mortality statistics are collected and made available by the WHO [http://globocan.iarc.fr] [49].
- Eurocare (EUROpean CAncer REgistry-based study on survival and care of cancer patients) is a cancer epidemiology research project on survival of European cancer patients. The registry includes data of 12 countries since 1978 in 4 projects up to 2002 [http://www.eurocare.it].
- SEER collects cancer incidence, mortality, and survival data from 18 geographic areas in the United States covering 26 % of the USA population to date [http://seer.cancer.gov].
- NORDCAN collects cancer incidence, mortality, survival, and prevalence data from the Nordic countries: Denmark, Finland, Iceland, Norway, and Sweden [http://www-dep.iarc.fr/nordcan/English/frame.asp].
- Eindhoven Cancer Registry (ECR) collects data on incidence, on mortality, on survival since 1955, and on comorbidity and quality of life [http://www.ikz.nl/page.php?id=97].

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Chapter 2
Pathology of Gynecologic Cancer

Deborah DeLair

Abstract This chapter will discuss the basic pathology of select gynecologic malignancies that occur in older women. First, endometrial cancer will be reviewed, including endometrioid carcinoma, the most common subtype, as well as less common entities such as serous and undifferentiated carcinoma and MMMT. Tamoxifen-associated endometrial cancer as well as Lynch syndrome, an important disorder in endometrial as well as ovarian cancer, will be briefly touched upon. Next, ovarian epithelial malignancies will be discussed with special attention to serous carcinoma and its association with BRCA abnormalities. Endometrioid, clear cell, and mucinous ovarian neoplasms will also be briefly discussed. Finally, the most common carcinomas of the cervix and vulva are reviewed.

Keywords Endometrial carcinoma • Elderly patients • Ovarian carcinoma • Cervical carcinoma • Gynecologic cancer

Endometrial Carcinoma

For almost 30 years, endometrial carcinoma has been divided into two categories based on epidemiology, histology, and clinical behavior. Type I carcinomas consist of low-grade endometrioid tumors (approximately 80 %) which arise in a background of endometrial hyperplasia in pre- or perimenopausal women with estrogen excess and tend to have an indolent clinical course. Type II carcinomas (approximately 20 %), the prototype of which is serous carcinoma, are high-grade estrogen-independent tumors which typically develop in a background of atrophic endometrium in postmenopausal women and have a poor clinical outcome [1].

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Endometrioid Carcinoma

Endometrioid adenocarcinoma is the most common type of endometrial carcinoma, comprising approximately 80 % of the cases. The average age of the patient is approximately 63 years who usually is under the influence of unopposed estrogen stimulation due to obesity, estrogen administration, estrogen-secreting tumors, or anovulatory cycles. Most tumors are low grade, confined to the uterus at the time of diagnosis, and are preceded or coexist with complex endometrial hyperplasia.

Endometrial hyperplasia consists of an increase of the gland to stroma ratio and is divided into four categories based on its behavior as described by Kurman et al. in 1985 [2]: simple hyperplasia, with or without atypia, and complex hyperplasia, with or without atypia. The glands in simple hyperplasia are increased but show little architectural complexity. Complex hyperplasia, however, shows glands with marked glandular complexity including branching, budding, and papillary outpouching. Atypia refers to nuclear abnormalities including nuclear enlargement, rounding, loss of polarity, pleomorphism, prominent nucleolus, and vesicular chromatin. Atypia has been shown to be the most important parameter in this classification as Kurman et al. found that less than 3 % of patients with hyperplasia (simple or complex) without atypia progressed to carcinoma compared to approximately 25 % of the hyperplasias with atypia [2]. Although the diagnosis of atypical hyperplasia has long been plagued with reproducibility issues [3], an alternate classification system has not been widely accepted in clinical practice.

Endometrioid adenocarcinoma found in hysterectomy specimens from patients diagnosed with atypical hyperplasia on endometrial sampling is a frequent finding and has been described to occur in up to 42 % of the patients [4, 5]. Morphologically, carcinoma is distinguished from atypical hyperplasia predominantly based on greater architectural complexity and the absence of intervening stroma between glands.

Endometrioid carcinoma is graded using a 3-tiered system based primarily on architecture and secondarily on cytologic atypia. The FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) grading scheme uses the amount of glandular versus solid architecture present in the tumor to determine grade: Grade 1 shows less than 5% solid architecture, grade 2 has between 5 and 50 % solid architecture, and grade 3 contains a solid component greater than 50 %. If a significant amount of marked cytologic atypia is present, the tumor is then upgraded (from 1 to 2 or 2 to 3). Despite certain limitations, the FIGO grading system does have prognostic utility when applied correctly [6]. There has been interest in applying a binary grading system in which endometrial carcinomas are divided in to low- and high-grade tumors; however, they are not currently used in clinical practice [7–10]. Currently, endometrioid adenocarcinoma is often informally dichotomized into two groups: low grade (FIGO grades 1–2) and high grade (FIGO grade 3). Low-grade endometrioid adenocarcinomas usually have indolent clinical behavior, while FIGO grade 3 endometrioid carcinoma is a high-grade tumor which can show aggressive clinical behavior. It has been

associated with deep myometrial invasion, cervical involvement, and lymphovascular invasion [11]. These tumors may thus be more closely related to other type II cancers. Although some studies have shown a better outcome than other high-grade endometrial carcinomas such as serous or clear cell [12], others have shown similar prognoses [13, 14].

There are a number of different metaplasias that may be present in endometrioid carcinoma, usually in low-grade tumors. These include squamous, spindle cell, mucinous, eosinophilic, and papillary syncytial metaplasias [15, 16]. More infrequently, there may be osteoid or chondroid metaplasia which may mimic a carcinosarcoma [17]. The tumors may also show clear cell or secretory change, sex cord differentiation, or a corded or hyalinized growth pattern [18–20]. These changes are only important in terms of diagnosis, as they may mimic other types of tumors; they have no clinical ramifications.

Different types of myometrial invasion of endometrioid carcinoma have been reported. One of these is the so-called MELF or microcystic, elongated, fragmented pattern of invasion [21] which most frequently occurs in low-grade endometrioid carcinoma. This type of invasion shows a detached glands and tumor cells, often with an attenuated epithelium with a prominent myxoid inflammatory reaction. These tumors have an increased incidence of lymphovascular invasion and possibly lymph node metastases [22, 23]. When present as lymph node metastases, the cells are often single with prominent eosinophilic cytoplasm and can mimic histiocytes [24].

Several different genetic abnormalities have been described in endometrioid carcinoma. These include microsatellite instability, alterations in the gene *PTEN*, and mutations in the genes *PIK3CA*, *KRAS*, and *CTNNB1*. Unlike serous carcinoma, they usually do not show mutations in the gene *Tp53* [25].

Serous Carcinoma

Serous carcinoma of the endometrium is the prototype of Bokhman's type II endometrial cancers as it is usually not associated with estrogen excess, occurs in postmenopausal women, and typically has a poor clinical outcome. It is much less common than endometrioid type and consists of approximately 5–10 % of all endometrial cancers. It is an aggressive subtype of endometrial cancer, often presenting at advanced stage and accounts for a disproportionate amount of deaths and recurrences [26].

Serous carcinoma typically arises in a background of atrophic endometrium or atrophic polyp, as opposed to endometrioid type which is usually present in a background of atypical hyperplasia. It arises in a precursor lesion referred to as endometrial intraepithelial carcinoma (EIC) which is a proliferation of malignant cells, confined to the endometrial surface or glands, without myometrial invasion [27]. The aggressive behavior of this tumor is related to the fact that it may spread

beyond the uterus without invasion into the myometrium. In a large series of patients with uterine serous carcinoma, 32 tumors showed no myometrial invasion; however, surgical staging revealed that 37 % of these tumors had FIGO stage III or IV disease [28].

The tumor suppressor gene *Tp53* has been implicated in the pathogenesis of serous carcinoma as mutations in this gene are present in up to 93 % of uterine serous carcinomas which may be detected by immunohistochemistry [29–31]. Studies have also shown identical p53 mutations in the precursor lesion (EIC) as well as the invasive and metastatic disease [30–32].

Clear Cell Carcinoma

Clear cell carcinoma of the endometrium (ECCC) is a rare entity which has been reported to comprise between 1 and 6 % of endometrial cancers; however, the actual incidence is probably closer to 1 % [33–36]. The discrepancy is due to the fact that many tumors may show clear cell change or similar architectural features, including a papillary growth pattern, resulting in misclassification in many cases. If these types of cases are excluded, unequivocal pure clear cell carcinoma is very rare [33]. ECCC is an example of Bokhman's type II cancers in that it frequently presents in postmenopausal women, often shows a poor clinical outcome, and appears unrelated to estrogen excess.

ECCC may arise in a background of atrophy or a polyp, like serous carcinoma [36, 37]. The most common architectural patterns include papillary, solid, and tubulocystic. There is an oxyphilic variant which shows eosinophilic, rather than clear cytoplasm. These tumors are usually negative for estrogen and progesterone receptors [38, 39]. ECCC has been shown to have a heterogeneous molecular makeup with mutations in *PIK3CA* and *ARID1A* and shows infrequent mutations in *PTEN* and *Tp53* [40].

Undifferentiated Carcinoma

Undifferentiated or dedifferentiated carcinoma is a very aggressive endometrial tumor which has been recently described [41]. It is a tumor in which DNA mismatch repair protein abnormalities have been observed (see section "Lynch Syndrome"). Although some of the abnormalities are sporadic, some of them are associated with Lynch syndrome [42, 43].

Undifferentiated carcinoma is a tumor which shows sheets of discohesive or loosely cohesive cells that may resemble lymphoma. It may also refer to as dedifferentiated when it is associated with a low-grade endometrioid component. It is important for pathologists to recognize these tumors as they appear to have a worse outcome than FIGO grade 3 endometrioid carcinoma and appear to be associated with Lynch syndrome [41, 42].

MMMT (Malignant Mixed Mullerian Tumor/Carcinosarcoma)

MMMTs comprise approximately 2–5 % of uterine malignancies and usually occur in postmenopausal women and have an aggressive clinical course [44]. Although these tumors are biphasic neoplasms consisting of both carcinomatous and sarcomatous components, it is now believed that these are actually variants of carcinoma or "metaplastic" carcinomas. The tumors are usually polypoid endometrial masses. The carcinoma component may be any type of Mullerian carcinoma, and the sarcomatous component may show homologous (leiomyosarcoma, fibrosarcoma) or heterologous (rhabdomyosarcoma, chondrosarcoma) differentiation. Both components are usually high grade.

Tamoxifen and Endometrial Cancer

Tamoxifen is often used in patients with estrogen receptor-positive breast cancer due to its antiestrogenic effects. In the endometrium, however, tamoxifen acts as a weak agonist and is associated with the development of endometrial polyps and endometrial carcinoma [45, 46]. Overall, patients who use tamoxifen have a relative risk of endometrial cancer of approximately seven which appears to be related to the duration of administration [47]. In addition to endometrioid cancers that develop as a result of estrogen exposure, non-endometrioid tumors have also been described including serous carcinoma, clear cell carcinoma, and MMMT [48–50]. Tumors may arise during exposure to tamoxifen or after its discontinuation, a setting in which the incidence of high-grade cancers is increased [51].

Lynch Syndrome

Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer (HNPCC) syndrome is an autosomal dominant condition in which patients develop colorectal, endometrial, and other carcinomas including ovarian, due to a germ line mutation in one of the DNA mismatch repair proteins [52]. While colorectal cancer is the most common tumor to affect these patients, women with LS have up to a 60 and 13% lifetime risk of developing endometrial and ovarian cancer, respectively [53, 54].

The most common DNA mismatch repair proteins to be affected include MLH1, MSH2, MSH6, and PMS2. These proteins function to repair replication errors in repetitive nucleotide sequences, or microsatellites, the deficiency of which frequently results in microsatellite instability (MSI) which may eventually lead to the development of malignancies [55]. Many sporadic endometrial carcinomas show MSI due to mismatch repair deficiency, the majority of which are due to epigenetic *MLH1* promoter methylation in contrast to patients with LS who have a germ line mutation in one of the genes [56, 57].

The development of gynecologic malignancies in LS is often overlooked; however, its recognition is important. In a study of women with LS who developed both gynecologic and colorectal cancers, 51 % had their endometrial or ovarian cancer diagnosed first [58]. In addition, women have an equal or even higher incidence of endometrial cancer than colon cancer, especially those with mutations in *MSH6*, which appears to be frequently associated with endometrial cancer and presentation at an age older than that typically seen in colon cancer [54, 59–62].

In addition to an older age of presentation, many women with Lynch syndrome and endometrial cancer do not have a personal or family history of cancer and are thus undetected with standard screening criteria [63]. Beyond screening at the clinical level, certain pathologic features have been identified in tumors with deficient mismatch repair function. Grossly, it has been noted that the lower uterine segment is an overrepresented location of endometrial cancer associated with Lynch syndrome [42, 64]. Histologically, endometrioid carcinomas are the most common; however, it appears that there is an increased incidence of higher grade tumors and non-endometrioid histologies in younger patients including undifferentiated and clear cell carcinoma [43, 65]. Other pathologic features suggestive of Lynch syndrome include prominent peritumoral lymphocytes, tumor infiltrating lymphocytes, and tumor heterogeneity [42, 66].

When clinical or pathologic factors are present which raise the possibility of Lynch syndrome, the pathologist may perform immunohistochemical studies as a screening tool. This has been found to be a rather sensitive and specific method in detecting patients with the syndrome [67]. If abnormalities are encountered in any of the proteins by immunohistochemistry, the patient is then referred to genetics to undergo confirmatory testing.

Ovarian Carcinoma

Ovarian cancer is the most deadly of the gynecologic malignancies, accounting for approximately half of all mortalities [68]. Although ovarian cancer is traditionally managed as one disease, there is abundant data to support that ovarian cancer is highly heterogeneous with distinct pathogeneses, morphology, and clinical behavior based on histologic subtype.

Serous Carcinoma Including BRCA

Ovarian serous carcinoma (OSC) is the most common ovarian epithelial malignancy, consisting of approximately 80 % of the cases. It carries a poor prognosis due to the fact that up to 95 % of patients present at an advanced stage (FIGO stages II–IV) [69]. Recently, it has become evident that the OSC can be separated into two

categories, based on molecular composition, appearance, and clinical behavior, low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC).

Despite the existence of different grading schemes (FIGO, World Health Organization [WHO], Gynecologic Oncology Group [GOG], and Shimizu-Silverberg), a single grading system is not currently used universally. Malpica et al. have developed a two-tier grading system specifically for serous carcinoma which evaluates mitotic index and nuclear atypia [70]. Tumors with a uniform nuclear appearance and fewer than 12 mitoses per 10 high-power fields are classified as LGSC, and those with marked cytologic atypia (greater than or equal to 3 times variation in nuclear size) or 12 or more mitoses are classified as HGSC. On multivariate analysis, tumor grade based on this two-tier system was a significant independent prognostic factor of overall survival [70]. Furthermore, this grading system has shown excellent interobserver and intraobserver reproducibility among both gynecologic and general surgical pathologists [71].

In addition to the clinical behavior, molecular studies also support this classification. LGSC is thought to develop in a stepwise progression from cystadenoma and serous borderline tumor (SBT). In fact both SBT and LGSC have been found to have mutations in either KRAS or BRAF in approximately two-thirds of cases [72]. In addition, there are a number of shared allelic imbalances which progressively increase during the development of LGSC from SBT [73]. HGSC, conversely, shows mutations in *Tp*53 in over 80 % of the cases; these are rarely seen in LGSC and SBTs [74, 75]. In addition, SBT and LGSC coexist in approximately two-thirds of the cases, and SBT is rarely seen in association with HGSC [70].

In an effort to identify a precursor of HGSC, women with *BRCA* germ line mutations, a population that is at increased risk for both ovarian and breast cancer, have been extensively studied. *BRCA1* and *BRCA2* are tumor suppressor genes which are involved in DNA repair by homologous recombination and, when lost, additional mutations and genomic instability ensue, which may lead to cancer. It is estimated that at least 10 % of ovarian cancers are due to hereditary susceptibility, and *BRCA* mutations account for the large majority [76]. The lifetime risk of ovarian cancer in patients with a *BRCA1* germ line mutation is approximately 54 %, while the risk for *BRCA2* is 23 % [77]. Due to the increased risk of ovarian cancer, many *BRCA*-positive women have undergone prophylactic bilateral salpingo-oophorectomies, which have been shown to significantly reduce the subsequent development of ovarian cancer by up to 96 % [78, 79].

Occult carcinomas or serous tubal intraepithelial carcinoma (STIC) has been detected in these prophylactic specimens ranging from 2.3 to 17 % of the time [79–84]. A large majority of these STICs have involved the fallopian tube epithelium or, more specifically, the fimbria, which has led to the hypothesis that the majority of HGSCs arise in the fallopian tube. Accordingly, a specific protocol was developed called “SEE-FIM” (sectioning and extensively examining the fimbriated end) [83, 85] in which the tubes are sectioned in a specific manner after fixation and submitted entirely for microscopic examination. This protocol ensures maximum exposure of the fimbrial mucosa in order to detect these occult carcinomas.

In addition to tumors occurring in patients with *BRCA* germ line mutations, sporadic HGSC may also show *BRCA* abnormalities. Specifically, *BRCA* gene

inactivation may occur by several mechanisms including somatic mutation or epigenetic silencing by promoter methylation; these abnormalities have been reported to occur in approximately 30 % of sporadic HGSC [86]. In addition to showing *BRCA* abnormalities, sporadic HGSC has also been shown to have prominent tubal involvement, including the fimbriae. STIC has previously been shown to be present in the majority of tumors classified as primary ovarian, peritoneal, and tubal, some of which have shown identical *Tp53* mutations in both sites [87].

Morphologically, STIC consists of a focus of secretory cells with loss of cilia, cellular stratification or pseudostratification, nuclear enlargement, atypia, mitotic activity disorganization, and loss of polarity [85, 87]. Invasive HGSC can show a wide range of morphologic appearances. The classic appearance is that of a complex papillary architecture with hierarchical branching and slit-like spaces. Other less-described patterns include glandular, cribriform, transitional solid, trabecular, and microcystic. It is for this reason, "serous" is the preferred term as opposed to "papillary serous"; serous carcinoma is not necessarily papillary, and non-serous carcinomas may show papillary architecture. Cytologically, the tumor cells show high nuclear grade.

HGSCs that harbor *BRCA* abnormalities appear to have a characteristic morphologic appearance, particularly those with *BRCA1* germ line mutations and promoter methylation, compared to non-*BRCA* altered cases. A combination of solid, transitional cell-like, or pseudo-endometrioid architecture, the presence of diffuse tumor infiltrating lymphocytes, and high mitotic index have all been significantly associated with *BRCA1* abnormalities [88].

Morphologically, LGSC is not as diverse as HGSC. As described previously, they are usually associated with SBT and have low nuclear grade with a low mitotic index. They often have a micropapillary pattern and may show a distinctive pattern of invasion with small clusters of cells or papillary fronds embedded in stroma with retraction artifact, in addition to the more traditional pattern of destructive stromal invasion.

Endometrioid Carcinoma

Ovarian endometrioid carcinoma (OEC) is the second most common epithelial malignancy, representing approximately 10 % of cases [69]; however, it is the most common carcinoma to present at FIGO stage I, which usually portends a favorable outcome [89].

Many OECs arise in a background of endometriosis and endometrioid borderline tumor. Carcinoma is distinguished from borderline tumor if stromal invasion is identified, either destructive or expansile (confluent growth). Morphologically, OECs resemble those seen in the endometrium. Unlike serous carcinoma, OECs are usually WT1 negative [90, 91]. Like its endometrial counterpart, mutations in *CTNNB-1*, *PIK3CA*, and *PTEN* have been described [91–94]. Microsatellite instability has also been reported in OEC which may be part of the spectrum of Lynch syndrome [95].

Clear Cell Carcinoma

The reported incidence of ovarian clear cell carcinoma (OCCC) has ranged from 3.7 to 12.1 %, [96, 97] in North America, but in Japan, OCCC comprises up to 25 % of ovarian carcinomas [98]. Due to the frequent presence of clear cell change in other ovarian tumors, OCCC is often misdiagnosed. Accurate diagnosis is important in order to improve treatment options, however, as it is well documented that OCCC does not respond to the traditional platinum-based chemotherapy. Most OCCCs present at an early stage (FIGO stages I–II) which confers a favorable prognosis; however, at advanced stage, the prognosis is poor; accordingly all OCCCs are considered to be high grade [98, 99].

OCCC have frequent mutations in *PIK3CA* and *ARID1A* [100–103]. Unlike its serous counterpart, they typically do not show mutations in *Tp53* [100, 104]. Morphologically, OCCC usually arises from endometriosis [105], and occasionally a benign or borderline adenofibroma may be present as well. An oxyphilic variant, or cells with eosinophilic cytoplasm, has been reported. OCCC typically has a combination of growth patterns, including papillary, tubulocystic, and solid. Tumors with papillary architecture may show psammoma bodies; other common features include hyaline globules, an associated lymphoplasmacytic infiltrate, and a characteristic densely hyalinized stroma [106]. OCCCs are typically negative for estrogen and progesterone receptors. A recent immunohistochemical marker, HNF-1beta, has been found to be rather sensitive and specific in OCCC and may serve as a useful tool in its correct classification [107].

Mucinous Carcinoma

In the past, ovarian mucinous carcinomas were reported to be the second most common type of ovarian cancer, accounting for approximately 12 % of the cases [108]. More recently, however, it is clear that these tumors are much less common, comprising only approximately 3 % of primary ovarian carcinomas [69, 109]. This is due to the fact that in older studies, many tumors which were assumed to be primary, especially those at advanced stage, were actually metastases from extraovarian sites. It is now known that the vast majority of tumors that are associated with pseudomyxoma peritonei are of appendiceal origin [110, 111]. Other common mucinous carcinomas to metastasize to the ovary include other gastrointestinal and pancreatobiliary tumors. Factors favoring a metastatic tumor include bilaterality, small size (less than 10–13 cm), surface implants, and an infiltrative pattern of stromal invasion. Factors which favor a primary mucinous neoplasm include unilaterality, larger size, a smooth external surface, and a background mucinous borderline tumor or adenoma [112, 113]. Mucinous carcinomas which are indeed primary to the ovary are usually present at low stage and have a favorable clinical outcome.

Leiomyosarcoma

Leiomyosarcoma, although a rare tumor, is the most common pure sarcoma of the uterus and comprises approximately 1 % of all uterine malignancies [114]. They usually occur in peri- or postmenopausal women, with a mean age of approximately 50–55 years and are highly aggressive neoplasms [115].

Morphologically, the tumor is composed of intersecting fascicles of smooth muscle fibers and usually demonstrate the following malignant features: coagulative or tumor cell necrosis, a mitotic index of more than 10 per 10 high-power fields, and nuclear atypia [116]. Variants include epithelioid and myxoid leiomyosarcoma.

Cervix

Infection by human papilloma virus (HPV) may result in squamous or glandular neoplasia. Squamous cervical intraepithelial neoplasia (CIN) is graded based on the proliferation of immature squamous epithelium. CIN 1, 2, and 3 show neoplastic proliferations in the lower third, lower two-thirds, and entire thickness, respectively, of the squamous epithelium. CIN 1 often shows koilocytes which are wrinkled or "raisinoid" nuclei with perinuclear halos. CIN1 is a low-grade squamous intraepithelial lesion (LSIL), while CIN 2 and CIN3 are high-grade squamous intraepithelial lesions (HSIL), according to the Bethesda classification system. HSILs are caused only by high-risk HPV (HR-HPV), while LSILs may be caused either by low-risk HPV or HR-HPV [117]. Progression to invasive squamous cell carcinoma (SCC) is rare with LSIL (1 %), while HSIL shows higher rates of progression (12 %) [118]. Patients with cervical squamous dysplasia are also at increased risk for dysplasia elsewhere in the female genital tract, especially the vagina [119].

Studies have shown problems with the reproducibility in identifying and grading SILs [120]. Ancillary tests have been developed in order to improve accurate diagnosis. The gene *p16INK4a* is a tumor suppressor gene involved in the pathogenesis of cervical cancer, and its protein product p16 is overexpressed. This protein may be detected by immunohistochemistry with diffuse nuclear and cytoplasmic staining. Thus, in the appropriate setting, p16 is considered to be a surrogate marker for HR-HPV [121–123].

Invasive squamous cell carcinoma (SCC) of the cervix is the most common histologic subtype, accounting for approximately 80 % of the cases and occurs in women with a mean age of 55 years. Like SILs, it is directly related to infection with HPV. The carcinoma is "microinvasive" if the depth of invasion is ≤5 mm and the horizontal component is ≤7 mm. A number of subtypes of SCC have been described including keratinizing, basaloid, papillary, lymphoepithelioma-like, and squamotransitional, all of which have been shown to be associated with HPV [124–127].

Adenocarcinoma in situ (AIS) of the cervix is a glandular dysplasia, also etiologically related to HR-HPV infection and may coexist with SIL [128]. AIS can extend far into the endocervical canal and may be present multifocally more often than SIL [129]. Morphologically, AIS consists of columnar cells with hyperchromatic nuclei and typically shows numerous apical mitotic figures and apoptotic bodies. The subtypes include "usual" type in which mucin is usually present, intestinal type, which shows prominent goblet cells, and "endometrioid" type which has little or no mucin. The term "endometrioid" refers to the histologic appearance; these tumors do not show true endometrioid differentiation. The different subtypes all show infection with HPV and, besides the descriptive nature, have no additional clinical significance. Invasive endocervical adenocarcinoma consists of approximately 20 % of invasive cervical cancer and occurs in women with a mean age of approximately 50 years [130]. The criteria for microinvasive carcinoma are the same as those in SCC. Subtypes of invasive endocervical carcinoma are similar to those seen in AIS.

Vulva

Vulvar carcinoma is a relatively rare tumor, representing approximately 4 % of all cancers of the female genital tract. These tumors occur more frequently in older patients, as approximately two-thirds of cases occur in women over the age of 60 years [131]. There are two types of intraepithelial and invasive squamous neoplasia that affect the vulva, those associated with high-risk HPV and those which are associated with chronic inflammatory skin disorders. Regardless of the underlying lesion, the incidence of associated invasive cancer appears to increase with advanced age [132].

HPV-associated vulvar intraepithelial neoplasia (VIN) or usual VIN (uVIN) includes the warty or basaloid subtypes. This type of VIN usually occurs in younger women [131, 133]. Previously, VIN was graded similar to cervical intraepithelial neoplasia, but in 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) did away with the grading system and recommended that only VIN 2–3 be used for uVIN, due to problems of reproducibility [134–137]. Histologically, uVIN is a proliferation of squamous cells with decreased maturation, increased nuclear to cytoplasmic ratio, pleomorphism, and increased mitotic activity. Warty VIN may have a slightly papillary appearance, while basaloid VIN is usually flat. Approximately 3–6 % of women with treated uVIN eventually develop invasive squamous cell carcinoma (SCC), while up to 15 % of untreated lesions may progress [132, 138, 139]. The warty and basaloid types of SCC invade as sheets or nests of cells and bulbous or jagged nests, respectively. Keratinization may be present, but is usually not as extensive as that seen in non-HPV-associated SCC.

The other type of VIN is known as differentiated or simplex VIN (dVIN) which usually occurs in postmenopausal women and is associated with chronic

inflammatory skin disorders such as squamous hyperplasia and lichen sclerosus (LS); dVIN is typically not associated with HPV [140, 141]. It appears that mutations in the gene *Tp53* may play a role in the pathogenesis [142, 143]. Unlike the usual type of VIN, dVIN is very frequently associated with invasive SCC and has been reported to occur at some point in up to 85 % of cases [144]. Histologically, dVIN and its associated SCC have a different appearance than the warty and basaloid types. In dVIN, the cells appear "differentiated," which contrasts with the appearance of uVIN and also leads to the lesion being underrecognized. The epidermis is usually thickened and is composed of squamous cells with abundant eosinophilic cytoplasm, prominent intercellular bridges, and prominent nucleoli; these changes are more prominent in the basal layers. Invasive SCC arising in this setting is usually keratinizing and has a higher incidence of recurrence compared to HPV-associated SCC [145].

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Chapter 3
Geriatric Issues in Ovarian Cancer

Miriam Rodin

Abstract Older age is an independent prognostic indicator in ovarian cancer. Population data and case series over recent decades show poorer survival of older women regardless of stage. In Western countries, older women are less likely to receive the optimal surgery and standard chemotherapy established in clinical trials. However, in some series older women do well, and in some they do not tolerate standard of care if it is given. This chapter presents geriatric measures that may help in selecting which older women will be fit for standard surgical and medical therapy, geriatric management principles which modulate risk factors for adverse treatment effects, and direct supportive measures for older women with advanced disease.

Keywords Ovarian cancer • Elderly patients • Clinical oncology • Operative mortality • Chemotherapy

Introduction

Ovarian cancer is one in which stage at diagnosis and survival by stage is strongly influenced by age. Marked differences in tumor biology as, for example, in breast cancer or hematologic malignancies do not appear to explain the magnitude of the age disadvantage. Differences in the receipt of standard surgical and cytotoxic chemotherapy are evident in most European and American population-based data and in case series. The data on how well elderly women tolerate standard therapy is inconsistent and likely represents both referral and selection biases. Nonetheless,

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some do well. Some ideas are presented for how adopting geriatric management practices may improve treatment tolerance and potentially increase appropriate optimism in treating ovarian cancer in elderly women.

Incidence, Survival, and Disparities

Ovarian cancer has not proven to be one of the great success stories in clinical oncology, but there has been slow and steady progress with this stealthy disease. The median age at diagnosis is 63 years, so just under half of the affected women are Medicare age [1]. Incidence rates rise steadily with each decade of age, beginning in the perimenopausal decade between 45 and 54 (14.8–22.0/100,000) and continuing through age 85 (55.5/100,000) according to age- and race-adjusted SEER data through 2008 [1]. An apparent slight drop in incidence among women over 85 may well represent underdiagnosis bias on death certificates. Mortality among diagnosed cases rises steadily to 56.3/100,000 among women over 85 [1]. Viewed over 50 years, incidence rates for new ovarian cancers have leveled off and may even have declined slightly by about 1.6 % since the 1990s [1]. There is as yet no convincing explanation for this good news. There is another hopeful information in the numbers.

Looking at it from the cup half-full perspective of survival, the good news is a small but steady improvement in 5-year survival for all women with ovarian cancer, from 36.1 % in 1975–1977 to 43.6 % in 2001–2007 [1]. But this positive trend obscures several marked and growing disparities. For white women under age 65, survival has improved from 43.6 % in 1975–1977 to 56.9 % in 2001–2007, over 13 %. Survival for white women over 65 during the same period has improved by only 5.1 % and remains 30 % lower than the younger cohort. Among Black women, in 1975–1977, both older and younger women had 5-year survival rates about equal to white women. Instead of improving over time, survival rates have declined for both younger and older Black women. In 2001–2007 Black women's survival was 4 % worse in both age groups than they had been 30 years earlier [1].

Stage at diagnosis does not explain this disparity. Older Black women were only slightly more likely to be diagnosed at a more advanced stage, but stage for their survival is worse. Five-year survival for younger vs. older women of both races with localized disease was not markedly different in these most recent data [1]. Among women with advanced stage disease, 5-year survival was good: 79.9 % for younger women with regional disease compared with 55.6 % for older women. Women with distant metastasis fared poorly regardless of age, 35.6 % compared with 18.1 % 5-year survival, respectively, among young and old [1].

In summary we see a familiar epidemiologic picture in ovarian cancer. Incidence rises with age regardless of race. Absolute mortality is somewhat lower in Black women at all ages because their incidence rates are lower. However, improvements in 5-year survival have been essentially confined to younger white women. Late diagnosis among Black and elderly women does not appear to explain these

disparities. We wonder whether disparities in treatment may in part explain the observed differences in survivorship. The role of age in treatment decisions and treatment response will be the subject of the next discussion.

What Is the Standard of Care?

As shown in Table 3.1, ovarian cancer, specifically ovarian epithelial cancer, is the fifth leading cause of female death in the USA. Among the 11 most common malignancies, ovarian cancer ranks seventh in percent for 5-year survival (see Table 3.2) [2].

The most common histology over all is ovarian epithelial. Less common neoplasms of low malignant potential include serous and mucinous histologies which occur in elderly women about as often as in younger women. There are other uncommon histologies, including germ cell tumors, ovarian stromal tumors, Mullerian tumors, and carcinosarcomas. The survival statistics are different for each type of tumor [3]. Among older women, the epithelial histology is most common.

Table 3.1 Five most common sites of cancer mortality: U.S. older adults, 2009 [2]

Ages	60–79 years		>80 years	
Sex	Men	Women	Men	Women
Site	Lung	Lung	Lung	Lung
	Colon	Breast	Prostate	Colon
	Prostate	Colon	Colon	Breast
	Pancreas	Pancreas	Urinary bladder	Pancreas
	Esophagus	Ovary	Pancreas	NH lymphoma

Table 3.2 Median age at diagnosis and percent 5-year survival: U.S. women by age and cancer site, 2005–2009 [1]

		5-Year survival by age at diagnosis		
Site	Median age	<65	65–74	>75
All cancers	65	75.3	59.7	47.4
Breast	61	89.2	90.4	86.8
Urinary bladder	74	82.8	75.3	62.4
NH lymphoma	68	80.6	72.1	53.0
Colon	73	74.5	68.0	53.3
Ovary	*63*	*56.4*	*36.0*	*20.2*
Lung and bronchus	71	25.3	21.9	14.2
Esophagus	72	21.9	19.2	10.1
Pancreas	74	11.3	5.6	2.9

Guidelines have been published on-line [4]. They reflect the common scenario in which a tissue diagnosis has been made, but the clinical staging is unclear. The guideline is based on the consistent finding that optimal debulking surgery, that is, the complete removal (CR) of all abdominal reproductive organs, peritoneum, lymph nodes, and other visible tumor deposits whether primarily or after neoadjuvant chemotherapy offers the best survival outcomes. There is no other validated method to measure intraabdominal tumor mass except by laparotomy performed by an expert surgeon. Thus, optimal surgical treatment will often involve two surgical procedures, at least one of which is considered intermediate to high risk by standard stratification systems [4].

Cytoreductive Surgery and the Elderly Woman

There are four questions to ask. First, are older women equally or less likely to receive recommended surgery? If they do receive guideline driven surgery, do they achieve equivalent benefit for the risk? If they do not, do we know why age is associated with less definitive surgery? Should surgical risk for elderly women with ovarian cancer be assessed differently than for any other elective abdominal procedure?

Examining data from Olmstead County, 280 women over age 65 were more likely to have had increased risk for surgery based on low albumin [5]. This risk factor and age were independently associated with survival, but neither was independently associated with the extent of debulking surgery. Less extensive surgery was not associated with age in these data. The proportion of women with residual disease (RD) after debulking surgery was approximately the same among women aged 65–69 as among those aged 80 or more. Survival was independently predicted by age and extent of surgery. In other words, surgical risk and age were independent and neither was associated with how aggressively surgery was pursued. But older women and women who received more extensive surgery had lower survival. They noted over 1/3 of women over 75 experienced postoperative complications. The reasons for less than complete surgery were not reported, and the authors concluded that such studies are needed.

Other population-based studies similarly have observed higher 30-day postoperative mortality among women aged over 75 with advanced disease and comorbidities [6]. Using the SEER-Medicare data, Janda et al. [7] risk stratified women over 80, finding 0, 8, and 21 % postoperative mortality based on their algorithm of age, comorbidities, and organ function. An analysis of state level hospital discharge data found that age, race, low income, and treatment at a low-volume or non-teaching hospital were associated with less complete surgery [8]. These findings were confirmed by an American College of Surgeons multi-institution survey in which 1,115 women over 80 had poorer survival at any stage of disease and were less likely to receive complete (CR) surgery from a specialist surgeon and less adjuvant or neoadjuvant chemotherapy [9]. A meta-analysis of 23 acceptable quality reports

estimated very low overall postoperative mortality for cytoreductive surgery but higher mortality with older age and more extensive surgery [10].

The problem with this literature is that the majority of studies are retrospective; single institution studies with small numbers of women over 70 accumulated over ten or more years during which surgical and anesthesia practice may have changed. When the samples are large enough, as in the population-based studies, to compare young-older women 65–74 with women over 75 or 80, the women under the 75–80-year age barrier generally do well, but administrative data give only limited insight into surgical decision-making with very old women. The scatter among the small series is considerable, reflecting the quality of institutions' care, individual surgeons' risk tolerance, underlying referral bias for more or less fit women, and technical differences in the surgeries performed. Few studies give details about how patients and surgeons decided on whether, how, or when to proceed. The small series studies fall essentially into two groups. One group of studies reports few complications and improved overall survival (OS) for women over 70 who receive optimal debulking [11–17]. A second group of studies finds that older women are in poorer health when they present for surgery and have less definitive surgery [18–21]. However, all the studies agree that even over 80 years of age selected, healthy women can withstand optimal CR and benefit with improved OS [22–24].

Single institution case series and population studies confirm the observation that older women are less likely to receive definitive complete reductive surgery (CR). Although on the one hand it may seem obvious that older, sicker women would appropriately receive palliative rather than definitive surgery, it is very difficult to pull this out of the published data. The extent of multidisciplinary consultation between medical oncologists and surgeons is not always documented outside of multidisciplinary cancer centers where it is assumed [9]. In the Netherlands [20] reported improved survival with CR regardless of age, but that women over 70 were less likely to receive CR. A Greek series reported on 170 women over 70. Compared to women under 70, they had poorer performance status, less CR surgery, less chemotherapy, higher grade tumors, and poorer survival [18]. By contrast a series reported from a comprehensive cancer center indicated no such differences [23]. From these data the relative contributions of patient characteristics and treatment given to OS survival cannot be separated, and both appear to be strongly related to whether women are referred to specialized cancer care. Few studies examine the medical decision-making process, whether less aggressive surgery, or no surgery, is the doctors' recommendation or the patients' choice [25].

Once older women do undergo surgery, they are less likely to receive optimal debulking. From available data we cannot determine whether patient safety concerns for surgical complications explain surgeons' reluctance to undertake CR in older women or whether intraoperative factors cause surgeries to be scaled down. Single institution series are unlikely to answer these questions. Earle et al. [26] addressed whether the process of cancer surgery affected the outcomes. Using the Medicare-SEER files, 33 % of women over 65 were operated on by gyne-oncology surgeons, 45 % by general gynecologists, and 22 % by general surgeons. The outcome measures in median survival were clearly superior for both gynecological sur-

geons compared to general surgeons and not markedly different by oncology as a focus of practice. However, the association is confounded with the referral patterns that may direct healthier women to specialists and older, sicker women to more convenient local surgeons [25, 26]. Other process measures include how smoothly transitions between surgical and medical oncology care are accomplished. In at least one study, transition processes appear to be less standardized for older women [17]. Indeed one large single institution study limited the analysis only to patients who were successfully transitioned from CR to standard chemotherapy [22].

There is currently a great deal of interest in surgical risk stratification for older cancer patients and whether the standard preoperative schemes capture the appropriate measures of fitness. An important reason for questioning whether cardiac risk and general ASA risk stratification is generalizable to cancer surgery because the cancer patient does not have surgery to repair the problem and then go home. Cancer patients must be fit enough to withstand neoadjuvant chemotherapy and then surgery, or recover quickly enough from surgery to undergo adjuvant therapy. Perhaps the bar is higher. One forum in which these concerns have been studied and discussed is the PACE (Preoperative Assessment of Cancer surgery in the Elderly project) [27]. Studies are emerging in the literature in which geriatric measures such as cognitive screening, functional assessment of ADL and IADL performance, depression screening, and nutritional status improve the predictive value of "standard" preoperative indicators such as albumin, GFR, and comorbidity scores [27–29]. In single institution studies there are some suggestions that these measures stand up to statistical adjustment, but how they might affect the process of surgical care specifically for ovarian cancer has yet to be described and would be a welcome addition to the literature.

Key Points
Older women with ovarian cancer:
1. Experience lower OS regardless of stage of OC.
2. Are less likely to receive definitive CR surgery.
3. Who undergo definitive CR surgery have improved OS compared to those who do not.
4. In unselected populations surgical complications are higher among older women.
5. Research is needed to determine whether geriatric measures improve operative risk stratification above that of existing risk stratification tools.

Chemotherapy and the Older Woman with Ovarian Cancer

Overall survival for women with ovarian cancer has improved in recent decades largely due to the introduction of platinum and taxane chemotherapy [30]. The influential clinical trials have generally excluded elderly women [31]. The reasons

are complex including patient preferences and physician reluctance [32]. A review of available studies examines the extent to which older women are likely to receive standard therapy as initial therapy and on reports of the effectiveness of first-line chemotherapy compared to less treatment. Finally, the studies will be reviewed for predictors of treatment toxicity, the presumed most common cause of treatment reduction and abandonment. For reference, shows the current NCCN Guideline for chemotherapy in ovarian cancer [4].

The SEER-Medicare data set for 1992–1996 for Stage II [33] and Stages III–IV [34] OC showed about 50 % of women received recommended platinum treatments. Age was an independent predictor for not receiving platinum. Platinum treatment produced a small, several-month benefit in 5-year survival among women who completed all or most cycles regardless of age. The OVAR-3 Phase III trial from the same period using platinum and taxane combination therapy enrolled 103 women over age 70. The EORTC-QoL was included in baseline and continuing assessments. Older women did not differ in any significant way from younger women in terms of disease characteristics, EORTC-QoL subscale scores, or non-hematological toxicities. The older women however had less complete CR going into the trial, that is, more RD before chemotherapy, and a higher proportion with ECOG-PS 1–2 as compared with ECOG-PS = 0, no performance limitations among the younger women. 26 % of the older women were withdrawn early due to toxicity, mainly febrile neutropenia and fatigue [35].

Intraperitoneal therapy (IP) was introduced as a way to deliver drug directly to the tumor while limiting whole body toxicity from IV drug. Recent data from a small series showed that 23 women over 70 were less likely to complete a combined IV/IP protocol than younger women even though there was no difference in the total IV dose delivered. The investigators had no explanation [36]. However, a GOG study, which enrolled women over 60 with PS <2 included 27 women over 70, reported very high levels of abdominal discomfort and poorer function among IP patients regardless of age, and only 50 % of the experimental patients could complete the study [37].

Standard geriatric measures were gathered in a French study which included 83 women over age 70. Only 21 % had had optimal CR surgery, of this select group, 72 % tolerated all planned 6 cycles of platinum and cyclophosphamide. That is, only 15 % of the older women enrolled in this trial completed recommended combined treatment. We do not know if the same factors which predicted less complete CR also predicted chemotoxicity. Severe toxicity was predicted by preoperative depression, ADL dependence, and PS >0. OS was associated with disease stage, depression, and >6 prescribed medications [38]. A second GINECO study enrolled 158 Frenchwomen over 70. Nearly 1/3 was IADL dependent in at least one domain, and 15 % had lower than normal cognitive screening scores. In this trial depression and anxiety were stronger predictors of OS than the chemotherapy regimen [39]. Again, relatively few of the women in a small cohort had measureable geriatric impairments, so the statistical power of any individual indicator to detect vulnerability is low.

At each step of multidisciplinary cancer treatment, the published research shows that age plays a critical role in the receipt of optimal therapy. One series of 131

women over age 70 included 41 over age 80. Surgical debulking was complete for 80 % of the women under 80 but for only 25 % of those over 80. The women over 80 were equally as likely to complete platinum treatment but half as likely to complete combined platinum-taxane treatment. Both age groups were about equally likely to experience dose reductions and dose delays. With such small numbers, only the difference in surgery by age was statistically significant [40]. In another, similar series, investigators specifically tried to identify toxicities associated with treatment termination. Women over 80 were less likely to get combination therapy and even then were only half as likely to complete it with no particular differences in self-reported toxicity [41]. The toxicity measures were standardized, and these measures typically inquire about specific adverse events, such as neutropenia and symptoms, such as neuropathic pain. It may be that despite the theoretical likelihood that older women will experience more neuropathy, for example, the actual event is the cumulative toll of several toxicities.

Oncologists have many choices within the platinum-taxane paradigm. Drug can be delivered before surgery to reduce the volume of tumor to be removed, or it can be delivered after surgery to treat visible or microscopic RD [42]. Dosing can be done IV or with a combination of IP and IV to reduce toxicity. If necessary, doses can be reduced or spaced out in time, but treatment effectiveness is strongly associated with tolerating the full dose of combination therapy delivered on schedule. If necessary, single agent treatment can be given. How age affects these decisions has been studied [44–46]. In one surgical series, the timing of chemotherapy did not affect disease or survival outcomes nor was there any difference in dose delivered to women over and under age 80 [15].

Most chemotherapy for OC is given as outpatient infusions. Unfortunately delayed toxicity may lead to unplanned hospitalizations for which the elderly are at increased risk [43]. Examination of SEER-Medicare data sought to identify whether there were any differences among the various OC regimens for this level of severe toxicity. The chemotherapy patterns identified were platinum alone, platinum-taxane combination therapy, other non-platinum therapy, and no chemotherapy. The highest rates of hospitalization were among those receiving non-platinum, that is, nonstandard therapy. Comorbidity and age were associated with infections and cardiovascular hospitalizations, but age was not associated with gastrointestinal or hematological toxicity in these population data [43]. This study cannot determine to what degree less fit women were given less than standard chemotherapy in an unsuccessful attempt to reduce toxicity, or whether nonstandard chemotherapy was indicative of system and provider characteristics such as nonurban residence, low-volume practice, or absence of community support resources for the elderly. These system and provider factors have been shown to predict cardiovascular outcomes, and it would not be surprising that similar systems characteristics affect oncology outcomes.

Current practice favors neoadjuvant to adjuvant chemotherapy after complete CR surgery. Current practice also favors IP with IV infusion of 6 cycles of platinum-taxane combined therapy. Evaluation of surgical outcomes is confounded by the type of chemotherapy delivered, and evaluation of chemotherapeutic regimens must make adjustments for the surgical results [46]. In order to evaluate therapy then, it

takes a number studies, none individually definitive, in order to triangulate an optimal approach. Thus far, clinical trial evidence supports the idea that fit women, and some over age 80, derive benefit from standard therapy without unacceptable toxicity. More often, older women are not offered standard therapy or do not tolerate it.

Where women are treated appears to be a strong predictor of treatment given. Age, comorbidities, and PS are routinely recorded, and so they are easier to study, but new studies indicate that many different geriatric measures can predict treatment intolerance [41]. Examples include the inclusion of standardized geriatric scores in the protocols of the CALGB breast cancer trials group. At least in the setting of dedicated cancer centers, it was feasible to collect multiple geriatric measures of fitness. Recently, these data were used to create a multifactorial algorithm that included traditional physiologic measures, comorbidities, tumor characteristics, and many geriatric measures [47]. The algorithm performed well in predicting which women would go on to experience grade 3–5 toxicities. As a proof of concept then, this algorithm or others incorporating geriatric measures might more accurately identify women at high vs. low risk for treatment-limiting toxicities in ovarian cancer as well. Having such a tool would set the stage for interventions to improve treatment tolerance and thus outcomes for older women with OC.

Key Points

Older women with ovarian cancer:

1. Achieve a relative improvement in OS from receiving standard combined chemotherapy.
2. Women over age 80 appear less able to tolerate standard protocols of chemotherapy.
3. Neoadjuvant and adjuvant chemotherapy appear to be equally efficacious in the elderly.
4. IP chemotherapy does not appear to be well tolerated by the elderly.
5. Chemotoxicities in the elderly do not appear to be qualitatively different; however, reduced renal function, neutropenic fever, and bone marrow suppression are more likely.
6. Toxicity is associated with age, comorbidity, polypharmacy, decreased cognition, depression, anxiety, ADL, IADL, reduced CrCl, low albumin, and poorer ECOG-PS.

Contradictions and Questions

Reviewing the chemotherapy and the surgical literature leads us to ask whether elderly women with ovarian cancer who would benefit from standard therapy are being systematically undertreated. Equally we should ask whether women who receive less than standard treatment have been appropriately identified as being unlikely to tolerate standard treatment. It has been reported that women who are not

optimally debulked also are less likely to receive any or standard chemotherapy. Surgical oncologists and medical oncologists seem to be identifying the same patients, or there is systematic migration of the fit patients to the highest quality centers. The published literature does not directly answer these follow-up questions. Perhaps promulgating a standard assessment that is sufficiently robust to identify women who regardless of age are physiologically fit to withstand standard therapy and linking this to more integrated cancer treatment would address the questions about age-related disparity or age-related fitness. Are there reliable ways to lower the risks of surgery and chemotherapy to increase the pool of fit elderly women? If so, are these individual interventions, changes to practice, or systems interventions? Although there are presently no trials specifically designed for ovarian cancer patients, there are studies of cancer patients that report results of geriatric multidisciplinary interventions [48].

Geriatrics in Ovarian Cancer Care

There is a strong referral bias for more fit elderly in cancer clinical samples [7], and clinical trials have usually excluded or not been able to recruit older participants for many practical reasons including transportation. Extrapolating from clinical trials to clinical practice is thus somewhat subjective. Analyses of population treatment data through the linked SEER-Medicare database suggest that frail elderly are unlikely to be referred to specialty cancer centers from community practices. The geriatric concept of frailty describes a phenotype of slowness, weakness, subjective exhaustion, and slow weight loss [49]. It is distinct from the assessment of functional status which seeks to inventory exactly what an elderly woman can and cannot do to take care of herself while enduring cancer treatment. The geriatric approach includes individual interventions to improve performance and environmental interventions to lower the demand to what the patient can do. Thus, frailty alone is not a complete picture of what is possible with an elderly patient.

Balducci has adapted the consensus frailty phenotype as defined by Fried and colleagues to making decisions about cancer therapy [50]. He also includes ADL and IADL disability, non-cancer severe comorbidity, and presence of "geriatric syndromes." Geriatric syndromes are easily recognized [51]. Most lists include cognitive impairment, falls, delirium, and preexisting severe weakness as probably excluding an older cancer patient from receiving full dose or, depending on the situation, any chemotherapy [50]. The frailty model explains in terms of cancer-related life expectancy why the allostatic load of surgical, disease, and chemotherapy stressors can overwhelm the homeostatic reserve of apparently well elderly and, even in the absence of specific organ toxicities, result in geriatric syndromes and physiologic collapse. There appears to be a tacit agreement in community practice not to subject obviously frail and otherwise incapacitated elderly to toxic therapy. Primary frailty and terminal disease are recognizable in a common sense way. Geriatricians on the other hand are interested in identifying markers of impending disability that

can be remediated. Geriatricians are also interested in early risk factors for decline and assessing the likely impact on recovery from stress of illness. There are two adverse scenarios with respect to recognition of vulnerability. In the first, an elderly patient who might benefit from treatment by having an extended period of symptom-free survival is not treated due to concern for toxicity. In the second instance, for a patients who will likely die from the cancer whether or not it is treated, we should consider whether the risks of the treatment will shorten survival or impair the quality of remaining time with friends and family.

Functional status as used by geriatricians refers to activities of daily living (ADL), the ability to care for oneself at home, and instrumental ADL (IADL), the ability to live alone and manage one's own household affairs. Very frail, cognitively intact women can often perform these tasks for years, slowly and perhaps not up to their own expectations, but well enough to keep "help" out of the house. This is different from the oncologists' construct of performance status which has more to do with grading activity levels from fully physically active outside the home to bedbound. Using a summary Karnofsky Performance Score or Eastern Cooperative Oncology Group Performance Score (ECOG-PS), oncologists make very accurate predictions about survival and ability to tolerate further toxic therapies. These are rapid, intuitive, and can be serially performed over the course of treatment. Summary KPS or ECOG scores describe present status but do not predict risk for future functional decline, and they fail to identify the so-called vulnerable elderly who look good but are high risk for catastrophic decline [52]. The summary scores do not identify specific functional disabilities that might be reversible, nor do they suggest how that might be done. These scores miss important nonphysical performance measures such as cognition, fatigue, anorexia, mood, and social support. If not specifically asked, this useful information is missing. Furthermore, the hallmark of aging is loss of reserve, the ability to meet increased demand [53]. That may refer to a specific organ including pulmonary, renal, and cardiac response to fever, anemia, and toxins. Delirium is essentially brain failure as a result of similar stressors.

A short functionally based screening such as the ACOVE VES-13 has been proposed as a quick way to select apparently fit elderly cancer patients who may be at risk for functional failure for further evaluation [55, 56]. A more extensive battery of screening tools has been shown to be quite feasible to perform in the outpatient oncology setting [57]. Several studies have suggested that abbreviated geriatric measures of function provide actionable data [58, 59]. For example, a fall risk audit for hospitalized cancer patients reported profiles consistent with those in the geriatrics fall literature [60]. An outpatient survey identified a high prevalence of previously underreported falls among prostate cancer patients on hormonal deprivation therapy [61]. Fall risk should be routinely assessed among elderly cancer patients. Ovarian cancer patients in particular are at risk due to the double challenge of abdominal surgery and chemotherapy on cognition, nutrition, gait and balance, mood, sleep, elimination, and pain.

Functional status has been measured a number of different ways using different scales and observational data points. There are many, many validated and widely used rating scales for each of several domains important to determining the ability

of an elderly ovarian cancer patient to live alone or with only limited support [62]. The specific tool is not in my opinion critical, but the sampling of the several domains that contribute to functional independence is critical. And the use of standardized scales improves communication between team members and consultants. As summarized by the NCCN expert panel, key assessments include scores for physical, psychological, and cognitive impairment and instrumental social supports and environmental demand [48]. The various domains sampled in a CGA and the specific tools were developed for determining rehabilitation needs and need for external supports for elderly people. They will not calculate chemotherapy doses. They will identify patients who if they do develop toxicities are at substantial risk of unplanned hospitalization or catastrophic events including injurious falls. Awareness of the likelihood of injurious falls should guide clinical decisions about full or reduced dose regimens.

There has been increasing interest in identifying tools with particularly good performance with the elderly cancer patient. Any battery must meet the criteria of being acceptable to oncology providers, and easily scored and interpreted. Assessments should lead to actions including other medical referrals, rehabilitation, social and home care services, and polypharmacy review. Oncologists should approach geriatric patients with preemptive supportive measures including GCF, nutrition, and control of specific toxicities including mucositis, bowel function, nausea, and painful neuropathy. For an elderly patient with arthritis and a slow gait, the accumulation of several low-grade toxicities even if none is rated as 4 or 5 can lead to the development of geriatric syndromes, such as delirium, incontinence and falls, and unplanned hospitalizations.

The concept of limited homeostatic reserve explains this “unraveling.” We can measure cardiac output and renal function, single organ functions. The geriatric concept of homeostatic reserve also applies to the integrated function of organs needed to perform the activities of daily living safely and consistently. Normally, an elderly woman has the cardiac function to go about her daily activities. In the presence of fever and anemia, she will go into congestive failure. An elderly woman may be able to shop with her daughter and fix her own meals. If she is feeling queasy and fatigued, she may not eat the food that is brought in and a little diarrhea will lead to dehydration. If she is cognitively intact but she is unable to sleep and is taking several prns for symptoms, she might develop a low-grade delirium, become confused about time of day, and forget important medications and meals. Polypharmacy taxes the memory, and the sheer number of pills increases the likelihood of nonspecific drug interactions that cloud the sensorium and disrupt appetite and sleep.

Because of this, an expert panel of the NCCN developed guidelines for assessing elderly cancer patients; similar considerations were addressed by the European collaboration (EORTC) [63]. The NCCN Clinical Practice Guidelines offer a decision tree based on their assessment of the strength of the evidence for routine use of geriatric assessments in a variety of tumor types. The expert panel grades the evidence 2A, that is, acceptable quality with no dissent among the panel members [48]. A significant limitation at this time is that we have few trials or demonstration

projects showing the impact of applying the methods. It is hoped that this will soon be remediated.

Step 1 is to determine whether the patient's pre-cancer life expectancy would have been long enough to benefit from treatment. For example, with advanced ovarian cancer (based on stage and malignant potential), what is the predicted best outcome of treatment?

This is actually the most difficult question. Data on median survival has been previously reviewed, and we see that published survival figures are based on clinical trials with few elderly women or small series collected over a decade in single institutions or from population databases such as the SEER-Medicare files from which few direct measures of functional status are available [64, 65]. In other words, in a patient with similar disease and similar comorbidities and similar functional limitations who receives standard therapy, how likely is she to live another 2 years? Another 5 years? Oncologists routinely use their optimism and experience to match the patient with the pattern. Walter and Covinsky published a now well-known graph showing median survival by age and quartile of health as a guideline [66]. It remains useful but the underlying data and assumptions should be interpreted for individuals as probabilistic rather than prognostic. Survival was calculated using historical cohorts and comorbidity estimated from administrative data. It remains an extremely useful heuristic tool. Balducci suggests that oncologists make treatment decisions based on their estimate of the best probable, not possible, outcome based on the stage/grade of disease in 3 prognostic groups: patients with estimated RLE >5 years if they receive best treatment with best response, patients who may live 2–5 years with treatment, and those will live <2 years with or without treatment such as patients who are already nursing home-confined [50]. He thus recommends staging the aging as carefully as the malignancy as shown in Table 3.3.

Example: An 82-year-old woman is diagnosed by CT-guided biopsy with epithelial ovarian cancer. Radiologically it appears to be Stage IIIb. She takes medications for HTN and coronary artery disease although she has no clinical history of infarction or stroke. Her renal function is mildly impaired, with eGFR 48 mg/ml/min.

Her cardiac risk factors for noncardiac surgery are age over 75 and HTN. The surgeon would also take into account chronic renal insufficiency. She is at slightly

Table 3.3 Staging the aging [50]

Stage of aging	Probable RLE (years)	Treatment approach
Fit	>5	Standard therapy NCCN guidelines [4]
Vulnerable	2–5	Comprehensive assessment reveals physiological, functional, psychological, and social risk factors. Multidisciplinary interventions for a pretreatment tune-up include rationalizing polypharmacy, optimizing cardiovascular and pulmonary condition, optimizing nutritional status, analysis of home supports and instrumental needs, and gentle conditioning [67]
Frail	<2	Palliation based on symptoms

increased risk for cardiac events in an intermediate risk noncardiac surgery. Her anesthesia risk also includes renal impairment. Again her risk is intermediate and not unacceptably high. Her 30-day surgical mortality risk in a high volume center should be <3 % [7]. Using population estimates of remaining life expectancy (RLE) according to overall health status [66], before the diagnosis of ovarian cancer, she would be in average health, median RLE of about 6 years. After the diagnosis she would be classified as poor health, and median RLE would be around 3.5 years. Based on these tools, she would benefit from standard treatment.

There are several key aspects of geriatric assessment that are particularly salient for surgical cancer treatment. In addition to standard preoperative risk stratification, preoperative assessments should be able to anticipate whether recuperation at home or at a long-term care facility (LTCF) will be needed. Will she be ambulatory and performing ADLs within a week of surgery? Will she have complex wound care needs? Has the decision been made about placing an IP catheter? Excellent surgical and anesthesia technique reduce operating time, blood loss, and infection. Excellent postoperative care includes strict nursing protocols for mobilization, bowel, nutrition, and pain management. Nonetheless, a major postoperative complication such as delirium has significant adverse impact on surgical outcomes in oncology and often can be predicted by CGA. Delirium is very common on oncology floors, and it is important to recognize it and manage it appropriately [68–70].

Delirium guidelines for hospital inpatients are now available. Environmental adjustments to hospital routines should promote normal day-night sleep-wake entrainment and mobilization, and nutritional supplementation is feasible [54]. When the example patient is postoperative, vitals and medications should be restricted to only those that are absolutely necessary during the night shift. Unless there is hemodynamic instability, it is not necessary to obtain blood pressures at 2 a.m. nor should blood draws be timed at 5 a.m. per hospital routine. Labs drawn at 7 or 8 will be resulted during the day shift. Patients should be encouraged to get out of their rooms as early as the first postoperative day if they are able. Physical and occupational therapy evaluations should not be delayed. Appetite is a key vital sign. There is a delicate balance between appropriate pain management and over sedation that should be re-evaluated with physician, nursing, and pharmacy input.

The most consistent toxicities for the elderly are platinum renal toxicity and taxane neuro- and marrow toxicity [44–46]. Several chemotherapy studies have included elderly women. Median survival for women over 70 who completed standard treatment was 33 months in one series [71]. Women over 70 had about an 18 % 5-year survival in another series [72]. In any series, there are long-term survivors. Optimally, median survival data should be presented by stratum of age and stratum of age by health status but these data not readily available for ovarian cancer for women over 70. If the data do not calculate survival by age, I would suggest that overall median survival is an appropriate measure to extrapolate to elderly women with no severe risk factors. Study results expressed as hazard ratios and percentage difference in 1 and 5-year survival are difficult to translate into life expectancy. Returning to the example, available data suggest that if optimally treated this patient could have 3 years survival. This agrees with general population estimates [66] and

at least one published series [71] and places her in the vulnerable group according the Balducci stratification [50]. Thus, she should have a comprehensive geriatric assessment during the course of her treatment planning.

Step 2: Geriatric Assessment. The NCCN Guidelines for Senior Oncology list functional risk factors and suggest alternative screening tools. The purpose of these assessments is to identify risk factors that can be modified or compensated for. If no risk factors are identified, the recommendation is to proceed to standard therapy.

The example patient is living alone in a senior citizen building. Also she does not use an assistive device; her gait is slow, <1 m/s on the timed-up-and-go; and she wobbled briefly rising from the examining table. Her daughter who lives 15 miles away takes her shopping every Saturday and calls every evening. When asked, she denies previous falls but admits to reaching the wall the steady herself if she gets up quickly. Her ECOG-PS = 1. The church van picks her up every Sunday for services and supper.

Step 3: Risk factors are identified and addressed:

1. Fixable: She will need transportation. Social work can apply for senior transportation if she lives within the transportation zone. If she is out of zone, she may have to continue treatment elsewhere.
2. Not fixable: She does not have absolute contraindications to standard platinum-taxane therapy: advanced dementia, nursing home residence, or renal insufficiency.
3. Remediable: Multidisciplinary staffing to determine how risk factors will respond to targeted individual interventions.
   The patient's blood pressure medications are making her orthostatic. Her blood pressure regimen is changed. She has a PT/OT evaluation that focuses on household task performance and gentle conditioning.
4. Modifications of the patient's environment during the treatment period, by reducing environmental demand and constructing a safety net: Delirium protocols for postoperative patients, short stay in a rehabilitation facility, home health services, and electronic fall monitors [73].

The example patient did not want to move in with her daughter. Homemaker services were initiated to reduce housekeeping burdens, a visiting nurse was instituted, and physical therapy was started. This provided someone in the apartment 4 days a week. The building manager was advised of her health status so the doorman could keep an eye out for changes in her routine. The patient was given a fall monitor. Hospital-based transportation took her to and from appointments.

The resources required to screen for vulnerability are modest, as shown by several studies [55, 56, 58]. However once vulnerability is suspected, a comprehensive assessment is more time consuming than small oncology practices can undertake. A multidisciplinary approach to older women with advanced ovarian cancer and one or more risk factors requires ready access to and a willingness to engage with rehabilitation, social work, consulting pharmacists, psychiatry and nutritionists. We have few models for how to do this specifically for older cancer patients. Most cancer centers have these ancillary services but they may not be

specialized in the elderly. We do not know the extent to which local oncology providers are aware of or use ancillary geriatric resources. There are few well-described programs in geriatric oncology and fewer outcome studies on which to base specific recommendations.

The geriatric literature is consistent in showing that performing assessments by themselves has no benefit. However, implementation of recommendations especially when part of an organized system of transitions has shown benefit [74]. A clinical trial of continuity of care randomized several thousand geriatric veterans to inpatient geriatric assessment and intervention with follow-up in outpatient GEMs and home-based care [75]. Post hoc subgroup analysis revealed that older veterans with a cancer diagnosis benefitted the most from an integrated continuum of geriatric care. Although they did not live longer, quality of life measures were statistically significantly improved [76]. So mainstreaming elderly cancer patients through a continuum of geriatric care had a measureable benefit.

The patient in the example we are discussing has several medical risk factors, notably renal function, individual risk including gait and balance problems, and safety net risks including living alone and relying on a distant support person. Each risk factor requires a different discipline to be involved and to be serially reassessing the patient's status. The goal is to prevent unplanned hospitalizations that result in permanent nursing home placement. This is different from a planned short SNF stay following surgery. Shopping for acceptable facilities should begin early. It is upsetting to patients and families to be handed these decisions on the day of discharge. Precipitous discharges are also fraught with risks associated with transitions of care. The transitions should be carefully orchestrated with specific instructions regarding diagnosis, plan for further treatment, nutritional support, mobilization, and wound care [77]. Cancer surgery outcomes for the elderly are improved by early mobilization and early nutritional support [78].

Restaging the Aging: Use Structured Methods Serially to Assess the Functional Impact of Treatment

Just as the oncology team restages the tumor after a trial of therapy, it is necessary as well to restage the aging over the course of therapy. The tumor board coordinates disease-oriented care plans and should also serially restage the aging. The short-term impact of chemotherapy on functional capacity should be assessed proactively. Is the patient at risk for delirium? Did the patient experience postoperative delirium? Has the patient's baseline cognitive function and decisional capacity been documented in a standard format? [79] This bears directly on the patient's ability to self-manage over the typical course of 6 cycles of chemotherapy. An elderly person living alone who manages quite well in their usual state of health is judged fit for chemotherapy by having an ECOG-PS of 2 or less. They are likely to do well in the infusion suite but develop delayed toxicities and become ill a week later. An extensive summary of the evidence for the NCCN guidelines summarized above has been

prepared by the International Society for Geriatric Oncology (SIOG) based in Geneva [80]. This document identifies a number of validated standardized assessment tools. It remains to be shown however which assessments are most sensitive and specific for anticipating clinically significant adverse events.

Part of treatment planning is to establish the patient's goals for ovarian cancer treatment. Neither SIOG nor NCCN guidelines suggest specific ways to periodically revisit patient goals and expectations over the course of treatment. Older patients are open to discussing their prognosis and making plans for their own care ahead of the need. Advance directives should be part of the initial and ongoing conversation. In one study over 65 % oncologists report that they do not routinely discuss prognosis, advance directives, or end-of-life until the patient is within days to weeks of death. This contrasts with younger and non-oncology physicians who report having these discussions before the need [81]. There is an interesting correspondence with patient preference in this study. A similar >60 % of cancer patients preferred not to have these discussions with their oncologists; rather, they expressed no unwillingness to discuss advance directives and end-of-life with hospital doctors, that means typically hospitalists and house staff [81]. However, the conversation is broached it should be documented.

Supportive Management During Cancer Treatment Is Just Good Geriatric Care

Supportive oncology is the management of symptoms due to cancer and to the effects of cancer treatment with the goal of maintaining patients' quality of life. All major cancer centers have invested in supportive care because it offers the best chance for patients to be able to complete treatment. Often palliative care is thought of as end-of-life care, but aggressive supportive care uses essentially the same modalities whether in parallel with or when efforts at disease management are no longer desired.

Four randomized clinical trials have compared palliative care delivered with cancer treatment to usual care with optional palliative referral as determined by the treating physician. 322 patients with advanced cancer in rural Vermont, mean age about 65 years, were randomized to monthly telephone follow-up by nurses. At the end of the study, quality of life and mood scores were higher in the intervention group, but there was no difference in symptom intensity or hospital days [82]. Two additional trials also showed improvements in self-reported quality of life among patients randomized to palliative care along with usual cancer care, but the differences were not statistically significant [83, 84]. Similarly a Norwegian trial was suggestive but inconclusive [85]. Part of the weakness of such designs is that inherently the specific interventions are individualized, not standardized, and most of the studies included several cancer types with different symptom patterns. In other words, the inherent methodological limitations of the randomized clinical trial are similar in palliative care and in geriatric interventions [86]. The interventions are

inherently not standardized. There is no "dose" of palliative or geriatric care. The spectrum of disease, the combinations of symptoms and disabilities, cannot be totally standardized the way tumors can be graded and staged. It is therefore very impressive that positive results are obtained when studies are powered to perform.

A recent study had the methodological advantage of strictly staged patients all receiving care at the same cancer center. 151 advanced stage non-small cell lung cancer outpatients were randomized to concurrent palliative care or usual care. The mean age was about 65 years. Mean change scores on symptom scales and quality of life scales favored the experimental group, but the differences were not statistically significant. However, the experimental group survived on average 2.7 months (30 %) longer and used fewer hospital days at the end-of-life [87]. Similarly designed studies of supportive and geriatric interventions for ovarian cancer patients may reproduce the finding of less hospitalization, less cost, and improved subjective quality of life. If survival is longer as well, this is hard evidence.

In the palliative care and supportive oncology literature, it is clear that the burden of symptoms as well as the stage of disease drive functional status. Targeting the most troublesome symptoms should improve functional status. In most studies the numbers are small, patients are not particularly old, and a variety of tumor types and stages are included. Furthermore, the definition of quality of life is rather broad and includes everything from psychological well-being, social connection, energy levels, spiritual peace, functional status, and freedom from symptoms. One review enumerated over 100 different definitions of quality of life [88]. It is easier to focus on studies of specific symptoms [89], but new designs will be needed to understand how complex interventions such as geriatric team management affect the balance of clusters of symptoms and to see if and how these interventions improve ovarian cancer treatment outcomes for elderly women.

Key Points

1. Geriatric tools and best oncology evidence should be combined to classify ovarian cancer patients as fit, vulnerable, or frail.
2. Vulnerabilities should be addressed by multidisciplinary interventions and serially reassessed throughout treatment.
3. Geriatric assessments should be directed to anticipating toxicities.
4. Concurrent supportive care is good geriatric care.
5. New research designs are needed to evaluate complex multidisciplinary interventions.

Conclusions

Disparities in treatment and disparities in outcomes for older women with ovarian cancer have been inadequately explained. A systematic approach including concurrent medical and surgical preoperative consultation should thoroughly evaluate

patients' fitness for combined surgical and chemotherapy. These evaluations should systematically inventory comorbidity and also functional and instrumental assets and deficits. So before surgery both surgical risk and chemotoxicity risk need to be assessed. A systematic approach must include risk stratifying the patient based on standard risks, seeing if that can be improved by medically optimizing comorbidities and by geriatric interventions to optimize functional status. The best way to do this is within the clinical trials groups, opening Phase II and III trials to risk stratified vulnerable women. I agree with Balducci that truly frail women, women confined to nursing homes or requiring aid and attendance in their homes, cannot be enrolled in trials for a number of practical and ethical reasons. We can obtain a set of standardized measures to broaden patient eligibility and representativeness. Clinical trials groups are a platform to disseminate best patient selection practices. The extent to which disease characteristics and treatment are standardized, evaluation of the impact of geriatric and supportive interventions will be improved. The immense influence of the trial groups on community practice can then be harnessed to promote appropriate care for older women. We need to identify and document functional measures for use in community practice recognizing that non-CCC providers can deliver this kind of care. Patient education should encourage older women to seek ovarian cancer care at centers that have high volume, specialist care, and multidisciplinary senior care even if the latter is not necessarily housed within the cancer practice.

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Chapter 4
Geriatric Assessment for the Oncologist

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Abstract The incidence of cancer, particularly gynecologic malignancy, increases with advanced age. The geriatric population is a heterogeneous group, and a patient's chronologic age does not always reflect their overall health status. Therefore, oncologists need to be adept at assessing physiologic and functional capacity in older patients. The comprehensive geriatric assessment is the gold standard for evaluation of the geriatric patient. The various components of the CGA have been shown to influence cancer-related therapy in a multitude of ways, as previously discussed. The combined data from the CGA can be used to stratify patients into risk categories to better predict their tolerance to treatment and risk for chemotherapy toxicity. However, the CGA is a comprehensive tool requiring significant time and training to perform. Therefore, a variety of screening tools have been developed which may be useful in the general oncology practice setting to identify patients that may benefit from further testing and intervention. Further research is still needed to evaluate whether these screening tools can predict cancer-related outcomes in older patients.

Keywords Geriatric assessment • Gynecologic cancers • Function • Disability

Introduction

Advanced age is an important risk factor for cancer incidence [1]. In concordance with this, elderly women represent a significant percentage of patients with gynecologic malignancy [2]. The geriatric population is a heterogeneous group with various levels of functional status at a given age. When considering prognosis and treatment options in this population, decisions should be based more on "functional"

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age versus chronologic age. Therefore, it is necessary for oncologists to be adept at efficiently and accurately estimating physiologic and functional capacity in older patients.

Older patients commonly have health status issues that can affect cancer outcomes. For example, up to 50 % of cancer patients require assistance with independent activities of daily living, which measure the ability for an older person to complete tasks necessary to live independently in the community [3]. Additionally, one quarter of patients have some form of cognitive impairment which can impact cancer-related outcomes [4]. The comprehensive geriatric assessment (CGA) is an evaluation tool utilized by geriatricians to assess a patient's physical, mental, and psychosocial well-being. The comprehensive geriatric assessment includes functional status, comorbidities, cognition, social support system, nutrition, and medication review. In community-dwelling older adults, impairments in these domains predict morbidity and mortality. Studies of geriatric oncology patients reveal that measures within geriatric assessment can predict postoperative morbidity, toxicity of chemotherapy, and mortality [3]. Results from the comprehensive geriatric assessment can aid oncologists in predicting outcomes and selecting appropriate treatment regimens and interventions for their patients. However, it is a comprehensive tool requiring significant time and manpower to adequately perform and may not be practical for the general oncologist in the outpatient setting. Therefore, a variety of screening tools have been developed which aim to assess patients for potential areas of impairment where further testing and evaluation may be necessary.

In this chapter, we will introduce the practical elements of geriatric assessment for oncologists. We will review the components of the geriatric assessment, addressing the relevance of each element in the oncologic patient. Wherever possible, we review the data that provide relevance to the evaluation of geriatric assessment components for the older gynecologic patient. We will review how the geriatric assessment can inform risk stratification of geriatric patients and aid in prediction of outcomes. We will also introduce pragmatic screening tools for oncologists to accurately and efficiently assess patients in the clinical setting.

Epidemiology

Malignancy of the gynecologic organs is common in the postmenopausal age group. Endometrial cancer is the most common gynecologic malignancy with an estimated 46,470 newly diagnosed cases in 2011 and ranks fourth in overall incidence of malignancy in females. The average age of diagnosis in patients with endometrial cancer is 60 years old [5]. It has been noted that elderly patients tend to have worse outcomes in endometrial cancer when compared to younger patients with identical tumor stage [6]. Yoney et al. revealed that endometrial cancer patients over 60 years of age at time of diagnosis had worse outcomes with lower overall survival compared to younger patients [7]. Additionally, Wright et al. showed that women greater

than 85 years at time of diagnosis were more likely to have higher grade tumors and more advanced disease. In this study, it was also observed that after adjusting for tumor characteristics, patients greater than 85 years of age were less likely to undergo hysterectomy and lymphadenectomy and less likely to receive radiation therapy [8].

Ovarian cancer is the second most common gynecologic malignancy in the elderly. The mean age at diagnosis is 63, with nearly half of patients diagnosed at an age >65 [5]. Elderly patients newly diagnosed with ovarian cancer are more likely to present at advanced stages when compared to younger patients [9]. Additionally, it has been observed that younger women with epithelial ovarian cancer have a survival advantage when compared to older patients despite adjustment for race, stage, grade, and surgical treatment [10]. Unfortunately, there is a lack of data on treatment outcomes in the geriatric population with ovarian cancer, as patients in this age group are frequently excluded from clinical trials [11].

Components of Geriatric Assessment

Functional Status

Functional status is a predictor of morbidity and mortality in the geriatric population [12]. Likewise, it has been shown that in the geriatric oncology population, decline in functional status has been associated with increased mortality as well as increased toxicity related to chemotherapy treatments [4]. Traditionally, oncologists have used performance status (i.e., ECOG or Karnofsky performance status scales) as an assessment of physical function. However, it has been shown that in geriatric patients with malignancy, performance status evaluation is not a sensitive tool to detect risk factors in this population. For example, Extermann and Hurria demonstrated that although only 20 % of geriatric oncology patients present with a performance status of two or greater, more than half of this population needs assistance with instrumental activities of daily living (IADLs), which measure the ability of a person to perform tasks that allow for living independently in the community (e.g., shopping, managing money) [3]. Similarly, Repetto et al. studied 363 elderly cancer patients and found that of those with good performance status, 37.7 % had IADL limitations [13].

Commonly utilized tools for evaluation of functional status in the geriatric population are evaluation of ADLs (activities of daily living) and IADLs. ADLs are skills required for basic self care, such as the ability to bathe, feed, dress, toilet, and transfer oneself as well as maintain continence [14]. These skills are necessary to maintain independence in one's own home, whereas IADLs are the skills necessary to maintain independence in the community. IADLs include the ability to perform housekeeping and laundry, meal preparation and grocery shopping, medication administration, finance management, ability to access transportation systems, and

use the telephone [15]. Dependence on others for ADL and IADL assistance has been shown to be predictive of mortality in geriatric oncology patients [16], and it has been observed that older patients with cancer have a higher incidence of ADL and IADL deficiencies when compared to age-matched controls [17]. Additionally, studies of functional status in the geriatric oncology population have revealed that functional status is a predictor of overall survival and mortality, chemotherapy toxicity, as well as postoperative morbidity. For example, Maione et al. evaluated 556 patients with advanced non-small-cell lung cancer receiving chemotherapy and found that deficits in IADLs were predictive of survival [18]. Likewise, Freyer et al. demonstrated that performance status was predictive of symptom toxicity in geriatric patients receiving chemotherapy for advanced ovarian cancer. More specifically, the patient's degree of autonomy as measured by limitations with IADLs was also a predictor of treatment–related toxicity in this study [4]. It has also been demonstrated that dependence on others for IADLs was associated with increased postoperative complications in geriatric patients undergoing cancer-related surgery [19].

Measurement of physical function can be assessed by self-reported estimation as well as basic objective measures. Objective measures include the Short Physical Performance Battery, walk speed, 6-min walk test, chair stands, isometric grip strength, and the "Timed Get Up and Go" test. Perhaps the most utilized of these given its feasibility is the "Timed Get Up and Go" test which involves timed evaluation of patient's arising from a chair, walking 10 ft, turning around and walking back to the chair, and sitting back down [20]. These directly observed measures can serve to confirm self-report measures of functional status.

Comorbidity

The relative incidence of comorbid conditions increases with age. This holds true for cancer patients as well. Yancek et al. evaluated 7,600 patients with cancer and found that those age 75 and greater had an average of 4.2 comorbid conditions whereas those less than 75 years of age had an average of 2.9 comorbid conditions [21]. Additionally, the presence of comorbid conditions in patients with cancer can affect prognosis. In a study of 19,268 patients with newly diagnosed cancer (including gynecologic malignancy), the duration of survival was compared between patients with no comorbid conditions and patients with mild, moderate, or severe comorbid conditions. In all tumor types, decreased duration of survival was seen in patients with mild, moderate, or severe comorbid conditions, as compared to patients without comorbid conditions. In gynecologic malignancies in particular, the hazard ratios for death in patients with mild, moderate, and severe comorbidity levels were 1.13 (0.94–1.35), 1.24 (1.00–1.54), and 2.04 (1.47–2.82), respectively, when compared to patients without comorbidity [22]. Several additional studies have shown similar associations between the presence of comorbid conditions and prognosis in older cancer patients [23–26]. Additionally, comorbid conditions may affect a patient's toxicity risk from treatment for their cancer. In a study by Wildes et al., 152

patients who underwent BEAM conditioning followed by autologous stem cell transplantation (ASCT) were studied to evaluate the impact of comorbidity on toxicity and mortality. Treatment-related mortality was similar between older (>60 years) and younger patients. However, the level of comorbid conditions, as assessed by the Charlson comorbidity index, significantly correlated with treatment-related mortality, and after controlling for age, the Charlson comorbidity index score was independently associated with decreased survival [27].

Analysis of a patients' life expectancy from comorbid conditions versus the malignancy–related mortality must be considered when evaluating treatment options. If an alternative comorbid condition portends a shorter survival time than expected from the malignancy, the risks of cancer therapy could outweigh the benefit. General life expectancy can be obtained from life expectancy tables published by multiple national organizations [28] and from Walters et al. [29].

Polypharmacy

Older adults are more likely to experience polypharmacy as they often have an increased number of comorbid conditions requiring treatment. Additionally, they often have multiple providers from a variety of specialties who are prescribing medications independently, which increases the risk of drug-to-drug interactions. The prevalence of polypharmacy in the elderly ranges widely and depends on the population studied as well as the definition of polypharmacy used. In studies evaluating community-dwelling individuals over the age of 65 in the ambulatory care setting, the prevalence of polypharmacy ranged between 15.6 and 94.3 % [30–33].

Historically, evaluation of polypharmacy has focused on the number of medications an individual is taking. However, this definition has evolved to encompass assessment of high-risk medications as well as evaluation of interactions between medications. High-risk medications are those medications which have been found to have an increased risk of adverse events in the elderly population. The Beers Criteria is a well-known index of high-risk medications in older individuals. The Beers Criteria identifies specific drugs or drug classes which may have increased side effect profiles in older patients in general, particularly when a safer alternative drug option exists. The Beers Criteria also includes medications which may be inappropriate for geriatric patients with particular preexisting medical conditions as these medications increase risks in this subset [34]. Lastly, it is important to assess a patient's nonprescription medication, including all herbals and supplements. Recent studies suggest the prevalence of complimentary/alternative medication use in the elderly population is 26–36 % [35, 36]. Herbal supplements increase the risk for drug interactions and may affect clearance rates of chemotherapy [37].

In efforts to minimize polypharmacy, some centers have incorporated a multidisciplinary approach involving pharmacist review of medication usage. Studies have shown that this can decrease suboptimal prescribing and potentially lead to a decrease of adverse drug events [32, 38–40].

Cognition

Cognitive impairments in geriatric patients with cancer often go undiagnosed. Epidemiology studies suggest that the prevalence of dementia in patients over the age of 70 is 13.9 %. This rate increases with advancing age, with 37.4 % of patients over the age of 90 affected [41]. Patients with mild cognitive impairment are often more difficult to identify and may present only with more targeted cognitive assessment. In studies of patients undergoing comprehensive geriatric assessment, approximately 20 % of patients screen positive for some degree of cognitive disorder [21, 42]. The presence of cognitive disorders, particularly more advanced disease, may limit life expectancy [43] and influence the decision to institute cancer-related treatment. Additionally, patients with cognitive disorders may have more difficulty reporting treatment-related side effects.

Another consideration is the development of cognitive impairment which may be induced by cancer-related therapies. A recent study by Hess et al. evaluated cognitive changes in patients with advanced ovarian cancer undergoing chemotherapy. Cognitive function was assessed prior to treatment and compared posttreatment and found that 86 % of patients demonstrated cognitive impairments over the interval [44]. Additional studies have demonstrated cognitive changes associated with chemotherapy treatment in other cancer types as well.

An additional component of the cognitive assessment is screening for depression as severe depression can lead to subjective memory loss in older patients. The most commonly utilized screening tool for this is the Geriatric Depression Screen (GDS). Depression in cancer patients has been shown to be associated with increased mortality [45]. Additionally, recent studies have identified depression as a significant prognostic factor in patients undergoing treatment for cancer [46].

Nutrition

Nutritional status is an important prognostic indicator in the geriatric population. Weight loss is a marker for declining nutritional status and often observed in the geriatric population, particularly in those that are frail. Weight loss is one of the criteria for frailty per Fried's criteria, for example [47]. In the non-cancer population, studies of community-dwelling geriatric patients found a twofold increased risk of mortality in those patients with weight loss of 5 % of body weight [48]. In the cancer population, weight loss [49] and malnutrition [46] prior to diagnosis have been associated with worse overall survival rates. In the gynecologic cancer patient in particular, it has been shown that malnutrition is an independent predictor of inability to complete a prescribed course of chemotherapy. Moore et al. looked at 246 ovarian cancer patients age 80 or older and determined that a 5 % weight loss or albumin level <2 g/dl prior to initiation of treatment were associated with a decreased ability for patients to complete chemotherapy [50].

A variety of screening tools are available to identify malnutrition. These include self-reported weight loss, calculation of body mass index (BMI) with BMI ≤20 associated with adverse outcomes, and the Mini-Nutritional Assessment (MNA). The MNA has been validated in the geriatric population and includes anthropometric measurements as well as questions related to diet and lifestyle, self-perceived health, mobility, and medications. It has been shown to be a sensitive and specific tool for identifying malnutrition in the elderly population as well as recognizing those patients at higher risk for malnutrition [51]. Its value for use as part of a CGA has been well described [46].

Social Support

Consideration of a patient's social support network is an important component of the comprehensive geriatric evaluation. Multiple studies have demonstrated that patients with strong social support are more likely to be compliant with medical care. Additionally, in both geriatric and oncology literature, social isolation has been associated with increased risk of mortality [52, 53]. Cancer patients, in general, require considerable support from a caregiver. They often require assistance with transportation for treatment sessions and support with symptom management if they experience side effects from their therapy. Research has also found that social support may have a more direct effect on cancer care as well. A study by Osborne evaluated a retrospective cohort of breast cancer patients using linked Medicare and SEER cancer registry data. The sample included 32,268 women, aged 65 and older. They found that unmarried women were more likely to be diagnosed with advanced stage cancer as compared to married women. Additionally, they were less likely to receive definitive care for their disease and more likely to die from their breast cancer [54].

Social support may be assessed in a variety of ways. The most commonly used method is the Medical Outcomes Study Social Support Survey. This is a survey of 20 items assessing a patient's perceived availability of social support. Additionally, the impact of overall health on social functioning is important to assess, given the increased association with mortality in patient with social isolation. This is often measured using the Medical Outcomes Study Social Activity Limitations Measure, which is a four-item questionnaire evaluating the extent that a patient's physical or emotional problems interfere with their social activities.

Risk Stratification

Information for the comprehensive geriatric assessment (CGA) can be utilized to create a comprehensive review of a patient's overall health and well-being. Patients can then be risk stratified based upon deficits in the CGA, although more information

is required to validate these risk-stratification schemes. Patients who have good functional and nutritional status, low level of comorbidity, and strong social support are classified as "fit" for treatment. Patients with multiple CGA deficits are considered "frail" and would have high risk for toxicity with treatments. Those patients in-between may have modifiable risk factors and are considered "vulnerable." These patients are at increased risk of treatment-related toxicity as compared to "fit" patients and should be evaluated for potential modification or dose reduction of their treatment (with escalation as tolerated) to facilitate completion of therapy with minimum toxicity.

Multiple recent studies have evaluated elements of the CGA to identify factors which may independently predict increased risk of toxicity. A study by Freyer et al. was performed in a cohort of geriatric patients with ovarian cancer [4]. Eighty-three patients age 70 and older were evaluated in a multicenter, prospective study to identify prognostic factors which predicted severe toxicity and influenced overall survival. Patients of any stage and performance status were included in the study. Seventy-five percent of patients had advanced stage disease (stage III or IV), and only 21 % had optimal initial surgery. Nearly half of patients (44 %) had an ECOG performance status of two or greater. Comprehensive geriatric assessment included analysis of patient autonomy (independent at home versus home with assistance versus resident of a facility), comorbid disease, nutrition status (evaluation of BMI, protein, albumin, and cholesterol level), cognitive evaluation by mini-mental status exam, and clinical symptoms of depression. Patients underwent treatment with carboplatin/cyclophosphamide for six cycles, and dose reduction was implemented for grade four hematologic toxicity, febrile neutropenia, or grade 2 neurotoxicity. Authors found that 72 % of patients were able to complete the full regimen of treatment without severe toxicity or tumor progression. Baseline characteristics that predicted severe toxicity were clinical signs of depression, dependence on others for functional assistance, and an ECOG performance status of two or greater. Additionally, they identified factors which independently influenced overall survival. These factors were polypharmacy (defined as more than six medications per day), clinical symptoms of depression, and stage IV disease [4].

Hurria et al. also sought to identify baseline characteristics of the geriatric oncology population which would predict increased risk for grade 3, 4, or 5 toxicity. They collected prechemotherapy data including tumor characteristics, basic laboratory data, treatment characteristics, and CGA results on 500 patients and followed them throughout their treatment course, monitoring for toxicity events. Patients with all tumor types were included (17 % with gynecologic malignancy), and the majority (61 %) had stage IV disease. A large percentage of patients developed chemotherapy–related toxicity (39 % with grade 3, 12 % with grade 4, and 2 % with grade 5). Nearly a third required dose reduction (31 %) or had a dose delay (31 %), and almost one-quarter were hospitalized during their treatment (23 %). They determined that baseline characteristics predicting increased risk for toxicity included age ≥ 72, cancer type (GI or GU malignancy), standard dosing of chemotherapy, polychemotherapy regimen, decreased hemoglobin (males < 11, females < 10), creatinine clearance <34, hearing impairment, one or more falls in

the past 6 months, limited ability to walk one block, need for assistance with taking medications, and decreased social activities. Authors were able to develop a risk stratification schema by assigning a risk score for each of these factors. They demonstrated that the total risk score for a patient correlated with the incidence of treatment–related toxicity events [55].

An additional study performed by Kanesvaran et al. evaluated the impact of CGA domains on overall survival and developed a prognostic scoring system including these elements for use by clinicians. This study included patients of any cancer type, stage, and functional status. The majority of patients had GI, GU, or lung cancer, and 84.7 % had advanced stage malignancy. The majority of patients (66.7 %) had an EGOC PS ≥ 2. They performed a retrospective analysis of 249 patients to determine items from the CGA which independently affected overall survival. Factors they identified included low albumin, EGOG PS ≥2, positive geriatric depression screen, advanced stage disease, malnutrition, and advanced age. They developed a nomogram for use by clinicians to predict 1-, 2-, and 3-year overall survival for individual patients by weighting each of these independent variables [46].

In conclusion, the CGA can provide more comprehensive assessment of a patient's overall health and well-being. Deficits in various areas of the CGA can help identify patients who may be at increased risk with treatment or may impact overall survival. Additional research is needed to identify the optimal mode of implementing the CGA and its results into daily clinical practice.

Screening for Impairments in the Oncology Clinic

Despite recent studies demonstrating feasibility of CGA in oncology, adoption as the standard of care has been slow due to lack of resources, difficulties with interpretation of results, and with implementation of targeted interventions in specialty clinic settings such as oncology [56–59]. A short, simple, validated screening procedure that could be adapted to the specialty clinic setting to quickly identify those patients who are at risk for further morbidity or mortality would be valuable. While impaired patients could then be offered referral to more comprehensive geriatric programs for interventions, older patients who are not at risk would be spared the more cumbersome CGA. Currently, little is known about the usefulness of brief screening tools in selecting those older cancer patients who would most benefit from the full CGA with targeted interventions.

In the following sections, we highlight screening measures utilized in geriatric oncology to identify older adults who have characteristics that place them at high risk for adverse outcomes from underlying health status, cancer, and/or cancer treatment. For each measure, we provide a description of the following: components of the measure, any data regarding reliability and validity in community–dwelling older adults and/or those older adults with cancer, comparisons to a full CGA, and any data available regarding prediction of adverse outcomes in community–dwelling older adults and/or those with cancer. A short screening tool should exclude the

possibility of vulnerability with a high negative predictive value, and positive results should indicate the need for a more complete geriatric evaluation [60].

There is still a dearth of evidence regarding the predictive value of screening measures for adverse outcomes in older cancer patients compared to the CGA. As a whole, the available studies have limitations. Defining a "gold standard" for detection of impairment in geriatric domains on CGA is somewhat arbitrary as there are a plethora of tools for identifying geriatric deficits. Studies have utilized different definitions of "gold standard." Patients with multiple impairments within the CGA are "vulnerable" and are at higher risk for future disability, decline, or death [61]. In addition, there is the potential for selection bias. In spite of investigators' efforts, all eligible patients may not have been captured. The patients who were not captured may have had inherently different characteristics than the patients included in our study as healthier patients may not have been recognized as candidates for these studies. Further research in the assessment of the older cancer patient should investigate the associations of these underlying screening measures or tools for predicting adverse outcomes for older cancer patients with specific subtypes and stages of cancer, including those with gynecologic cancers.

Vulnerable Elders Survey-13

The Vulnerable Elders Survey-13 (VES-13) is a self-administered survey that consists of one question for age and an additional 12 items assessing self-related health, functional capacity, and physical performance [62, 63]. In the national sample of elders from the Medicare Current Beneficiary Survey (1993–1995) used to derive the VES-13, a score of ≥3 identified 32 % of individuals as vulnerable [62, 63]. This identified group had over four times the risk of death or functional decline over 2 years when compared to elders scoring <3. The VES-13 was validated in an outpatient group of community-dwelling older adults. Higher scores predict increasing risk for functional decline and/or death [64]. In this outpatient cohort of over 400 persons, increasing VES-13 scores strongly predicted death and functional decline. The estimated combined risk of death and decline rose with VES-13 score, increasing from 23 % for older people with a VES-13 score of 3–60 % for those with a score of 10 over the 11-month follow-up period. Other measures (sex, comorbidity) were not significant predictors of death or decline over this period after controlling for VES-13 score. A subsequent study of over 600 persons aged 75 and over whom screened positive for falls or fear of falling, urinary incontinence, and memory problems found that higher VES-13 scores were associated with greater predicted probability of death and decline (increasing ADL deficit and/or nursing home entry) in older patients over a mean observation period of 4.5 years [65]. For each additional VES-13 point, the odds of the combined outcome of functional decline or death was 1.37 (95 % confidence interval (CI) = 1.25–1.50). In these validation studies, the VES-13 was administered over the telephone or in person, and the average time elders took to complete the VES-13 was less than 5 min [66].

In an outpatient cohort of community-dwelling older adults, the abbreviated five-item functional status survey consisting of five activities of daily living (ADLs) included in the VES-13 reflected changes measured over 11 months similarly to the full 12-item functional status survey. Specifically, changes in short functional status survey scores were highly correlated to changes in long survey scores (correlation coefficient = 0.88). On average, a 1-point change in the short survey score was associated with a 1.4-point change on the long survey score ($P < 0.001$). The short survey correctly classified 93 % of those who declined according to the long survey and was responsive to decline in function (sensitivity 82–94 %, specificity 94–97 %) [67].

Because of the predictive value of the VES-13 for identifying at-risk elders in the community, further work was carried out to determine whether the VES-13 was useful as a screening tool for identifying at elders at risk for adverse outcomes from cancer and cancer treatment. An analysis comparing vulnerability characteristic in cancer patients to those without cancer, using a more recent cohort of the Medicare Current Beneficiary Survey (2005), found that a high proportion of elders with a history of cancer also scored as "vulnerable" on the VES-13 (45.8 %) and that this prevalence was statistically significantly higher than the proportion of elders without a history of cancer who scored as "vulnerable" (39.5 %, $P < 0.001$) [68]. In this analysis, a cancer diagnosis was associated with an increased likelihood of having a VES-13 score of 3 or higher (adjusted OR = 1.26, 95 % CI = 1.13–1.41; RR = 1.14) compared with those without cancer. In another study, 50 % of older patients with prostate cancer who were receiving androgen deprivation therapy were reported to have scored as "vulnerable" on the VES-13 [69]. In these studies, it is unclear whether a personal history of cancer or other comorbidities was independently associated with the increase in factors that are related to vulnerability. In the older prostate cancer cohort on androgen deprivation therapy [69], the VES-13 had high predictive value for identifying impairment when compared to the CGA using a cut point of ≥3. Cutoff points between 2 and 4 had testing characteristics that were very similar; these scores were all highly sensitive and specific and correctly classified approximately 80 % of patients. This study established the utility and feasibility of using a screening measure to detect geriatric impairment in an older, disease- and treatment-specific cancer population in the specialty clinic setting (i.e., older prostate cancer patients on androgen deprivation therapy).

Other studies to further clarify the testing characteristics of the VES-13 in a more heterogeneous population of cancer patients have also been conducted. Luciani et al. conducted a study to establish the accuracy of the Vulnerable Elders Survey-13 (VES-13) in predicting the presence of abnormalities revealed by CGA [70]. The population included a group of 419 patients aged 70 and over with any history of solid or hematologic malignancy. Fifty-three percent of the 419 elderly patients with cancer (mean age, 76.8 years) were vulnerable on VES-13; the rates of disabilities on CGA and activities of daily living (ADLs)/instrumental activities of daily living (IADLs) scales were 30 and 25 %, respectively. The sensitivity and specificity of VES-13 were 87 and 62 %, respectively, compared to CGA. Falci et al. reported their results in a letter to the editor in response to the Luciani investigation [71]. They reported that in 242 persons, VES-13 demonstrated rather unsat-

isfactory sensitivity and specificity; 30 % of elderly patients with favorable VES-13 scores were found to be vulnerable or frail at full CGA, and 40 % of patients with unfavorable VES-13 scores were found to be fit. They also reported that many patients had difficulty in completing the tool on their own.

Another study compared the accuracy of each of three proposed instruments, abbreviated CGA (aCGA), VES-13, and the Groningen Frailty Index (GFI) (see next section), in determining vulnerability in elderly patients by measuring sensitivity, specificity, and negative and positive predictive value as compared to the full CGA as gold standard [72]. The interviews were conducted by trained medical staff. The authors interviewed 113 patients with a cancer diagnosis. All patients were assessed using the aCGA, VES-13, GFI, and the full CGA. In this study, VES-13 had a moderate sensitivity of 61 % with a negative predictive value of 48 %. The aCGA had a sensitivity of 51 %, a specificity of 97 %, and a negative predictive value of only 48 %. The GFI had unacceptably low sensitivity and negative predictive value of 39 and 40 %, respectively, though specificity was good at 86 %.

The studies above reflect differing conclusions regarding the sensitivity and validity of the VES-13 compared to CGA. The "gold standard" definition of CGA varied among the studies. In addition, the population varied and several included patients with different cancers and at with varying stages of cancer. At this point, the use of VES-13 as a tool for identifying disabilities in older cancer patients should be undertaken with caution. Due to lack of consistent result, this tool should not serve as a substitute for a full CGA. Because comparisons with CGA are fraught with limitations, prospective evaluation of the utility of VES-13 to predict outcomes is necessary. It would help to develop these clinical studies for patients with similar cancers and stages in order to appropriately gain data that could be used for those specific populations in clinical trials and everyday practice.

Groningen Frailty Indicator (GFI)

The Groningen Frailty Indicator (GFI) is a screening instrument developed in 1991 in the community-dwelling geriatric population. It is a 15-item survey including questions focusing on mobility/physical fitness, vision/hearing, nutrition, comorbidity, cognition, and psychosocial. The score ranges from 0 to 15, and a score of four or higher is considered predictive of frailty, based upon consensus of a panel of geriatric experts [73]. The GFI has been shown in studies to demonstrate high internal consistency and construct validity [74]. The GFI has been compared to the comprehensive geriatric assessment (CGA) to evaluate its predictability as a screening tool for CGA deficits, and investigators found that there was correlation between the GFI score and the combined CGA results (Pearson correlation coefficient [R^2] = 0.45) [75].

A study by Aaldriks et al. evaluated the predictive value of geriatric assessment and the GFI in patients scheduled to undergo chemotherapy treatment. Patients of all types and stages of cancer were included in this study, and initial evaluation included screening with the GFI. Authors found that the mortality rate after initiation

of chemotherapy was increased for patients with higher baseline GFI scores (hazard ratio 1.80, 95 % CI 1.17–2.78) [76]. The GFI has also been evaluated as a predictive tool in a cohort of geriatric patients with lung non-small cell lung cancer treated with platinum-based doublet chemotherapy. Authors performed a comprehensive geriatric evaluation including the GFI on patients at baseline prior to treatment. They discovered that results were strongly prognostic and the main driving components were the GFI score and Geriatric Depression Scale scores [77].

The GFI has also been evaluated in the postoperative setting as a predictive tool for the development of postoperative delirium after vascular surgery. It was found the GFI score was associated with incidence of postoperative delirium ($p=0.03$) [78]. Currently, a study is evaluating the preoperative risk estimation of onco-geriatric patients comparing the GFI versus the preoperative assessment of cancer in the elderly (PACE) [79].

G8

The G8 is an additional screening tool which was developed in a cohort of geriatric cancer patients. It was extrapolated from the Mini-Nutritional Assessment (MNA), which is a nutritional assessment tool developed in the 1990s specifically for the geriatric population. The MNA has been shown to have prognostic significance for functionality, morbidity, and mortality of the elderly in a variety of settings [80]. The G8 is an eight-item questionnaire assessing domains of nutrition, mobility, cognitive deficit, polypharmacy, age, and self-perceived health status. Scoring ranges from zero (poor status) to 17 (good prognosis), and authors recommend a score of 14 as a predictor of CGA deficits (90 % sensitivity and 60 % specificity). This was validated in a study comparing the G8 to the VES-13 as a predictive tool for CGA deficits in geriatric cancer patients. Sensitivity of the G8 was found to be superior to the VES-13 (76.6 %, 95 % CI [74 %; 79 %] vs. 68.7 %, 95 % CI [65.9 %; 71.4 %]). However, the specificity for CGA deficits was inferior to the VES-13 (64.4 %, 95%CI [58.6 %; 70 %] vs. 74.3 %, 95%CI [68.8 %; 79.3 %]) [81].

Predicting Chemotherapy Toxicity: The CARG and CRASH Tools

Two large prospective studies were completed that have helped elucidate factors that are independently associated with severe chemotherapy toxicity. In a study of 500 patients led by Dr. Hurria in the Cancer and Aging Research Group, GA factors were associated with grade 3–5 toxicity [55, 82, 83]. Patients age ≥65 years with cancer from seven institutions completed a prechemotherapy assessment that captured sociodemographics, tumor/treatment variables, laboratory test results, and geriatric assessment variables (function, comorbidity, cognition, psychological state, social activity/support, and nutritional status). Patients were followed through

the chemotherapy course to capture grade 3 (severe), grade 4 (life-threatening or disabling), and grade 5 (death) as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events. The GA assessment revealed a number of findings that would not have been detected on routine history and physical exam: 41 % of patients needed assistance with instrumental activities of daily living despite a mean physician-reported KPS of 85 (range 50–100), 92 % had ≥1 comorbid medical conditions (mean 2.5; range 0–9), 95 % took ≥1 medications (mean 5; range 0–23), 16 % had >1 falls in the past 6 months, 6 % had gross cognitive impairment on the cognitive screening test, and 39 % had >5 % weight loss in the past 6 months. Grade 3–5 toxicity occurred in 53 % (50 % grade 3, 12 % grade 4, 2 % grade 5). Risk factors for grade 3–5 toxicity included (1) age ≥73, (2) cancer type (GI or GU), (3) standard dose, (4) polychemotherapy, (5) falls in last 6 months, (6) assistance with instrumental activities of daily living, and (7) decreased social activity. A risk stratification schema (number of risk factors: % incidence of grade 3–5 toxicity) was developed—1: 23 %, 2: 36 %, 3: 50 %, 4: 60 %, 5: 83 %, 6: 90 %, and 7: 100 %. Although this predictive model has clinical application, it has yet to be validated.

A second study which developed The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score in over 500 patients was led by Dr. Martine Extermann [84]. In this study, patients aged ≥70 years who were starting chemotherapy completed a GA. Grade 4 hematologic or grade 3/4 nonhematologic toxicity according to version 3.0 of the Common Terminology Criteria for Adverse Events was defined as severe. Twenty four parameters were assessed including GA domains, physical exam findings (diastolic blood pressure), cancer, and chemotherapy characteristics. Toxicity of the chemotherapy regimen was adjusted using an index to estimate the average per-patient risk of chemotherapy toxicity (the MAX2 index): Severe toxicity was observed in 64 % of patients. Predictors of hematologic toxicity included lymphocytes, aspartate aminotransferase level, instrumental activities of daily living (IADL) score, lactate dehydrogenase (LDH) level, diastolic blood pressure, and toxicity of the chemotherapy regimen. The best model included IADL score, LDH level, diastolic blood pressure, and chemotherapy toxicity—risk categories: low, 7 %; medium-low, 23 %; medium-high, 54 %; and high, 100 %, respectively (P(trend) < 0.001). Predictors of nonhematologic toxicity were hemoglobin, creatinine clearance, albumin, self-rated health, Eastern Cooperative Oncology Group performance, mini-mental status score, Mini-Nutritional Assessment score, and toxicity of the chemotherapy regimen. The best predictive model included performance status, mini-mental score, Mini-Nutritional score, and chemotherapy toxicity—risk categories: 33, 46, 67, and 93 %, respectively (P(trend) < 0.001). Information from two-thirds of the patients were used to develop the risk stratification scheme, and the tool was validated in the remaining one-third of patients.

Overall, these predictive risk stratification schemes have tremendous clinical potential. They allow clinicians to identify which patients are at highest risk for chemotherapy toxicity and should be utilized in further research to identify and apply interventions to reduce the development of chemotherapy toxicity in vulnerable older populations.

Predicting Morbidity and Mortality After Surgery: The PACE Tool

A number of elderly cancer patients do not receive standard surgery for malignancies because they are considered unfit for treatment as a consequence of inaccurate estimation of the operative risk. CGA has been found to be helpful for predicting morbidity and mortality after surgery. Audisio et al. investigated the value of an extended CGA in assessing the suitability of elderly patients for surgical intervention [85]. The authors developed the "preoperative assessment of cancer in the elderly (PACE)" which incorporated validated instruments including the CGA, an assessment of fatigue and performance status, and an anesthesiologist's evaluation of operative risk. An international prospective study was conducted using 460 consecutively recruited cancer patients aged 70 and over who received PACE prior to elective surgery. Mortality, postoperative complications (morbidity), and length of hospital stay were recorded up to 30 days after surgery. Patients had a variety of cancer, and those with gastrointestinal and genitourinary malignancies had the highest risk of toxicity. Poor health in relation to disability (assessed using the instrumental activities of daily living (IADL)), fatigue, and performance status (PS) were associated with a 50 % increase in the relative risk of postoperative complications. Fatigue, a dependent IADL, and an abnormal performance status were important independent predictors of postsurgical complications. Disability assessed by activities of daily living (ADL), IADLs, and performance status as associated with an extended hospital stay. The authors concluded that a validated instrument such as the CGA was able to predict short-term surgical outcomes and offered more appropriate information when counseling patients on the risks of surgery (see Table 4.1).

Conclusion

The incidence of cancer, particularly gynecologic malignancy, increases with advanced age. The geriatric population is a heterogeneous group, and a patient's chronologic age does not always reflect their overall health status. Therefore, oncologists need to be adept at assessing physiologic and functional capacity in older patients. The comprehensive geriatric assessment is the gold standard for evaluation of the geriatric patient. The various components of the CGA have been shown to influence cancer–related therapy in a multitude of ways, as previously discussed. The combined data from the CGA can be used to stratify patients into risk categories to better predict their tolerance to treatment and risk for chemotherapy toxicity. However, the CGA is a comprehensive tool requiring significant time and training to perform. Therefore, a variety of screening tools have been developed which may be useful in the general oncology practice setting to identify patients that may benefit from further testing and intervention. Further research is still needed to evaluate whether these screening tools can predict cancer-related outcomes in older patients.

Table 4.1 Comparison of selected screening tools for CGA deficits

Tool	Components	Data in community-dwelling elderly	Data in oncology patients
VES-13	Age, self-rated health, functional capacity, and physical performance	Score predictive of increased risk of death or functional decline over 2 years	Demonstrates mixed results for identifying CGA impairment in different populations
GFI	Mobility/physical fitness, vision/hearing, nutrition, co-morbidity, cognition, psychosocial	Correlation between the GI score and the combined CGA results	Mortality rate after initiation of chemotherapy increased in patients with higher baseline GFI score
G8	Nutrition, mobility, cognitive deficit, polypharmacy, age, self-perceived health status	Derived from MNA which has predictive value in community-dwelling older adults	Sensitive for predicting deficits on CGA
Hurria toxicity	Age, cancer type, chemotherapy dosing, polychemotherapy, fall history, IADL dependence, decreased social activity	None	Predictive of grade 3–5 toxicity with chemotherapy
CRASH	CGA, PE findings, cancer type, chemotherapy characteristics	None	Predictive of hematologic and nonhematologic toxicity from chemotherapy
PACE	CGA, fatigue assessment, performance status (PS), anesthesiology evaluation	None	IADL impairment, fatigue, and abnormal PS associated with 50 % increased relative risk of postoperative complication

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Chapter 5
Pharmacology of Chemotherapy

Christopher B. Steer and Gabriel W.H. Mak

Abstract Chemotherapy is a key component of treatment of women with epithelial ovarian cancer regardless of age. Increasing comorbidities and changes in drug pharmacodynamics and pharmacokinetics with increasing age can lead to increased toxicity. The assessment of renal function is vital for accurate dosing of renally excreted agents such as carboplatin. While data from clinical trials specifically in older adults is limited, data from subgroups of elderly patients informs clinicians of the utility and toxicity profiles of chemotherapy. The pharmacological characteristics of the commonly used chemotherapeutic agents are further explored.

Keywords Pharmacology • Chemotherapy • Elderly patients • Comorbidity • Renal function

Introduction

As part of the aging process, elderly patients have physiological changes comprising of decreased reserve in multiple organ systems, including renal, hepatic, bone marrow, and cardiac. This leads to changes in the pharmacokinetics (PK) and pharmacodynamics (PD) of chemotherapeutic agents when used in this population, as well as potential toxicities [42, 43]. Despite this, few studies have shown a direct correlation between aging and PK changes [44].

Historically, elderly patients have been underrepresented in clinical trials – thus it is difficult to directly extrapolate algorithms to treat this population [32, 58, 91]. Furthermore, concerns of causing toxicity in a more frail and susceptible population potentially lead to undertreatment [8, 17, 91]. The field of geriatric oncology has been prioritized by groups such as the International Society of Geriatric Oncology

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(SIOG) and specialist societies within the EORTC and ASCO. The aim of these groups is to improve the standards of care for older patients and design clinical trials specifically for this demographic [55, 60]. However, in the absence of direct guidelines for the treatment of older adults, regimens tailored to minimize toxicity while maintaining efficacy are paramount to deliver optimal care [54].

Comorbidity and Polypharmacy

With advancing age, patients have a higher rate of comorbidity, although it is difficult to ascertain the precise relationship with regard to overall prognosis. Studying comorbidities is complex, as it requires multidimensional assessment and consideration of multiple conditions which may have prognostic impact [29]. One recent review reports that there is generally a correlation of decreased use of chemotherapy and reduced overall survival in patients with comorbidities. However, this was a review of multiple studies with heterogeneous design not specifically aimed at researching the impact of comorbidity, and further studies are required [39].

Nonetheless, retrospective data shows that patients aged 75 and over have an average of 4.2 comorbid conditions [54, 92]. As such, there is accompanying polypharmacy to manage these conditions [40, 61]. Polypharmacy increases the probability of adverse drug reactions (ADRs), which in turn is associated with increased mortality [36]. A patient's regular medications can interact with chemotherapy. For example, carboplatin reduces warfarin metabolism and may lead to an increased anticoagulant effect – thus, close monitoring of the patient's INR is recommended when these drugs are used concurrently [40].

Various studies estimate the median number of medications being taken by patients with cancer to be between 5.5 and 9.0 [10, 27, 59, 72, 86]. This does not necessarily take into account over-the-counter medications or complementary and alternative medications (CAMs), the use of which may be underreported by patients. Greater number of medications correlates with a higher nonadherence rate, with some studies estimating a 50 % nonadherence rate in patients with chronic disease and a rate of between 29 and 59 % in older patients in general [78]. Furthermore, this demographic is usually managed by both specialist and general practitioners, which also puts them at higher risk of polypharmacy [26].

Chemotherapy regimens typically consist of multiple agents – including supportive therapies such as antiemetics, corticosteroids, and antimicrobial agents [33]. Polypharmacy can lead to potential adverse drug reactions (ADRs) and interactions [26, 40]. Of note is the higher frequency of ADRs associated with anticoagulants (specifically warfarin) and benzodiazepines – classes of agents used commonly in elderly patients [36].

Comorbidities must also be taken into account when evaluating potential toxicities of treatment – examples such as usage of taxanes in the diabetic with peripheral neuropathy or anthracyclines in those with preexisting cardiomyopathy or liver disease.

Decisions regarding the use of chemotherapy will depend on functional status and comorbidities – which may not necessarily be directly correlated [22, 63]. The comprehensive geriatric assessment (CGA) is one approach that is multidisciplinary and multidimensional, in helping to guide clinical decisions [22, 36, 48, 54], however in practice – it can be cumbersome and time-consuming. Thus, multiple other screening tools are now being developed and validated, to guide clinical decision-making [20].

Physiologic Changes with Aging

Aging is an individualized heterogeneous process that is not defined by one single underlying pathological process. However, there can be generalized processes affecting multiple organs resulting in loss of reserve, which need to be considered clinically. Chronological age does not necessarily correlate to biologic age; and within the individual patient, different organs and systems may be affected at different rates. All these changes would influence the pharmacokinetic (PK) and pharmacodynamics (PD) of a drug, in each particular patient [3, 31].

The common changes of aging include [3, 30, 31, 65, 68]:

Decreased total body water and total body proteins and lean mass and increased total body fat

With aging, total body fat increases by 20–40 % and total body water decreases by 10–15 %, with an estimated 15–20 % decrease also in total body proteins [68, 82].

These factors affect the pharmacokinetic aspect – volume of distribution (see below).

Decreased renal function resulting from reduction in glomerular filtration rate and tubular function

Renal mass decreases by 25–30 % over the lifespan; renal blood flow decreases by 1 % each year after age 50; GFR decreases by 35 % in healthy individuals between age 20 and 90 [82].

There are changes in glomerular and tubulointerstitial components, resulting in decline in overall renal function.

Renal function commonly declines with age thus renal excretion and clearance decreases in predictable manner, although in some individuals renal function may be preserved despite aging.

Nonetheless, in general older patients have less renal reserve to cope with dehydration thus counseling of adequate fluid intake; and careful administration of intravenous fluids with chemotherapy is vital.

Serum creatinine is not a good direct correlate of renal function, as loss of muscle mass will also result in lower creatinine [77].

Thus, more accurate measures of creatinine clearance are recommended (see below); renal function is a key aspect of the pharmacokinetic of drug excretion.

Reduction in splanchnic circulation, liver size, and Phase 1/cytochrome P450-mediated reaction [31, 67]

While literature suggests that there is indeed age-related changes causing decreased in hepatic size, blood flow, and enzyme activity [65] – both Phase 1 and Phase 2 reactions seem to maintain their activity in senescence [3] hence proving not to be clinically significant with regard to overall drug metabolism.
Nonetheless, in the context of polypharmacy in the elderly population, the interference with enzyme systems can lead to interactions and adverse drug reactions.
Decreased intestinal mucosal surface and ability to regenerate the mucosa after injury, decreased gastric secretions, digestive enzymes, and gastric motility [85].
These factors are important with respect to the pharmacokinetic aspect of drug absorption with regard to oral medication.
With these changes, the elderly are more susceptible to gastrointestinal toxicity such as mucositis as a complication of chemotherapy, as they have reduced capacity to regenerate mucosa [76].
Reduced hematopoiesis [4, 68] and higher rates of anemia in the elderly [1]
Bone marrow cellularity can decrease by 30 %, with a variable decline in bone marrow activity and stem cell reserve [85]. The function of all blood cell types – erythrocytes, leucocytes, and platelets – also declines with age, thus impacting oxygenation capacity, immune function, and clotting, respectively.
As myelosuppression is a concerning side effect of many cytotoxic agents, close monitoring of blood counts is paramount; and the use of supportive agents such as erythropoiesis-stimulating agents (ESA) and G-CSF may be utilized to support patients through treatment.
The use of ESAs has been controversial in recent studies as there have been decreased rates of overall survival and increased risk of thromboembolic events [5, 7]. Current ASCO guidelines recommend discussion with patients about the potential risks and benefits of using ESAs, only in those receiving concurrent chemotherapy with a hemoglobin of <10 g/l [62].
Some chemotherapeutic agents are bound to red blood cells, thus anemia may result in higher concentrations of the drug in the circulation [85].
With regard to immunity, chemotherapy-induced neutropenia is more common, more severe, and associated with higher rates of infectious complications, higher hospitalization rates with longer hospitalization periods (approximately 25 %), and higher mortality rates in the elderly population [3, 85]. Thus, there is compelling argument to using G-CSF to reduce the risk of neutropenia and neutropenic infection and enable the administration of chemotherapy with full intensity [35].
Reduced cardiac reserve
Aging-related changes lead to a decrease in cardiac functional reserve limiting capacity with regard to physical activity and stress responses. There is also a concomitant increased risk of cardiovascular diseases including ischemic heart disease, valvular disease, and arrhythmias [65].
Chemotherapeutic agents are recognized for causing cardiotoxicity – especially anthracyclines and trastuzumab. Treatment with chemotherapeutic agents is also

associated with higher rates of hypertension, thromboembolic disease, pericardial disease, arrhythmia, and myocardial ischemia; thus, close monitoring of cardiac function and collaboration with cardiologists is required in the event of chemo-related toxicity [19, 53, 93].

Reduced brain volume and peripheral nerve conduction

Peripheral neuropathy is a side effect that can have profound implications for a patient's ability to function; with even Grade 2 toxicity affecting ability to carry out activities of daily living (ADLs).

Age is a risk factor for developing peripheral neuropathy, especially in the context of receiving alkaloids, epipodophyllotoxins, taxanes, epothilones, and platinum derivatives [84].

Substitution of certain agents within a class may decrease the risk of peripheral neuropathy (e.g., carboplatin in place of cisplatin, docetaxel in place of paclitaxel); however, there may be a trade-off in other toxicities [3].

Endocrine changes: reduced production of sex hormones and growth hormone and increased production of adrenal steroids and catecholamines

Reduced bone density thus osteopenia, and osteoporosis

This is a pertinent factor in the elderly cancer population, especially those who use long-term corticosteroids, rendering patients liable to minimal trauma fractures.

Thus, it is important to ensure calcium and vitamin D levels are replete and monitor bone mineral density; decrease the use of corticosteroids if possible and consider the use of bisphosphonates and RANK-L antibodies [13, 14, 52].

Pharmacokinetics

Pharmacokinetics (PK) encompasses the aspects of drug absorption, distribution, metabolism, and excretion in the body. As outlined above, the physiologic changes of aging may affect these domains.

Absorption

Changes to the gastrointestinal tract outlined above may not have a role with regard to absorption of most chemotherapeutic agents in the context of gynecological cancers as the majority of agents are administered parenterally. One exception may be the use of oral etoposide in small cell variants of tumors and platinum- and paclitaxel-resistant ovarian cancers.

However, most of our supportive agents such as antiemetics and analgesia are administered orally. Despite the changes of aging, the effect on absorption may be on the rate of absorption, rather than reduced absorption – and may have no clinical effect [3].

Oral chemotherapeutic agents may be developed for use in this population in the future, and practical issues such as drug compliance may need to be addressed.

Distribution

Distribution of the drug occurs when it reaches the systemic circulation. Volume of distribution (Vd) of a drug is dependent on body composition and concentration of circulating plasma proteins to which drugs bind such as serum albumin and red blood cells [82].

Changes in body composition – being that of decreased lean muscle mass and total body water, with increased total body fat – change the Vd; increase in total body fat leads to an increased volume of distribution (Vd) for lipophilic drugs and decreased Vd for hydrophilic drugs. Some literature suggests that highly lipophilic drug dosing should be increased by 10–20 % whereas highly hydrophilic drug doses should be decreased by 10–20 % [65].

Plasma albumin levels decrease by 15–20 % with aging [50] and in the context of concurrent malignancy, may be even lower due to chronic inflammatory responses and malnutrition. Thus, there may be an increased concentration of drugs which are normally bound to albumin.

As already mentioned, anemia is more common with aging; and this may impact on the concentration of drugs which are normally bound to hemoglobin. Toxicities may be exacerbated when a patient is anemic [21]. Interestingly, the hemoglobin level is only aspect of Vd that may be amenable to medical intervention [3].

Drug Metabolism and Hepatic Function

Drug metabolism predominantly takes place in the liver; dependent on hepatic blood flow, rate of drug extraction by hepatocytes, mass of hepatocytes, and intracellular drug-metabolizing enzymes [16]. Hepatic mass and blood flow changes occur with age, although the impact on function is controversial [30].

Drug metabolism in the liver takes place by two types of reactions:

Phase 1: oxidation, reduction, and hydrolysis reactions
Phase 2: conjugation with endogenous substance – for example, glucoronic acid, sulfate, or glycine – to enable excretion in urine or bile

Phase 1 enzyme activity (CYP mediated) can be reduced by up to 30 % by aging [34], but baseline genetic differences may be more influential than aging [70]. The variability in enzyme activity may lead to PD differences between individuals. The family of CYP microsomal enzymes is involved in metabolism of many chemotherapeutic agents – with regard to gynecological cancers,

these include cisplatin, docetaxel, paclitaxel, cyclophosphamide, doxorubicin, and topotecan [67].

Phase 2 enzyme activity appears to be maintained throughout aging [34].

Concomitant medications and polypharmacy may affect metabolism by interaction with these systems; and other comorbidities (e.g., nonalcoholic fatty liver disease) may also decrease overall hepatic function. Monitoring of hepatic function and dose adjustments of chemotherapeutic agents may need to be considered.

Excretion and Renal Function

The majority of chemotherapeutic agents are excreted by the kidneys. Renal function is the most influential variable with regard to pharmacokinetics.

Measurement of Renal Function

It is generally accepted that renal function declines in the elderly patient population. This is due to the presence of comorbidities and a decline in renal reserve. Care must be taken not to assume that a reduced glomerular filtration rate (GFR) is a normal part of aging. Studies suggest that the principal cause of the decline seen in the general elderly population is hypertension [45, 46]. This debate aside, most studies show a decline in GFR with increasing age.

Assessment of patients' renal function is therefore critical prior to the administration of therapy with renally excreted and potentially nephrotoxic drugs. Reliance on the serum creatinine alone is inappropriate in the elderly population as it yields potentially inaccurate results [38, 42, 43, 75]. There are a number of more accurate ways to estimate renal function.

Glomerular Filtration Rate (GFR)

The best estimate of renal function is the GFR. True GFR is measured in ml/min. Standardized GFR is routinely used by clinicians such as nephrologists as a marker of patients' renal function. This is an adjusted figure that assumes an average body surface area of 1.73 m^2. Standardized GFR is reported in ml/min/1.73 m^2. GFR is commonly measured using nuclear medicine techniques wherein timed blood samples are taken after an injection of radiolabeled isotope (e.g., 51Cr – EDTA ([51Cr] f-ethylenediamine tetraacetic acid) and 99mTc – DTPA (technetium-99m diethyl triamine penta-acetic acid)). These techniques can be considered the gold standard means of measuring GFR.

Creatinine Clearance (CrCl)

Creatinine clearance is an estimate of GFR. CrCl can be calculated using formula based on the serum creatinine. CrCl can also be measured using a 24-h creatinine clearance; however, this method is time-consuming, inefficient, and inaccurate; its use is not recommended in the routine management of patients with ovarian cancer [15].

Calculation of CrCL Formulae

The CrCl can be estimated using various formulae based on the serum creatinine. The most commonly used formula is the Cockcroft-Gault equation. This was derived from a population of 249 men in a veterans' hospital. As no women took part in the study, the formula employs an arbitrary correction factor of 0.85 when calculating the CrCl of female patients. Despite this, it gives adequate results when dosing carboplatin in women with ovarian cancer.

Other formulae that have been used to estimate CrCL include the Chatelut equation, the Calvert, and the Jelliffe formulae. The Wright formula was derived from a population of cancer patients; and it may be the more accurate and precise equation to use in an elderly population [49, 90].

The CrCl can then be inserted into the Calvert equation to enable more accurate dosing of carboplatin in patients with ovarian cancer.

Pharmacodynamics

Most of the age-related differences in cancer patients are in the realm of pharmacodynamics – that is, the effect the drug has on the body [25]. As already mentioned, the physiological changes of aging can render elderly patients more liable to the toxic effects of chemotherapeutic agents. In managing these toxicities, this may involve dose reductions, changing administration intervals, or a combination of both – which may affect the efficacy of the treatment [42, 43].

Specific Chemotherapeutic Agents Commonly Used in Gynecological Cancers

Chemotherapy regimens will be discussed in other chapters of this textbook. Suffice to say, there are many agents used to treat gynecological cancers in the older woman; and tailoring management to the individual is the key.

While there is data in the literature regarding the pharmacology of specific chemotherapeutic agents, these studies and trials have not been designed to

specifically answer questions regarding age-related pharmacological changes – there are few trials that test efficacy and toxicity of age-related dose adaptation, versus standard dosing. Thus, dose adaptation based on expected physiological and pharmacological changes is an unvalidated approach [87].

Furthermore, some of the regimens involve combination chemotherapy – and while their efficacy and toxicities are studied, there is limited pharmacological evidence with regard to PK and PD of such regimens.

Carboplatin

Platinum-based chemotherapy is the cornerstone of the management of all women with epithelial ovarian cancer, regardless of age. Carboplatin when given either as a single agent orin combination with paclitaxel is well tolerated in patients of all ages, and its use should not be withheld on the basis of age alone [18, 28].

Carboplatin is 95 % excreted via the kidneys, and care is required when the drug is used in older adults [42, 43]. It is advised to use a formula to calculate CrCl (e.g., Cockcroft-Gault, Wright or Jelliffe) and use the derived figure in the Calvert formula to calculate the desired dose. The area under the curve (AUC) range of carboplatin prescribed is usually between 5 and 7.5 [79]. The Chatelut formula is another valid method of carboplatin dosing, more commonly used in Europe. Increasing age is taken into account in the formulae allowing clinicians to tailor doses individually [42, 43].

Compared to cisplatin, carboplatin has lower rates of nephrotoxicity and peripheral neuropathy. However, myelosuppression rates are higher, and appropriate supportive care and dose and interval adjustments may be necessary.

Paclitaxel

Paclitaxel in combination with carboplatin is considered standard first-line therapy in patients with epithelial ovarian cancer regardless of age, and use of it in the elderly population is common place [12, 18, 83].

However, given the similar efficacy of single-agent carboplatin with less toxicity and the subgroup analysis of the over-65 age group in the ICON 3 trial showing no efficacy advantage in the combined carboplatin/paclitaxel group, single-agent carboplatin is also a reasonable alternative [56]. Other studies have shown that combination of paclitaxel increases rates of neutropenia, thrombocytopenia, infection, alopecia, and peripheral neuropathy, as well as alopecia and debilitating arthralgias and myalgias [37, 80].

The pharmacokinetics of paclitaxel has been studied – it is 97 % protein bound and metabolized by the cytochrome P450 system and excreted in bile. Thus, drugs known to interact with Phase 1 reactions may result in interfering with paclitaxel concentrations, affecting efficacy and toxicity.

With regard to the a regimen of paclitaxel 175 mg/m^2 over 3 h, every 3 weeks in a total of 153 patients, a study on behalf of the cancer and leukemia Group B showed the AUC of paclitaxel increased, and the mean paclitaxel clearance decreased correlating with increasing age. The older patients experienced increased incidence of neutropenia; and a lower absolute neutrophil count nadir than the younger cohorts but this did not result into a clinically significant adverse sequelae – there were no higher rates of hospitalization, fever >38 °C or administration of intravenous antibiotics [41–43].

The results of studies with regard to the pharmacokinetics of paclitaxel administered weekly are conflicting. Small cohort studies have found either slight decrease in paclitaxel clearance in the elderly compared to younger patients [71] or no variation with at all [24].

However, decreased clearance reported in the CALGB and Smorenburg studies may be accounted for by decreased clearance of the paclitaxel formulation delivery vehicle, Cremophor EL. This polyoxyethylated castor oil solvent forms micelles in the bloodstream and binds paclitaxel preventing it from distributing into tissues [74].

Indeed, there is a difference in pharmacokinetics between Cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007, marketed as Abraxane) and paclitaxel formulated in Cremophor (Taxol). Abraxane, in comparison to Taxol, has higher plasma clearance and a larger volume of distribution [73].

Docetaxel

Docetaxel is 94 % protein bound, extensively metabolized in the liver by cytochrome p450 enzymes, and excreted in bile [42, 43]. Age is not believed to be major factor with regard to pharmacokinetic behavior of docetaxel, with one study of 640 patients showing a modest 7 % in clearance in an older patient.

As mentioned, the drug is predominantly cleared by the liver and a decrease in docetaxel clearance was a strong predictor of grade 4 neutropenia and febrile neutropenia. Hence, dose adjustment in patients with hepatic impairment is recommended [9, 30].

Doxorubicin and Pegylated Liposomal Doxorubicin (PLD)

Anthracyclines, especially doxorubicin, were part of first-line treatment in ovarian cancer. This has been superseded by the platinum-taxane combination in the first-line setting. Doxorubicin causing cardiomyopathy is a well-documented toxicity and limits its use, especially in the elderly patient setting.

Pegylated liposomal doxorubicin (PLD) is doxorubicin in hydrocholoric acid, encapsulated in a liposome and stabilized by attaching methoxypolyethylene glycol to the surface. Thus, this serves to evade the immune system/reticuloendothelial system (RES), increases its serum half-life, and thus has different PK and PD profiles compared to conventional doxorubicin [11].

Conventional doxorubicin is estimated to be between 50 and 85 % protein bound and metabolized by the liver, 50 % of the drug is excreted in bile, with estimated ~12 % renally and the rest in feces. It has a larger volume of distribution. Thus, consideration should be given in states of hypoalbuminemia and hepatic dysfunction [51].

In contrast, the liposomal component of PLD slows down drug release and hence bioavailability thereby reducing renal clearance of the drug. With longer circulation time, the drug accumulates more in tissues with increased permeability – tumor concentrations of doxorubicin are 4–11 folds higher in PLD compared to conventional doxorubicin [23]. Liposomes are cleared by the reticuloendothelial system (RES). The pegylation component protects liposomes from opsonization and delays its clearance by the RES [51, 89].

PLD has been used in combination as second- and third-line therapy, and there is data that it has activity in the first-line setting – as reported in the MITO-2 trial [57]. In the context of relapsed ovarian cancer, the recent CALYPSO study shows that in the elderly population group of 157 patients aged over 70, the carboplatin-PLD (C-PLD) arm had favorable side effect profile compared to the carboplatin-paclitaxel (C-P) arm, with reduced rates of peripheral neuropathy and alopecia [37].

The side effect profile of PLD differs, in that it causes less myelosuppression, cardiotoxicity, and alopecia, but more mucositis, stomatitis, and hand-foot syndrome (HFS) versus conventional doxorubicin [23, 42, 43, 64].

Topotecan

Topotecan, of the camptothecin family, is a topoisomerase inhibitor used in recurrent or refractory ovarian cancer; and its role has been investigated in cervical cancers [47].

While there is an oral formulation available, this is not used in gynecological cancers. Topotecan has a high volume of distribution, thus good tissue penetration and also good penetration into the cerebrospinal fluid [6, 47, 66].

The half-life of topotecan is 3 h, and renal clearance accounts for 30 % of drug excretion, although the other mechanisms of excretion are to be fully understood in humans [42, 43, 47]. It is advised that patients with moderate renal dysfunction undergo dose reduction and perhaps weekly administration, otherwise, this leaves them at risk of fatal myelosuppression [2, 87].

Gemcitabine

Gemcitabine has a role in relapsed or recurrent ovarian cancer and it is generally well tolerated. While there is marked interindividual variability in gemcitabine clearance, with an approximately 30-fold difference in clearance rates, it may not be of clinical significance as its median half-life post-infusion is 8 min [88].

Toxicities reported include neutropenia and thrombocytopenia, and dose modifications are suggested for significant hepatic and renal impairment. Gemcitabine is well tolerated as a single agent in the older population, with minimal toxicity [42, 43, 69, 81].

Conclusions

Chemotherapy is a key component of treatment of women with epithelial ovarian cancer regardless of age. Increasing comorbidities and changes in drug pharmacodynamics and pharmacokinetics with increasing age can lead to increased toxicity. The assessment of renal function is vital for accurate dosing of renally excreted agents such as carboplatin. While data from clinical trials specifically in older adults is limited, data from subgroups of elderly patients informs clinicians of the utility and toxicity profiles of commonly used chemotherapy agents. With care and careful assessment, chemotherapy can be given to older adults without significant toxicity.

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Chapter 6
Preoperative Risk Assessment

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Abstract Surgical excision and/or cytoreduction currently represent the treatment of choice for most gynecological tumors, regardless of the patients' age. A robust body of evidence supports this. Despite operative complications and mortality, long-term cancer-related survival may be significantly improved by an aggressive surgical approach in the older age group as it is for younger women.

As older patients are characterized by a marked heterogeneity that increases with advancing age, it is important to establish preoperatively whether the older surgical patient is fit or has limited physiological reserves. Elements of a geriatric assessment, such as functional status including gait speed, comorbidity, nutritional status, depression, and cognitive function have all been found to be associated with postoperative morbidity. Some of these factors may be optimized before surgery. Thus, adding geriatric assessment to the standard preoperative protocol in older women with gynecological cancers may provide a more precise risk assessment and guide preoperative interventions.

Keywords Preoperative risk • Comorbidity • Gynecological cancer • Cytoreduction Geriatric oncology

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Surgical excision and/or cytoreduction currently represent the treatment of choice for most gynecological tumors, regardless of the patients' age. A robust body of evidence supports this [1–5].

Despite operative complications and mortality, long-term cancer-related survival may be significantly improved by an aggressive surgical approach in the older age group as it is for younger women [6].

Age is never the less considered to negatively impact on overall survival in gynecological oncology [7]. Historical series have so far failed to clarify the reasons behind this [8–13] since differences in tumor biology, number of comorbidities, malnourishment, patients' preference, and variations in patterns of care play a significant role in the decision-making process, ultimately affecting the outcome. Furthermore, most studies lack information about these issues. It should be recognized that these factors are closely interrelated. Their combination unfortunately results in underutilization of surgery as well as chemotherapy in the treatment of older women [7, 8, 12].

The knotty relationship between advanced age and comorbid conditions has been targeted by some research groups, but a final conclusion could not be reached [7]. One of the reasons for this is that methods for measuring comorbidity vary substantially between studies. Some studies simply count the number of comorbidities reported by the patient, other studies measure the number *and* severity of comorbidities, while yet other studies measure comorbidity burden through their impact on physical performance.

The severity of comorbidity associates with survival in elderly cancer patients, independent of cancer stage [14]. Not surprisingly, it has been shown that the prognostic importance of overall comorbidity depends on the mortality burden of the index cancer: comorbidities seem to have the greatest prognostic impact among groups with the highest survival rate and least impact in groups with the lowest survival rate [15]. Cancer treatment may be harmful if tumor complications are unlikely to occur during the patient's remaining life time.

The available evidence indicates that comorbidity is an independent contributing factor for adverse outcomes after cancer surgery, both when studying the comorbidity burden and independent comorbidities.

Risk Assessment

To bring new light on the impact of comorbidity and physical function on outcomes after surgery, it is crucial to collect specific data and to provide a clear assessment of the patients' frailty before treatment takes place, even before a treatment plan is designed. Too many scientific articles from highly rewarded institutions are still reporting on highly biased onco-geriatric series where a few super-fit older patients are targeted [16]. More on lack of understanding of frailty is likely to be responsible for the unacceptable variation in the surgical management of older cancer patients.

This variation is also reflected between more or less aggressive procedures, with older patients being more often undertreated or not treated at all [17].

Older cancer patients represent a very diverse population, and it is crucial to frame each individual according to frailty in order to tailor treatment plans. This information is also very useful when consenting older cancer patients and when discussing the real advantages of a procedure against the risks it entails. Sharma and colleagues looked at cytoreductive surgery with focus on complications and survival in patients with surgical risk factors such as high age and multiple comorbidities. They found that aggressive optimal cytoreduction could be achieved in the majority of patients with multiple surgical risk factors and was associated with a low complication rate [3]. Of note, this was a retrospective series, and complications might have been underreported. Nevertheless, survival was influenced by residual disease and not by patient's age. Furthermore, there are a number of older individuals for whom a careful assessment may detect early stage disability and geriatric syndromes some of which could be promptly treated thus resulting into better short-term outcomes.

Over the last decade, lessons have been learned from geriatricians, and the use of validated assessment tools is being considered in oncological practice [18]. It has been shown that a comprehensive geriatric assessment (CGA) adds substantial information on the functional assessment of older cancer patients, particularly those with a good performance status (PS). The role of PS as the sole reliable marker of functional status has lost consistency for older cancer patients. The American Society of Anesthesiologists score (ASA) is helpful in predicting mortality on the general population but was not found to be predictive of postoperative complications and hospital stay in onco-geriatric series [19].

The Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) and its modification P-POSSUM have been prospectively validated in surgical series, but they seem to be useless in predicting the risk of patients undergoing gynecological cancer surgery [20].

It is only recently that CGA has been applied to an onco-geriatric surgical series in which 460 cases were prospectively entered into an observational study with the aim of defining the general health condition of senior cancer individuals (preoperative assessment of cancer in the elderly) [19]. Different measurements of functional status seemed to be the most important predictors of postoperative outcomes: 30-day morbidity is principally related to instrumental activities of daily living and brief fatigue inventory (BFI), whereas the postoperative hospital stay correlates with activities (of daily living ADL). There is mounting evidence relating frailty to adverse surgical outcomes, but studies in gynecological cancer surgery are lacking.

At present, efforts are being made to develop reliable tools on the basis of previous experience, with the prerequisite of being quick and user friendly. The decision-making process would certainly benefit by screening patients in clinic, with the more vulnerable ones requiring multidisciplinary management under specialist care and with the geriatricians' involvement. The ongoing PREOP research project is looking at the reliability of new assessment instruments, that is, Groningen Frailty

Index, Vulnerable Elders Survey, or an objective functional assessment such as the timed "up and go."

For those patients who are asking for surgery, it is critical to get them patiently and carefully informed about the possible occurrence of complications. It is crucial to get them in the right frame of mind; patients should be prepared to hold on if they develop an infection or any substantial postoperative problem. A positive and determined attitude is the indispensable and essential ingredient that will assist reemerging from a troubled postoperative course. Poorly motivated and depressed patients are not optimal candidates; Geriatric Depression Scale (GDS) helps to carefully frame the patient's attitude and state of mind. Furthermore, depression may often be successfully treated, for example, with selective serotonin reuptake inhibitors.

Among gynecological cancer patients, the prevalence of malnutrition is approximately 20 % at time of diagnosis [21]. It has been suggested that up to one fifth of patients with cancer die from the effects of malnutrition than from the malignancy itself [22]. Malnourishment is particularly prevalent in older patients. Adequate nutritional status affects gynecologic oncology patients' survival and quality of life as it can improve a patient's ability to tolerate oncological therapies including surgery [23]. In the surgical patient, the association of malnutrition with poor postoperative outcomes has been well established [24, 25].

Malnourishment as a predictor of postoperative complications in gynecological cancer patients has been rarely investigated (never on older patients). Prealbumin was evaluated as a criterion to determine whether cytoreductive surgery ought to be performed for ovarian cancer and low prealbumin levels correlated with occurrence of postoperative complications. Postoperative complications are commonly associated with low albumin and prealbumin levels [26, 27].

In a recent experience by Kathiresan and colleagues, decreased albumin significantly associated with a higher rate of postoperative complications, hospital readmissions, reoperations, ICU admissions, and cancer recurrence [28].

An accurate prehabilitative program entails the identification of weaknesses such as malnourishment, dehydration, iron deficiency, infections, cardiovascular conditions, electrolytic imbalance, depression, and physical performance, in view of actively engaging the patient into an intensive program to allow correction (or at least optimization) of the deranged functions.

The association between physical fitness and outcome following major surgery is well described – less-fit patients having a higher incidence of perioperative morbidity and mortality. This has led to the idea of physical training (exercise training) as a perioperative intervention with the aim of improving postoperative outcome [29].

Preoperative exercising, physical training and inspiratory muscle training, associates to better outcomes. Prehabilitation using continuous or interval training has been shown to improve fitness, but the impact on surgical outcomes remains ill defined. Taken together, these findings are encouraging and supporting the notion that pre- and postoperative exercise training may be of benefit to patients. There is an urgent need for adequately powered randomized control studies addressing appropriate clinical outcomes in this field [30–32].

Patients' Perspectives and Targets

Before embarking in any treatment planning with older patients, it is crucial to appreciate the patient's targets and expectations as these might be substantially different from what the care team might be predicting.

Despite that operative morbidity as well as prolonged hospitalizations may occur, the majority of patients will be able to receive oncological treatment without unreasonable delays. In addition, most patients will be discharged to home rather than intermediate care facilities indicating maintenance of independence and quality of life [33].

Congestive heart failure is the most common complication, and postoperative deaths predominantly occur in patients with preexisting cardiovascular disease.

Technical skills, both surgical and anesthetic, may influence short-term outcomes. The operating team should be up to date with recent technical advancements and careful handling, but, most importantly, older surgical cancer patients should be considered for early discharge (from hospital as well as intensive care units), prompt mobilization, early oral feeding, and the use of suprapubic urinary catheters in males, which has been shown to reduce urinary complications.

It is also important to realize how quality of life gains absolute priority in the older subgroup. Any alternative treatment that might cause significant disabilities should be critically considered.

Delirium is frequently reported as being highly prevalent in elderly surgical series, although most surgical teams are unaware of it because the time spent with the patient is so short that cognitive changes go undetected. Although there is no publication clarifying the occurrence, prevalence, and severity of postoperative delirium in older patients operated for gynecological malignancies, its detection is important as its occurrence impacts on the length of hospital stay, morbidity, and mortality rates. Furthermore, it is important to know that the most common risk factor for postoperative delirium is preoperative cognitive dysfunction. As delirium may be prevented, a preoperative work-up in older patients should include a cognitive screening [34, 35].

More clinical research is needed to tailor treatment to onco-geriatric series. Until this has occurred, it is not appropriate to offer substandard surgery or not to consider a definitive surgical operation based on chronological age.

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Chapter 7
Genetics and Gynecological Cancer

Beth Overmoyer

Abstract Several characteristics are associated with familial cancer syndromes, e.g., the disease onset usually occurs at a younger age than that associated with sporadic cancers. However, an inherited predisposition to gynecologic malignancies remains an important component of the care of the elderly woman, not only as it effects her personal treatment of cancer and the prevention and screening for other malignancies that she may be at risk for, but also the implications for cancer risk among her relatives. For this reason, a discussion of the genetics associated with an inherited predisposition to gynecologic malignancy pertains to women of all ages.

Keywords Genetics • Gynecological cancers • Mutations • Ovarian cancer • Endometrial cancer • Colorectal cancer

Familial Linkage of Gynecologic Cancers

Familial cancer syndromes link multiple malignancies with rare but highly penetrant germline mutations. Other less well-defined genetic predisposition to gynecologic malignancies have been demonstrated among first-degree relatives evaluated within large population databases. Historical accounts of familial malignancies have been shown to be considerably erroneous in the description of first-degree relatives and even more inaccurate when describing diagnosis in second- or third-degree relatives [1]. Population databases provide confirmed documentation of cancer diagnoses and include an adequate number of cases that suggest a familial risk of developing either endometrial or ovarian cancer among first-degree relatives diagnosed

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with these diseases. A Danish population-based case control study demonstrated a 2.4 overall risk (OR) of developing ovarian cancer among first-degree relatives, i.e., mother, sister, or daughter. This was also associated with a greater propensity to develop disease at a younger age, i.e., ≤50 years (OR = 5.3), compared with the risk of developing ovarian cancer at an older age (OR = 1.8) [2].

A familial risk also appears to be associated with the development of endometrial cancer. Endometrial cancer among first-degree relatives was found to have a relative risk of 1.8 determined by an evaluation of the Utah population database (UPDB) [3]. This elevated risk was also extended to include second-degree relatives (RR = 1.22) and third-degree relatives (RR = 1.12). These findings suggest a more diverse genetic contribution to gynecologic cancer risk, which may be due to the inheritance of several low-penetrance genes.

Hereditary Breast and Ovarian Cancers (HBOC)

Clinical Aspects of HBOC

In general, the lifetime risk of developing ovarian cancer is approximately 1.4 %. Approximately 10–13 % of ovarian cancer is linked with an inherited susceptibility. Genomic mutations in the breast cancer-susceptibility genes known as BRCA1 or BRCA2 account for more than 90 % of ovarian cancers associated with the hereditary breast-ovarian cancer (HBOC) syndrome and between 65 and 85 % of all hereditary ovarian cancers. BRCA1 mutations are also associated with a higher risk of developing breast cancer, whereas other malignancies, such as pancreatic, prostate, melanoma, and breast (male and female) are linked with a BRCA2 mutation. Among BRCA1 mutation carriers, the estimated lifetime risk (up to age 70 years) of developing ovarian cancer is between 24 and 39 %. Although it is more common among younger women (age <50 years), after the age of 30 years, the risk continues to increase proportionately [4]. The average age of onset is older among BRCA2-linked ovarian cancers (older than age 60 years), and the incidence increases up to age 60, and then seems to decrease slightly. When compared with BRCA1 mutations, the estimated risk of ovarian cancer is less among those with BRCA2 mutations: 8.4–21 % [5–7].

The prevalence of these mutations in the general population is approximately 1:400 to 1:800. The penetrance of these mutations is affected by family history wherein the risk of ovarian cancer is increased when there are first- or second-degree relatives with ovarian or fallopian tube cancers [8–10]. This impact is most likely due to a combination of shared environmental factors and the coincident inheritance of genetic modifiers which influence BRCA penetrance [11]. Genome-wide association studies (GWAS) will improve the detection of common genetic variants, i.e., single nucleotide polymorphisms (SNPs), that are associated with a higher population frequency but a lower disease penetrance. The clinical importance of these findings are yet unknown.

The histopathology of ovarian cancer associated with BRCA mutations is predominantly invasive epithelial high-grade serous carcinoma with a high rate of TP53 mutations; however, there are infrequent occurrences of clear cell carcinoma (associated with BRCA2 mutations) and endometrioid carcinomas that do not arise from areas of endometriosis [12–15]. Details on the treatment and behavior of BRCA-linked ovarian cancer are discussed elsewhere in this textbook.

BRCA Genetic Function

BRCA1 is located on chromosome 17q21, and it, as well as BRCA2 positioned on chromosome 13q12.3, encodes very large proteins that function to preserve chromosomal stability by managing DNA repair, DNA recombination, cell cycle control, and transcription [16, 17]. BRCA1 and BRCA2 appear to function as tumor suppressor genes involved in common cellular pathways [18]. Loss of function of one BRCA allele caused by a genomic mutation is associated with an increased risk of developing cancer; however, loss of heterozygosity (LOH), defined as the somatic loss of function of the complimentary BRCA allele, is directly tied to cancer formation [19].

DNA double-strand breaks can be repaired in many ways, but the least error-prone mechanism involves homologous recombination wherein homologous DNA is exchanged between identical sister chromosomes. BRCA2 functions to control the localization and function of RAD51, a recombination enzyme that is critical for homologous recombination. The "partner and localizer of BRCA2," i.e., PALB2, is associated with 50 % of cellular BRCA2 and is necessary for recruitment of BRCA2 to the site of DNA damage [20, 21]. PALB2 also connects BRCA1 and BRCA2 to create a "BRCA complex" which supports a tumor suppression pathway consisting of a BRCA1-PALB2-BRCA2-RAD51 initiation of homologous recombination. In this way, the BRCA genes are considered "caretakers," which suppress genomic instability by avoiding deleterious mechanisms of DNA repair that are associated with significant risks of error, such as nonhomologous end-joining or single-strand annealing [18].

The integral association of BRCA function and chromosomal instability is exemplified by the genetic profiles of HBOC wherein a mean of 41 % of the genome was found to be altered in BRCA-linked cancers [22]. The BRCA1-mutated cancers were found to have gains in TP53 and ERBB2 genes, as well as others. This genetic complexity suggests that cancer development occurs along a diverse range of pathways and a greater understanding is needed to improve therapeutic targets for ovarian cancer.

BRCA Specific Mutations

The majority of deleterious germline mutations involving BRCA1 and BRCA2 are nonsense substitutions and small deletions or insertions resulting in the formation of

a truncated protein. In addition to the standard qualitative PCR-based methods of determining point mutations, other laboratory techniques are required to detect large genomic rearrangements (LGR), such as exon deletions and/or duplications [23]. LGR account for approximately 5–19 % of mutations associated with HBOC and occurs more commonly among BRCA1 mutations compared with BRCA2 [24]. This is most likely due to differences in the surrounding genetic structure, such as the higher incidence of Alu repeats found in BRCA1 [25]. The frequency of LGR within a population is most likely due to the effect of founder mutations. "Founder" mutations can be defined as genomic mutations present in specific ethnic populations which are relatively closed by means of geography or cultural restrictions. Locations of founder mutations contribute to the variation of risk in developing specific genetically linked malignancies.

The exact location of an inherited BRCA germline mutation is associated with variations in risk of developing multiple malignancies. Specifically, a region of BRCA2 known as the "ovarian cancer cluster region" (OCCR) encompasses a 3.3-kb region on exon 11, and mutations occurring within this region are associated with a lower risk of developing female breast cancer (33–52 %) and prostate cancer (19 %), and a higher risk of developing ovarian cancer (14–27 %) [26]. This region contains the RAD51-binding domain of BRCA2, which may contribute to the variation in cancer phenotype associated with mutations in the OCCR. Specifically, RAD51C is located on 17q25.1, and protein truncating mutations have been demonstrated in families with HBOC, but not in families with breast cancer only [27].

Several founder mutations exist in the BRCA1 and BRCA2 genes. Among the Ashkenazi Jewish population (Eastern European), three founder mutations account for more than 95 % of BRCA point mutations and, when combined, have a population prevalence of 2.5 %: BRCA1 – 185delAG and 5382insC, and BRCA2 – 6174delT [8, 24, 28]. The BRCA1 mutations are associated with a 37–54 % risk of developing ovarian cancer, whereas the BRCA2 mutation conveys a risk of approximately 21–23 % [7, 8]. LGR have not been found among the Ashkenazi population. The BRCA2 999del5 founder mutation accounts for approximately 6 % of ovarian cancers found in Iceland and is associated with an OR equaling 20.65 of developing ovarian cancer [29]. Ongoing investigations are finding founder mutations in other populations, such as Northeast Italy, Scotland, and Ireland [30, 31].

Fallopian Tube Malignancies

The incidence of fallopian tube carcinoma and primary peritoneal carcinoma is higher among BRCA mutation carriers, with an estimated 3.5–4.3 % risk of developing primary peritoneal carcinoma up to 20 years following risk-reducing bilateral salpingo-oophorectomy (RRSO) [32, 33]. Approximately 16–17 % of patients presenting with primary fallopian tube carcinoma are found to be BRCA positive [34, 35]. The histology of these malignancies is similar to BRCA-linked epithelial ovarian cancer, i.e., papillary serous carcinoma, and there is an increased frequency of early serous

carcinoma or tubal intraepithelial carcinomas (TICs) found in the distal fimbria of fallopian tubes in approximately 4–6 % of BRCA-positive patients undergoing RRSO [36, 37]. These changes have not been found in young women undergoing RRSO, i.e., less than 40 years, and have frequently been detected in women over the age of 60 years. There are molecular and histologic changes, e.g., TP53 mutations and increased cellular proliferation, detected within the distal fallopian tube that support the hypothesis of this being the site of origin for pelvic serous carcinoma [38–41].

Hereditary Nonpolyposis Colorectal Cancer (HNPCC): Lynch Syndrome

Clinical Aspects of HNPCC

Lynch syndrome, otherwise known as hereditary nonpolyposis colorectal cancer (HNPCC) is a familial cancer syndrome linked with an elevated risk of developing colon cancer at a younger age (<45 years) without excessive adenomatous colonic polyp formation. This syndrome is inherited in an autosomal dominant fashion, and although colon cancer is the dominant phenotype, it is associated with the development of endometrial and ovarian cancer in addition to cancer of the pancreas, stomach, upper urologic tract (ureter, renal pelvis), hepatobiliary tract, brain, and breast [14, 42, 43]. The diagnosis of HNPCC is based upon clinical criteria, originally developed in 1991 by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) and referred to as the Amsterdam I criteria [44]. The revised Bethesda criteria describe broader classification characteristics in an attempt to identify a greater number of potential carriers for testing (Table 7.1) [45]. The ICG-HNPCC modified the conditions required for testing,

Table 7.1 Revised Bethesda criteria for HNPCC (Lynch syndrome) testing [45]

1. Colorectal cancer that is diagnosed in a patient who is less than 50 years of age
2. Presence of synchronous, metachronous colorectal or other HNPCC-associated tumors (i.e., endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract and brain tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel)
3. Colorectal cancer with the MSI-H (i.e., microsatellite instability high – changes in two or more of the five NCI-recommended panels of microsatellite markers) histology (i.e., presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern) diagnosed in a patient who is less than 60 years of age
4. Colorectal cancer diagnosis in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Table 7.2 Amsterdam II criteria for HNPCC (Lynch syndrome) testing [46]

1. There should be at least three relatives with an HNPCC-associated cancer (i.e., colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
(a) One should be a first-degree relative of the other two
(b) At least two successive generations should be affected
(c) At least one should be diagnosed before age 50 years
(d) Familial adenomatous polyposis should be excluded in the colorectal cancer case(s) if any
(e) Tumors should be verified by pathological examination

now known as the Amsterdam II criteria, which are the standard set of guidelines that are currently in use (Table 7.2) [46].

Germline mutations in the DNA mismatch repair genes (MMR) (MLH1, MSH2, MSH6, PMS2) are the cause of Lynch syndrome and have a prevalence of between 1:600 and 1:2,000 [47, 48]. The lifetime risk (up to age 70 years) of developing endometrial cancer is between 40 and 72 % and a 9–12 % risk of developing ovarian cancer. Relative risks and phenotypic presentation are variable depending upon the specific germline mutation, in addition to other factors, such as race, ethnicity, gender, and age. MLH1 and MSH2 are related to 70–80 % of all HNPCC connected malignancies, and MSH6 is linked to approximately 10–20 %. Mutations in PMS2 are significantly less penetrant [49–51].

Endometrial Cancer

The incidence of endometrial cancer in the general population is 3 %; however, it is the most common extra-colonic malignancy in HNPCC. Among MLH1 and MSH2 carriers, the risk of endometrial cancer is approximately 44 % by age 70 years, with no rise in incidence associated with increasing age; cumulative risk with MLH1 is 40–54 % and cumulative risk with MSH2 is 21–42 % [50–52]. Several studies suggest a higher risk for developing endometrial cancers with MSH6 mutations [53]. This translates into a 16–26 % incidence by age 70 years and a 35–44 % incidence by age 80 years. The mean age at diagnosis is older among women with MSH6 mutations (54 years), and the risk increases sharply after the age of 50 years [53, 54]. A 15 % risk is associated with PMS2 mutation carriers to age 70 years [55]. In very young women, i.e., <40 years, the cumulative risk is less than 2 %. Most endometrial cancers are of endometrioid histology, though a spectrum of other histologies exists, such as uterine papillary serous carcinoma, clear cell carcinoma, and malignant mixed Mullerian tumor. MSH2 mutations may predispose the development of non-endometrioid cancers [48, 56].

Ovarian Cancer

HNPCC-linked ovarian cancer accounts for approximately 2 % of all ovarian cancer and 10–15 % of inherited cases of ovarian cancer. This disease usually occurs in

younger women aged 40–55 years; however, instances have been demonstrated in women living to 80 years [47, 57, 58]. The histopathology of ovarian cancer caused by MMR mutations is more commonly endometrioid; however, clear cell, mucinous, and serous subtypes are also present. In one analysis, endometrioid ovarian cancer accounted for 35 % of the malignancies, with 17 % clear cell and 28 % serous [58]. Patients with MSH2 mutations are at a twofold higher risk of developing ovarian cancer compared with those carrying MLH1 mutations – with a cumulative risk to age 70 years equaling 20 % with MLH1, a cumulative risk of 24 % with MSH2, and a cumulative risk of 1–8 % with MSH6 [51, 52, 59].

DNA MMR Genetic Function

There are many nonrandomly distributed, short repetitive DNA sequences that vary in length and are found in intragenic regions of the genome. They function to regulate gene expression through modifications of RNA stability, rates of transcription, RNA-protein interactions, and spicing efficiency [14, 49, 60]. These sequences, known as microsatellites, are highly variable, and as such, they are associated with a significant amount of replication errors which are predominantly corrected by DNA mismatch repair mechanisms (MMR). Genomic mutations of DNA MMR genes result in the inability to adequately repair these replication errors, resulting in variation of microsatellite allele length which adversely effects gene expression. This is known as microsatellite instability, which is extremely mutagenic, causing gene inactivation, activation, or overexpression. Variations in the genetic errors that occur in microsatellites contribute to the versatility of cancer phenotypes associated with HNPCC.

MSH2 (MutS homolog 2) is mapped to chromosome 2p22-21 and is only 1 MB separated from MSH6 in chromosome 2p21-16. There are multiple mechanisms of action: one being the formation of the complex hMutSα by binding the MSH6 protein to MSH2, and functions to correct single base pair errors, whereas the heterodimer hMUSα functions to repair errors of insertion and deletion. MLH1 (MutL L homolog 1) is located in chromosome 3p21, and PMS2 is in chromosome 7p22. PMS2 can complex with MLH1 forming hMutLα, which also serves to correct single base pair errors as well as insertion and deletion errors [61]. As in HBOC, a somatic mutation that occurs in the normal allele associated with the genomic DNA MMR mutation results in LOH and subsequent dysfunction of the MMR gene, with the consequent accumulation of MSI and cancer formation as the end result. Less commonly, the "second hit" to the normal allele may be an epigenetic phenomenon of promoter hypermethylation, specifically of MLH1, which results in inactivation of the allele [62, 63].

HNPCC Specific Mutations

Founder mutations also exist in HNPCC families. The founder mutation A636P (MSH2*190G→C) in the MSH2 gene has a prevalence of 0.4–0.6 % in the Ashkenazi

population and accounts for one-third of the HNPCC families in this population [64]. Twenty six percent of 122 women among 19 families with the A636P mutation developed endometrial cancer at a mean age of 51.2 years. Endometrial cancer was more prominent than colon cancer among these families, and 46.4 % were also diagnosed with a second malignancy. The cumulative risk of endometrial cancer by age 70 years was 55 % which translated to a hazard ratio (HR) of 66.7 [65]. Less common founder mutations have been detected in Swedish, Finish, and Canadian populations, often associated with the development of disease in older women [14, 66, 67].

Other Inherited Disorders

The development of gynecologic malignancies has been connected with other, less common familial cancer syndromes. Cowden syndrome (CS) is part of the PTEN hamartoma tumor syndrome (PHTS), and 80 % of patients with Cowden syndrome have autosomal dominant germline mutations in PTEN mapped to chromosome 10q23.3 [68, 69]. The criteria for the diagnosis of CS are complex due to variable age-related expression; however, endometrial cancer incidence is higher in this population, with a frequency of 5–17 % [68, 70, 71]. Li-Fraumeni syndrome (LFS) is associated with p53 mutations and has been linked to rare cases of early-onset ovarian cancer [72, 73]. Autosomal dominant mutations in the serine threonine kinase 11 gene (LKB1, STK11) result in characteristics of Peutz-Jegher syndrome (PJS), which is associated with a 20 % risk of developing ovarian cancer over a lifetime [74, 75].

Genetic Testing

The development of a malignancy among women at a younger age than the average expected age at diagnosis is a consistent feature of a familial cancer syndrome. However, genetically linked gynecologic malignancies can also occur in an older woman, and therefore a complete family history is necessary to avoid missing a potential inherited predisposition to cancer. The presence of small family size, few females in the family, adoption, hysterectomy or oophorectomy at an early age in multiple family members, and an inaccurate knowledge of family conditions can all contribute to an underestimation of a potential genetic linkage.

Several established medical associations have published recommendations on risk assessment for gynecologic malignancies which stress the importance of interacting with a physician, genetic counselor, or medical provider with expertise in cancer genetics in order to provide accurate assessment of risk, as well as options to optimize screening and prevention strategies [53, 76–80]. Counseling is paramount, since the decision to test is based upon risk/benefit perceptions. The Health Insurance and Portability and Accountability Act (HIPPAA) of 1996 prohibited the classification of a genetic test as a preexisting medical condition [77]. The federal Genetic Information Nondiscrimination Act of 2008 protects individuals from employment or health insurance discrimination due to genetic test results. In 2012, however, genetic discrimination is still a possibility when applying for disability or life insurance.

Table 7.3 SGO guidelines for genetic testing: HNPCC [76]

1. Approximately 20–25 % chance of genetic linkage – recommend testing:
   (a) Patients with endometrial or colorectal cancer meeting the revised Amsterdam criteria (see Table 7.2)
2. Approximately 5–10 % chance of genetic linkage – consider testing:
   (a) Patients with endometrial or colorectal cancer diagnosed prior to age 50 years
   (b) Patients with endometrial or colorectal cancer diagnosed at any age, with a synchronous or metachronous colon or other HNPCC-associated malignancy
   (c) Patients with endometrial or colorectal cancer diagnosed at any age, with ≥2 first- or second-degree relatives with HNPCC-associated malignancy, regardless of age
   (d) Patients with a first- or second-degree relative who meet the criteria discussed in 2a–2c

Table 7.4 SGO guidelines for genetic testing: BRCA [76]

1. Approximately 20–25 % chance of genetic linkage – recommend testing:
   (a) Women with a personal history of both breast and ovarian cancers
   (b) Women with ovarian cancer and a first-, second-, or third-degree relative with breast cancer diagnosed at ≤50 years or ovarian cancer diagnosed at any age
   (c) Women with ovarian cancer at any age or breast cancer at ≤40 years of Ashkenazi Jewish ancestry
   (d) Women with breast cancer diagnosed at ≤50 years and a first-, second-, or third-degree relative with ovarian or male breast cancer at any age
   (e) Women with a first-, or second-degree relative with a known BRCA mutation
2. Approximately 5–10 % chance of genetic linkage – consider testing:
   (a) Women with breast cancer at ≤40 years
   (b) Women with bilateral breast cancer
   (c) Women with breast cancer at ≤50 years and a first-, second-, or third-degree relative with breast cancer at ≤50 years
   (d) Women of Ashkenazi Jewish ancestry with breast cancer at ≤50 years
   (e) Women with ovarian or breast cancer at any age and >2 first-, second-, or third-degree relatives with breast cancer at any age
   (f) Unaffected women with a first- or second-degree relative that meets one of the criterion discussed in 2a–2f

The optimal individual to undergo genetic testing is usually the youngest affected individual, however, given the limitations of modern families; older women with gynecologic malignancies are often the first member to be tested, and limiting testing only to young women has been shown to miss up to 40 % of affected individuals in one study [53]. Some experts recommend genetic evaluation and testing of all women with endometrial or ovarian cancer, especially women with endometrial cancer older than 50 years, since up to 75 % of patients with endometrial cancer do not meet criteria for HNPCC [81–83]. The Society of Gynecologic Oncologists (SGO) Education Committee published guidelines that recommend genetic testing for individuals with a 20–25 % risk of carrying a germline mutation associated with cancer predisposition and offering genetic testing for those with a 5–10 % risk (Tables 7.3 and 7.4) [76, 84]. There are several mathematical models that can assist the calculation of probability of carrying a genetic mutation, such as BRCAPRO, the Tyrer-Cuzick Model (IBIS), and the Myriad Genetic Laboratories model for HBOC linkage, and the MMRpro for HNPCC risk [85–88].

Whereas genetic testing for BRCA mutations involves a simple blood test (described previously), the initial evaluation for HNPCC assesses MSI and MMR on a tumor block [23, 83, 89]. MSI testing evaluates the presence of instability among five markers. One mutated sequence is classified as MSI-low (MSI-L), whereas two or more mutated sequences are MSI-high (MSI-H). MSI testing is sensitive for HNPCC (5 % of HNPCC tumors will test negative), but not specific (20–25 % MSI-H with not have HNPCC); therefore, assessment of MMR should also be performed on the cancer [90]. The expression of MMR proteins is assessed by immunohistochemical analysis (IHC), which is 95 % sensitive for HNPCC. MSI due to promoter methylation should be differentiated from MSI due to MMR, particularly in endometrial cancer, since 25 % of sporadic endometrial cancers develop MSI due to the former process [81]. If either the IHC or MSI analysis is abnormal, germline testing is recommended via a blood test. Once a mutation is identified, all family members, including extended relatives, should be tested for the single mutation.

Variants of uncertain significance (VUS) can be found in 7 % of patients undergoing testing for HNPCC and 8 % of patients tested for BRCA mutations [53, 91]. The majority of VUS is eventually found to be genetic polymorphisms; however, until this is confirmed, the knowledge of carrying a VUS can be unsettling. Testing strategies for CS, LFS, or PJS are quite complex and beyond the scope of this textbook [68, 78].

Screening Strategies for Gynecologic Malignancies

Familial cancer syndromes as described are associated with variable risks of non-gynecologic malignancies. The recommendations for screening for non-gynecologic cancers can be found in the reference section [89]. The screening for ovarian and endometrial cancers in general is based upon expert opinion and is not evidence-based, i.e., routine screening strategies have not resulted in improved survival [92]. The screening recommendations begin at an earlier age than the general population, but they do not have an age cutoff unless preventive measures have occurred. Women under the age of 21 years are discouraged from testing.

Endometrial Cancer

Patients with HNPCC should initiate annual transvaginal ultrasound and endometrial sampling beginning at age 25–35 years [89, 90]. Premalignant pathology has been detected at an earlier stage with this screening strategy [93, 94].

Ovarian Cancer

Women with BRCA mutations should initiate transvaginal ultrasound and CA-125 screening every 6 months beginning at age 35 years or 5–10 years earlier than the age at diagnosis of the youngest individual with ovarian cancer in the family [78].

Prevention of Gynecologic Malignancies

RRSO among BRCA carriers has been shown to reduce the risk of developing ovarian or fallopian tube cancer by an estimated 80–85 %, reduce ovarian cancer mortality by 95 %, and reduce overall mortality by 76 % [32, 95, 96]. Although there may be a slight variation in outcome following RRSO when BRCA1 and BRCA2 carriers are compared, the difference in not substantial [95, 97]. Peritoneal lavage should be performed during RRSO in order to detect occult carcinoma by cytologic evaluation [98]. Although oral contraceptive use has been shown to reduce the risk of developing ovarian cancer among BRCA carriers (adjusted odds ration = 0.5), it is not considered an optimal prevention strategy given a potential increased risk of developing breast cancer [78, 99]. Women carrying BRCA mutations should consider undergoing RRSO between the ages of 35 and 40 years or after completion of childbearing. Because of the constant risk of developing ovarian or fallopian tube cancer over time and the difficulties associated with early detection, there is no acceptable age limit for the consideration of risk-reducing surgery.

In addition to RRSO, women with HNPCC are recommended to undergo prophylactic total abdominal hysterectomy (TAH) between ages 30 and 40 years, once childbearing is completed [89]. This prevention strategy has resulted in the reduction in risk of developing endometrial or ovarian cancer by more than 99 % among women with HNPCC [100, 101].

Conclusions

Understanding genetic predisposition to gynecologic malignancy has resulted in the development of testing, screening, and prevention strategies which have significantly improved morbidity and mortality. Because of variable penetrance, the focus on germline mutations should not be targeted only to young women but should include elderly women as well.

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Chapter 8
Radiotherapy

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Abstract Radiotherapy is well known that plays an essential role in the management of gynecological malignancies. It is delivered either for palliation or radical approach and often combined with other forms of treatment, such as surgery or chemotherapy. Though elderly patients tolerate irradiation treatment well, their particular physiological aspects should be always considered for the appropriate therapeutic decision making. The entry of technical advances in conjunction with the variability on treatment schedules makes the elder patients not to decline the irradiation when indicated while providing lower toxicity, rapidity of treatment delivery, and no impairment of therapeutic effectiveness. The encouragement of accrual enrolment of elder patients in prospective studies aiming to identify the best tailored irradiation treatment focusing on toxicity, efficacy, basing on their physiological and psychological aspects is mandatory.

Keywords Elderly • Radiotherapy • Gynecological • Malignancies

Abbreviations

EBRT	External beam radiotherapy
PORTEC	Postoperative radiation therapy for endometrial carcinoma trials
HIR	High-intermediate risk
EC	Endometrial cancer
LRR	Local recurrence rate
HRQL	Health-related quality of life
NAT	No adjuvant treatment
PORTEC	Postoperative radiation therapy for endometrial carcinoma trials

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VBT	Vaginal brachytherapy
GOG	Gynecologic Oncology Group trials
DFS	Disease-free survival
OS	Overall survival
DSS	Disease-specific survival
RR	Rate range
CSS	Cancer-specific survival
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
IMRT	Intensity-modulated radiotherapy
SEER	Surveillance Epidemiology and End Results
NCI	National Cancer Institute
5-FU	5-fluorouracil
FIGO	International Federation of Gynecology and Obstetrics
BT	Brachytherapy
LDR	Low-dose rate
SSR	Specific survival rates
HDRICB	High-dose-rate intracavitary brachytherapy
CCRT	Concurrent chemoradiation therapy
HDR	High-dose rate
GI	Gastrointestinal
GU	Genitourinary

Endometrial Cancer

The decision of postoperative adjuvant treatment in endometrial cancer is made by factors that influence the risk of recurrence. It is well known that patients with well-differentiated stage I tumors are generally treated with simple hysterectomy alone [1]. The impact of postoperative radiotherapy on local recurrence and survival in endometrial cancer has been examined by multiple studies [2].

A Cochrane systematic review and meta-analysis published in 2007, using data from all randomized studies with 1,770 stage I endometrial cancer patients, comparing adjuvant radiotherapy versus no radiotherapy following surgery, demonstrated that external beam radiotherapy (EBRT) reduces locoregional relapse but without differentiating survival or distant recurrences rates. With subgroup analysis, it was showed that EBRT should be considered, if multiple high-risk factors (including stage 1c and grade 3) were present and avoided in stage 1 endometrial cancer patients with no high-risk factors [3]. In fact, the PORTEC-1 trial revealed that pelvic radiotherapy reduced the 10-year locoregional relapses (5 % vs. 14 %) ($p < 0.0001$), but survival was not changed. Risk criteria for locoregional relapse were grade 3, age older than 60 years, and outer 50 % myometrial invasion. Multivariate analysis demonstrated that age greater than 60 to be a risk factor for a poorer outcome for both local control (4 % vs. 10 %) and death from endometrial cancer (4 % vs. 9 %)

[4]. In GOG-99, the highest benefit of adjuvant external beam radiotherapy was demonstrated in high-intermediate-risk (HIR) group, with a 2-year incidence of recurrence of 26 % versus 6 %. (HIR patients were defined as those with (1) moderate to poorly differentiated tumor, presence of lymphovascular invasion, and outer third myometrial invasion; (2) age 50 or greater with any two risk factors listed above; or (3) age of at least 70 with any risk factor listed above) [5].

The 15-year outcomes of PORTEC-1 confirm the relevance of HIR criteria for treatment selection. Multivariate analysis confirmed the prognostic significance of (a) grade 3 for local recurrence rate (LRR) ($p = .0003$) and for endometrial cancer (EC) death ($p < 0.0001$), (b) age >60 ($p = 0.002$ for LRR and $p = 0.01$ for EC death), and (c) myometrial invasion >50 % ($p = 0.03$ and $p = 0.02$), respectively. EBRT should be avoided in patients with low- and intermediate-risk EC [6].

Determining the long-term outcome and health-related quality of life (HRQL) of patients with endometrial carcinoma treated with or without pelvic radiotherapy in PORTEC-1 trial, among 714 patients with stage IC grade 1–2 or IB grade 2–3, randomly assigned to pelvic (EBRT) or no additional treatment (NAT), the 15-year actuarial locoregional recurrence rates were 5.8 % for EBRT versus 15.5 % for NAT ($p < 0.001$), and 15-year overall survival was 52 % versus 60 % ($p = 0.14$). Regardless the effectiveness of EBRT in reducing locoregional recurrence, its association with long-term urinary and bowel symptoms and lower physical and role-physical functioning, even 15 years after treatment, leads to its avoidance in patients with low- and intermediate-risk EC [7].

PORTEC-2 trial (postoperative radiation therapy for endometrial carcinoma – a multicenter randomized phase III trial comparing external beam radiation and vaginal brachytherapy) was based on PORTEC-1 findings that patients in the high-intermediate-risk group have improved local control with the addition of radiotherapy, and also when recurrences were present, 75 % of them occurred in the vagina [8]. In view of the conclusions above, PORTEC-2 aimed to answer the question of whether vaginal vault brachytherapy is a sufficient treatment to prevent vaginal recurrence. Over 400 patients were randomized to either external beam radiotherapy or vaginal vault brachytherapy with age greater than 60 and stage IC grade 1 or 2 or stage IB grade 3 and stage IIA (except grade 3 extending into the outer half of the myometrium). At 5-year, there was no significant difference in rates of (a) vaginal recurrence which was 1.8 % for vaginal brachytherapy (VBT) and 1.6 % for EBRT ($p = 0.74$), (b) locoregional relapse was 5.1 % for VBT and 2.1 % for EBRT ($p = 0.17$), and (c) rates of distant metastases were similar 8.3 % versus 5.7 % ($p = 0.46$), respectively. Rates of acute grade 1–2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of radiotherapy (12.6 % vs. 53.8 %). Consequently, VBT is considered as effective in ensuring vaginal control with fewer gastrointestinal toxic effects than EBRT and represents the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate-risk features [9].

Particular consideration should be given in stage IC, grade 3 endometrial cancer because analysis of 99 patients demonstrates high rate of distant metastases and endometrial carcinoma-related death. Even after pelvic RT, the locoregional relapse rates for these patients are higher than those of the other stage I patients, who were

shown to have excellent pelvic control rates after pelvic RT (97–99 %). Necessity of new strategies for adjuvant therapy should be explored to improve survival for this patient group. This raises the question whether adjuvant chemotherapy could have a positive impact in terms of reducing the risk of distant metastases and increasing survival [10].

It is still unanswered whether the high-risk patients should receive radiotherapy or chemotherapy or a combined treatment. The omission of pelvic RT was reported to leave the patients at substantial risk of pelvic failure [11]. Several groups are conducting randomized phase III trials comparing RT and chemotherapy with RT alone in high-risk endometrial cancer (stage IC, grade 3; stage II to III; and/or papillary serous or clear-cell histology) to investigate the effect of adjuvant chemotherapy [12, 13].

The PORTEC-3 will clarify many of the unresolved questions in the treatment of high-risk patients. The point is to establish overall survival and failure-free survival of patients with high-risk and advanced-stage endometrial carcinoma, treated after surgery with concurrent radiotherapy and chemotherapy and followed by adjuvant chemotherapy, in comparison with patients treated with pelvic radiation alone evaluating also the rates of treatment-related toxicity, quality of life, and pelvic and distant recurrence [14].

Controversy exists about whether high-risk patients receiving adjuvant chemotherapy should receive pelvic RT or vault brachytherapy alone, answers will be given by the ongoing randomized trial GOG 249 for patients with stage I–II EC with high-intermediate or high-risk factors that compare pelvic EBRT alone, with vaginal brachytherapy followed by adjuvant chemotherapy [15].

Unfortunately among problems encountered when considering the use of chemotherapy in the elder population are the concurrent morbidities, causing selection of the younger patients for phase II trials and leads to limited numbers of elderly women included in most reports.

Impact of Age on Treatment

Kaled M. Alektiar and colleagues showed that patient age ≥70 years was found to be a predictor of poor locoregional control, disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS) independent of other poor prognostic factors [16]. The data from the literature, in general, support this finding [17]. In the PORTEC randomized trial, which was limited to patients with stage IB, grade 2 and 3 disease and those with stage IC, grade 1 and 2 disease, older age was found to be an independent predictor of poor outcome and a significant predictor of poor DFS on multivariate analysis ($p = 0.004$). Therefore, it is reasonable to conclude from the current study as well as others that the influence of advanced age is independent of other poor prognostic factors such as deep myometrial invasion or aggressive histology.

With regard to radiation toxicity, sometimes it is assumed that elderly patients in general tolerate treatment poorly, but the available data in the literature do not support

that view. Citron and colleagues demonstrated that radiation treatment is well tolerated by elderly patients, and when acute side effects occurred, the symptoms were well controlled with medication, while significant chronic toxicity was even rarely observed [18]. The high effectiveness of radiotherapy and tolerance by the oldest old has also been described by Zachariah and colleagues concluding that age is not a contraindication to aggressive radiotherapy [19]. These are results that have been also confirmed by other studies [20]. Pignon et al. [21] reviewed nine trials of the European Organization for Research and Treatment of Cancer to investigate whether a threshold age exists beyond which pelvic radiation therapy generates more toxicity. There were 1,619 patients who were divided into 6 age categories beginning with age ≤ 50 years up to age ≥ 70 years. The rate range (RR) of severe late toxicity (grade > 2) was reported to range from 1 for those patients age ≤ 50 years to 1.55 to those patients age ≥ 70 years ($p = 0.32$). More specifically, in patients treated with adjuvant pelvic radiation therapy in the PORTEC trial, the 5-year rate of late complications was not significantly higher in patients age ≥ 70 years compared with younger patients ($p = 0.68$).

A retrospective study analyzing postoperative radiotherapy for early stage elderly endometrial cancer patients revealed that the patient and tumor factors that were correlated with an increased risk of recurrence included cervical involvement and grade 3 disease. Higher pelvic recurrence was observed among patients that have omitted radiotherapy. The high-risk patients treated with adjuvant RT also had better 3-year DFS and cancer-specific survival (CSS). Although acute side effects were common, these symptoms were well controlled with medication. Overall, only 1 (3 %) of 34 patients who received adjuvant RT developed a significant chronic toxicity [22].

The necessity of adjuvant therapy for elderly endometrial cancer patients may be influenced by comorbidity. In a retrospective study, analyzing the effect of age and comorbidity on endometrial cancer treatment and outcome in a cohort of 401 patients demonstrates that in stage IC disease, the use of postoperative RT declined with advanced age (96, 97, and 74 % in patients aged <65, 65–74, and ≥75 years, respectively, $p = 0.05$) and with increased co morbidities. Among stage IC patients aged ≥75 years, pelvic/vaginal relapse occurred in 2 of 6 patients treated with hysterectomy alone compared with 0 of 20 patients treated with postoperative radiotherapy ($p = 0.006$). Although surgical therapy for endometrial cancer was not influenced by age or comorbidities, the use of postoperative radiotherapy in stage IC disease was reduced in patients with advanced age and high comorbidity index. Higher pelvic/vaginal relapse rates were present in elderly patients not treated with radiotherapy. Chronologic age alone should not preclude patients from consideration of optimal local therapy [23].

Decision to irradiate or not rests on a careful assessment of the benefits and risks. Treatment selection should be based on the highest efficacy and lowest toxicity. Promising results have been reported using intensity-modulated radiotherapy (IMRT) in endometrial cancer. Among 31 patients with endometrial cancer received adjuvant intensity-modulated-pelvic RT ± VB showed excellent local control and low toxicity rates [24]. Beriwal among 47 patients with endometrial cancer received adjuvant IMRT, reported 3-year grade ≥2 = 3.3 % toxicity [25].

However, the promising results reported by the use of IMRT in endometrial cancer, longer follow-up, and higher patient recruitment are needed. The latest data from the RTOG 0418 phase II study postoperative pelvic IMRT ± chemo in cervix and endometrial cancer demonstrated that pelvic IMRT after surgery for patients with endometrial carcinoma delivered in a multi-institutional trial with centralized quality assurance is a safe and effective treatment [26].

Cervical Cancer

Cervical cancer is the second most common malignancy in women worldwide with an increasing incidence in many developing countries. Women aged 50–79 years most commonly are diagnosed at a late stage [27]. Furthermore, advanced stage is a strong, independent risk factor of poor prognosis [28]. These data confirm the groining need for treatment for this population.

The treatment modality for cervical cancer is based on the disease's stage, prognostic factors, and patient's general health. Surgery, radiation therapy, and chemotherapy are included in the standard treatments.

According to a research analyzing medical records of more than 1,500 patients treated for invasive cervical cancer at between 1986 and 2003 and dividing the records into two categories, women younger than 70 and women 70 or older, it was reported that regardless of the tumor stage, elderly patients were likely to receive less aggressive treatment. Surgery was used to treat only 16 % of the elderly group, whereas 54 % of the younger patients underwent surgery. The rest of the patients were treated with radiation without surgery. Elderly women with cervical carcinoma are more likely to receive primary radiotherapy, to forego treatment, and to die from their disease [29].

Same data appear by a recent study based on Surveillance Epidemiology and End Results records (SEER) in women diagnosed between 1988 and 2005 with cervical cancer. Stratifying patients by age <50, 50–59, 60–69, 70–79, and ≥80 years, it was demonstrated that in women with early stage (IB1–IIA) tumors, primary surgery was performed in 54.5 % of those 70–79 years old and 33.2 % of those ≥80 years old compared to 82.0 % of women <50 years old ($p < 0.0001$). Compared with patients <50 years old, those >80 years old were less likely to undergo radical hysterectomy (odds ratio [OR], 0.10; 95 % confidence interval [CI], 0.07–0.14) and lymphadenectomy (OR, 0.11; 95 % CI, 0.08–0.16) and to receive adjuvant radiation therapy (OR, 0.06; 95 % CI, 0.01–0.35). Among women with stage IIB–IVA disease, use of brachytherapy declined with age ($p < 0.0001$). Concluding that elder women with cervical cancer are less likely to undergo surgery, receive adjuvant radiation, and receive brachytherapy [30].

Despite the fact that elderly have the tendency as described above to forgo treatment, it is also demonstrated that in the management of cervical cancer, advanced age is not a contraindication to radical radiotherapy (RT). Evaluating the long-term results from 727 patients who underwent radical radiotherapy for cervical cancer divided in three age groups ≤64 years, 65–74 years, and ≥75 years when compared the treatment results of three age groups, it has been demonstrated that RT was well tolerated and age was not a significant prognostic factor[31].

For the early stages, surgery and radiation therapy are equally effective for small-volume disease [32]. In fact for women that are medically inoperable with stage IA and CIS of the cervix, irradiation alone, consisting of intracavitary implants, represents an excellent treatment [33].

As patterns of care studies showed that increasing tumor volume has a negative prognostic effect, the treatment approach may vary within each stage as currently defined by FIGO and will depend on tumor bulk and spread pattern [34].

Lindegaard et al. in a prospective study in 114 elderly patients with median age 75.5 years referred for curative radiotherapy demonstrated that elderly patients in good performance status with advanced cancer of the uterine cervix may tolerate radical radiotherapy consisting of both brachytherapy (BT) and EBRT with acceptable toxicity (grade 3 late complications were 11 %) and reasonable survival (5-year survival according to FIGO was 61 % (I), 34 % (II), and 25 % (III)). In fact in cases with tumor size less than 2 cm or surgically unfit patients with centrally located tumors up to 5 cm or when EBRT could not be sustained – frail patients – it was offered intracavitary BT only, with a significant tumor control. It has been also demonstrated that combinations of EBRT and BT should always be applied whenever are required. Among other findings from the study was that BT could also be a valid treatment alternative in medically inoperable patients with early stage cervical cancer and that tumor size was the most important prognostic factor with respect to both tumor control and survival, whereas age per se was not a significant factor for treatment outcome [35].

Evaluating the outcome of BT as an integrated part of the treatment of elderly patients with cervical cancer, a retrospective analysis was carried out with 113 patients aged over 70-year-old treated by conventional low-dose-rate (LDR) BT. The data showed that elderly women with cervical cancer tolerated BT well and had excellent local DFS and specific survival rates (SSR). Age did not influence the effectiveness of BT in elderly patients and should be considered whenever possible [36].

Analyzing the efficacy and complication rate for high-dose-rate intracavitary brachytherapy (HDRICB), consisting of a combination with EBRT, among 295 patients aged 70 years or older with carcinoma of the uterine cervix, with a minimum of 3 years of follow-up, it has been proved that three or four fractions of HDRICB are effective for older patients [37]. In fact high-dose-rate intracavitary brachytherapy is safety and technically viable procedure for elderly women with cervical cancer [38]. A retrospective review of all cervical cancer patients treated with radiotherapy divided into non-elderly (<70) and elderly (≥70) showed that even if elderly patients had poorer overall survival outcome, they did not fare any worse compare to their younger counterparts in terms of disease-free survival, and the radiotherapy treatment was also well tolerated in both groups [39].

Recently has been published a retrospective study of 138 patients with cervical cancer, who were ≥75-year-old, 32.6 % of whom had comorbidities and received only radiotherapy. According to the data, definitive radiation therapy in elderly patients of cervical cancer has good compliance and yields satisfactory outcome. Multivariate analysis revealed that only performance status had significance on survival curves ($p = 0.0007$). The high incidence of late adverse effect reported should be considered, and a possible dose modification in radiotherapy may be investigated in future trial for elderly patients when concurrent chemoradiotherapy is given [40].

A retrospective analysis in patients aged 55 years or older for treatment of advanced cervical cancer, undergoing concurrent weekly cisplatin (40 mg/m^2) with pelvic radiation, showed similar progression-free and overall survivals as younger patients [41]. Evaluating the toxicity of the combined modality concurrent chemoradiation therapy (CCRT) in locally advanced cervical cancer patients based on cisplatin, administered weekly at a dose of 40 mg/m^2 for patients who were younger than 65 years and 30 mg/m^2 for those 65 years or over, it has been shown that 40 mg/m^2 was correlated to significantly different hematological toxicity [42]. Whereas chemoradiation based on cisplatin is the standard treatment of locally advanced cervical cancer; however, weekly carboplatin concurrent with pelvic radiation can be well tolerated in elderly patients with comorbidities such as diabetes mellitus and/or high blood pressure, however, a marginally lower survival observed [43].

In prospective randomized controlled trial with 140 patients, >60 years old with invasive carcinoma of cervix, stage IB2–IVA, between April and December 2009, underwent concurrent chemoradiotherapy, randomly assigned (half in each group) to receive weekly cisplatin at a dose of 40 mg/m^2 compared to 20 mg/m^2. It was shown that acute toxicities in the first group were significantly higher, while in both arms, the treatment responses were still comparable. Before arriving to conclusions, longer follow-up is necessary to evaluate treatment efficacy and late treatment-related toxicity [44].

Intensive monitoring is necessary of the elderly patients when aggressive multimodal protocols of combined modality treatment are used, in order to change treatment protocol early due to acute morbidity [45].

With the fact that radiotherapy for elderly patients with cervical cancer is well tolerable and the survival outcomes satisfactory, emerge that radiotherapy is a useful modality for elderly patients with cervical cancer aged 75 years old and its importance will augment in the aging society [46].

Cancer treatment decision requires a multidisciplinary and multidimensional assessment of the characteristics of the malignant disease and patient's general health status. Suggestions for the use of more aggressive modalities should be evaluated carefully, even when patients are in properly good health. In order to establish appropriate treatment strategies, combining RT with surgery and/or chemotherapy, it is mandatory to perform larger and prospective studies.

Finally, better quality of life may be achievable for the growing elderly population with regard to radiotherapy, with the use of modern techniques such as IMRT and image-guided brachytherapy [47]. Promising results are given by IMRT in terms of tumor control and toxicity [48].

Vulvar Cancer

Vulvar cancer is a disease that mainly affects elderly women. At an early stage, it reaches high rates of curability. Most common histologic type is the squamous cell carcinoma. A multifactorial analysis of risk factors in squamous vulvar cancer demonstrated that nodal status and primary lesion diameter, when considered together,

were the only variables associated with prognosis. Risk factors for nodal metastasis are clinical node status, age, degree of differentiation, tumor stage, tumor thickness, depth of stromal invasion, and presence of capillary-lymphatic space invasion [49].

The cornerstone of treatments in vulvar cancer is surgery which is often combined with other treatment modalities because of the risk of local and regional recurrence in advanced stages and occasionally because of lack of surgical candidature.

While surgery for the primary tumor and the groins is the mainstay treatment in early stage, with a strong trend nowadays toward a less radical approach, on the other hand, radiotherapy could also be a valid alternative as a primary treatment in this stage of disease. This is the case of patients, considered unsuitable for surgery – because of site or extent of disease – or medically unfit, that with radical radiation therapy could have a long-term survival [50–53]. Conservative surgery and adjuvant radiotherapy could be an alternative to radical surgery with less morbidity in elderly patients [54].

The necessity of the postoperative setting of radiotherapy is depended on pathological findings from the operative specimens. It is well known that local recurrence rates are strongly correlated with the extend of surgical margins [55, 56]. Adjuvant local radiation therapy may be indicated for surgical margins less than 8 mm, capillary-lymphatic space invasion, and thickness greater than 5 mm, particularly if the patient also has ≥2 positive nodes [57–59].

Whether adjuvant radiotherapy may improve the disease-specific survival of patients with single-node-positive vulvar cancer is still unanswered. There are conflicting data by two recent studies. Parthasarathy et al. used data from the SEER database showed benefit in patients who underwent a less extensive lymph node resection (≤12 nodes removed) [60]. In the Fons et al. [61] study where the patients have a single positive node but without extra capsular spread, there was no demonstration of any beneficial effect of adjuvant radiotherapy. The impact of adjuvant radiotherapy on survival in patients with single-node-positive vulvar cancer should be procured by a prospective randomized controlled trial.

As mentioned before among other tumor characteristics, nodal status is very important to define the appropriate treatment. A randomized trial from the Gynecologic Oncology Group (GOG) demonstrated that patients with two or more pathologically positive groin nodes treated with radical vulvectomy and bilateral superficial and deep groin node dissections had a significant decrease in groin failure when received radiation therapy to the groin and pelvis compared with pelvic node dissection. Among the 114 patients examined, significant improvement in survival rate was noticed in the group receiving adjunctive radiotherapy ($p = 0.03$). The estimated 2-year survival rates were 68 % for the radiation therapy group and 54 % for pelvic node resection group. Significant poor prognostic factors were clinically suspicious or fixed ulcerated groin nodes and two or more positive groin nodes [62].

According to NCI treatment options for groins in stage I–II vulvar cancer, based on a retrospective study well designed and with superior radiation therapy, if compared inguinofemoral irradiation to lymphadenectomy for vulvar carcinoma, there is no significant survival advantage to groin dissection versus radiation therapy to the groin, for patients with clinical N0 disease. So groin irradiation could substitute

groin dissection in women with clinical N0 disease, who refuse or are considered medically unfit to withstand groin dissections [63].

Whereas primary radiotherapy to the groin is likely to lead to a lower morbidity, studies on the efficacy of primary radiotherapy instead of surgery, in terms of groin recurrences and survival, show contradictory results. Until better evidence is available, surgery should be considered the first choice treatment for the groin nodes in women with early squamous cell cancer of the vulva. Individual patients not physically able to tolerate surgery may be treated with primary radiotherapy [64].

The entry of sentinel node detection in early stage disease performed by a quality-controlled multidisciplinary team could lead to a significant patient gain. According to multicenter observational study on sentinel node detection in patients with T1/2 (<4 cm), squamous cell cancer of the vulva demonstrated that omission of inguinofemoral lymphadenectomy when the sentinel node was found to be negative at pathologic ultrastaging did not lead to a higher groin recurrence rate, while survival is still excellent, and treatment-related morbidity is low [65].

There is no standard approach for treating locally advanced vulvar cancer (FIGO stage III and IV). Combined treatment modalities have been developed. In advanced stages, radiotherapy can be used also in the preoperative setting, in selected cases to improve operability and even decrease the extent of surgery required [65, 66]. Radiotherapy alone or eventually in a combined modality (with concurrent 5-FU or 5-FU and cisplatin) can also be used, in locally advanced vulvar cancer or in unfit for surgical procedure patients, as primary definitive treatment [67–71].

Many elderly women have multiple health care problems, and the combined treatment such as radiochemotherapy in the advanced stage disease seems to be correlated to higher rates of death of intercurrent diseases or of treatment-related complications [72]. The low incidence of the disease, the lack of randomized trials, and even the minor participation of elderly patients to them render necessary future research on new paths for treatment strategies (chemoradiation) with particular regard to survival benefit, toxicity, and death from intercurrent diseases or treatment complications.

Vaginal Cancer

Vaginal cancer is a rare entity among gynecologic malignancies accounting for about 2 % of all neoplasms of the female genitals. It is found most often in women aged 60 or older, with maximum incidence between 70 and 80 years. The most common histologic type is squamous cell carcinoma. Prognosis depends primarily on the stage of disease, but also patient's age greater than 60 years, lesions of the middle and lower third of the vagina, and poor differentiation are negatively correlated with the treatment outcome [73, 74]. In addition, the length of vaginal wall involvement has been found to be significantly correlated to survival and stage of disease in squamous cell carcinoma patients [75].

The rarity of such patients, in concomitance with the advanced age of manifestation of the disease, renders difficult to define appropriate treatment. Therapeutic

alternatives depend on stage. Surgery or radiation therapy is highly effective in early stages, while radiation therapy is the primary treatment of more advanced stages. Treatment selection is based on the lesion size and area of distribution in the vagina. The proximity of vagina with critical structures such as bladder and rectum makes difficult the curative surgical approach because of the impossibility of organs spearing. Also the luck of candidacy for surgery for elder patient makes radiotherapy the preferred modality treatment. So carefully tailored radiation therapy must be always required.

Considering the factors mentioned above, excellent results can be achieved with definitive radiation therapy for invasive squamous cell carcinoma of the vagina. Frank et al. among 193 patients reviewed records that were treated with definitive radiation therapy for squamous cell carcinoma of the vagina and have demonstrated that DSS and pelvic disease control rates correlated with International Federation of Gynecology and Obstetrics (FIGO) stage and tumor size. At 5 years, pelvic disease control rates were 86 % for stage I, 84 % for stage II, and 71 % for stages III–IVA ($p=0.027$). The incidence of major complications was correlated with FIGO stage; at 5 years, the rates of major complications were 4 % for stage I, 9 % for stage II, and 21 % for stages III–IVA ($p<0.01$) [76].

Heggemann et al. using the definitive radiotherapy as primary treatment showed also very good results and reported good tolerance of the radiotherapy regimen. Considering the data cited above since primary vagina cancer is typically a disease of the elderly, the radiotherapy approach can be the treatment of choice for this population [77].

The role of high-dose-rate (HDR) brachytherapy has been examined in 86 patients treated with primary radiotherapy. Early stages of disease (stages 0–II) were treated with intravaginal HDR brachytherapy alone ($n=26/86$), whereas locally advanced diseases (stages II–IV) received HDR brachytherapy combined with external beam therapy ($n=55/86$). Five-year recurrence-free intervals for stages 0–IV diseases were 100, 77, 50, 23, and 0 %, respectively, and were well tolerated. Chronic side effects G 1–4 were observed in ≤2 % (bladder, rectum) and 1–6 % vagina [78].

For patients with carcinoma of the vagina in early stages, surgery or radiotherapy is highly effective. Consideration of combined treatment radiotherapy after surgery should be taken when close or positive margins are present [79]. When the lesion is superficial less than 0.5 cm thick, intracavitary brachytherapy is used. When the tumor is bulky, then EBRT is needed. When the lesion is greater than 0.5 cm thick, then intracavitary brachytherapy in combination with interstitial brachytherapy is required in order to deliver a higher dose to the lesion. EBRT still has a role when there is high probability of lymph nodal invasion, such as grade 3, or infiltrating tumors [80]. When the lower third of vagina is interested by the tumor, then EBRT is used to irradiate the pelvis and/or the inguinal nodes [81].

In stage II/III is preferred a combination of EBRT and brachytherapy (intracavitary, interstitial), in order to deliver a greater dose to the primary tumor [82]. In case that surgery is used, necessity of EBRT will depend on the findings of the specimen. In more advanced stages, the radiation treatment is preferred as the mainstay treatment or for palliation.

Incidence of complication rates increases with the increasing stage [76] and the higher radiation dose [83]. The proximity of the vagina to the bladder or rectum limits treatment options and increases complications involving these organs. Carefully tailored radiation completed without significant interruption, preferably within 9 weeks [84], with highly specialized techniques, could lead to high disease control rates under the experience of a multidisciplinary team.

Treatment-Related Toxicity

Pelvic radiotherapy for gynecological cancers causes moderate to severe intestinal complications in elderly female patients. McGonigle et al. in a retrospective study showed that acute grade 3–4 gastrointestinal (GI) complications were presented in 5 % of patients while chronic in 57 % and persisted for longer than 3 months after radiation therapy. At 3-year, the actuarial chronic complication rate was 45 % for GI compared to 17 % for genitourinary (GU) ($p=0.01$). A multivariate analysis showed that two or more preexisting medical problems ($p=0.03$) and dose of external beam radiation therapy ≥45 Gy ($p=0.07$) were correlated with the development of a chronic complication [85]. Pelvic irradiation is also correlated with a substantial risk of pelvic fractures in elderly women [86]. More sensible structure to fracture is the femoral head and, in relation to the irradiation dose, presence of osteoporosis and cigarette use [87]. Whereas the standard of care for the treatment in locoregional advanced pelvic cancers is chemoradiation [88], it should always bear in mind that that both modalities are myelosuppressive. With regard to irradiation, it is proved that the volume and radiation doses of the pelvic bone marrow within the treatment field are correlated to the hematologic toxicity [89]. Good results are given by new modern techniques such as IMRT [90–92]. Regarding the IMRT procedure as for the even more exciting area of research, the image-guided IMRT should be considered the costeffectiveness factor and the comorbidities that could affect the immobilization (e.g., Parkinson disease).

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Chapter 9
Ovarian Cancer: Symptoms and Presentation

Barbara Goff

Abstract The incidence of ovarian cancer increases with age however there is no screening protocol that has been shown to reduce the morbidity or mortality from ovarian cancer. Currently the best way to make a diagnosis of ovarian cancer is for clinicians to have a high index of suspicion in a symptomatic patient. As a result, delays in diagnosis are very common. The symptoms that are most commonly associated with ovarian cancer include bloating, abdominal or pelvic pain, difficulty eating and feeling full quickly. Symptoms that are of recent onset (6–12 months), that occur more than 12 times month and have persisted fort least 2–3 weeks are most concerning. Recently the development of a symptom index which takes into account the type of symptom, duration and frequency has been shown to have a sensitivity of 70% and a specificity of 80%. Symptoms in elderly women are no different than younger women and the symptom index has a higher sensitivity and specificity in older women. Currently symptoms are being evaluated as a possible low cost method for early detection of ovarian cancer.

Keywords Ovarian cancer • Cancer symptoms • Abdominal pain • Diagnosis • Screening

Over the past decade, there has been a considerable amount of research showing that the vast majority of women with ovarian cancer will have symptoms prior to their diagnosis. In the most recent technical bulletin from the American Congress of Obstetricians and Gynecologists, it stated that the best way to diagnose ovarian cancer is for practitioners to have a high index of suspicion in symptomatic women [1].

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Table 9.1 Frequency of symptoms in ovarian cancer patients and women without ovarian cancer visiting primary care clinic

Symptom	% Frequency in ovarian cancer patients	% Frequency in clinic controls
None	5	5
Increased abdominal size	64	19
Bloating	70	36
Fatigue	61	54
Abdominal pain	50	30
Indigestion	36	37
Urinary frequency	55	32
Pelvic pain	41	26
Constipation	25	32
Back pain	34	61
Unable to eat normally	36	5
Palpable mass	20	2
Vaginal bleeding	18	25
Nausea	3	22
Diarrhea	25	32

Adapted from Goff et al. [6, 7]

This is a new trend as, historically, ovarian cancer had always been called "the silent killer" because symptoms were not thought to develop until advanced stages, when chances of cure were very poor. Not that long ago most textbooks in internal medicine, family practice, and obstetrics and gynecology stated that ovarian cancer was an asymptomatic disease. However, as new research has shown that symptom identification is important in the diagnosis of this disease, there has been a focus on educating women and practitioners about these symptoms [2].

In the 1980s and 1990s, there were several retrospective studies that examined symptoms in women with ovarian cancer [3–5]. These studies found that ovarian cancer patients did have symptoms usually for 3–6 months prior to diagnosis; however, the symptoms were often vague and not necessarily gynecologic in nature. While there were significant similarities across these studies about the presence of symptoms prior to diagnosis, they were criticized because of small numbers and retrospective chart analysis for data collection.

In 2000, a survey of 1,725 women with ovarian cancer from the US and Canada was published evaluating the type of symptoms, if any, that women experienced prior to diagnosis and factors associated with delays in diagnosis [6]. While the study was retrospective (all women had been diagnosed with ovarian cancer 1–12 years previously), the findings were significant in that 95 % of women reported symptoms an average of 3–6 months before seeing a physician. The most common symptoms associated with ovarian cancer were abdominal (77 %), gastrointestinal (70 %), pain (58 %), constitutional (50 %), urinary (34 %), and pelvic (26 %). Interestingly, gynecologic symptoms were the least common (Table 9.1). Evaluation by stage revealed that in patients with early stage disease (having cure rates of 70–90 %), 89 % complained of symptoms prior to diagnosis. The type of symptoms did not vary based on

Table 9.2 Factors associated with clinician delay in diagnosing ovarian cancer

Physician factors
Omission of pelvic examination at first visit
Omission of diagnostic studies (ultrasonography, CT, CA 125)
Wrong initial diagnosis:
Nothing wrong
Depression
Stress
Irritable bowel syndrome
Gastritis
Patient factors
Having a multitude of symptoms
Younger age
Ignoring her symptoms

Adapted from Goff et al. [6]

stage; women with early stage disease had the same symptom presentation as those with advanced stage disease. There was also no difference in symptom presentation based on age or menopausal status of ovarian cancer patients.

Of the 1,725 survey respondents, 35 % reported more than a 6-month delay in diagnosis [7]. Both physician- and patient-related delays in diagnosis were common. Physician delays were commonly associated with misdiagnosing women with irritable bowel syndrome, stress, gastritis, or depression before the diagnosis of ovarian cancer (Table 9.2). In this study, 30 % of women were treated with a prescription medication for another condition within the months preceding their ovarian cancer diagnosis. Physician misdiagnosis was correlated with more advanced stage of disease at presentation. Patient-related delays were primarily associated with women not recognizing their symptoms as something that could be serious. In this study, women who said they ignored their symptoms were significantly more likely to be diagnosed with advanced stage disease as compared to those who felt they did not ignore their symptoms. Factors associated with delays in diagnosis are shown in Table 9.2. While this was an important study documenting the presence of symptoms in women with ovarian cancer, there were significant weaknesses in study design. First, there were no controls for comparison and second, there were unavoidable issues of recall bias as all the women knew they had ovarian cancer.

In 2001, a case control study of symptoms in ovarian cancer patients from Memorial Sloan-Kettering Cancer Center was published [8]. Women with ovarian cancer ($n=168$) and controls ($n=251$) were interviewed about symptoms experienced during the preceding 6 months. The investigators found that ovarian cancer patients were significantly more likely to complain of bloating, lack of appetite, abdominal pain, fatigue, urinary frequency, and constipation than controls (Table 9.3). In this study, evaluation of women with early stage disease found that 89 % of women complained of symptoms prior to diagnosis, and there was no significant difference in the symptoms reported between those with early versus late-stage disease. When the authors compared symptoms in women with early stage disease to controls, the odds ratios were still significant:

Table 9.3 Comparison of symptoms between ovarian cancer cases and controls

	OR (95 % CI)		
Symptom	Olson et al. [8]	Goff et al. [7]	Lurie et al. [9]
Bloating	25.3 (15.5–40.9)	3.6 (1.8–2.0)	21.2 (121.4–32.3)
Difficulty eating/lack of appetite	8.8 (4.3–18.2)	2.5 (1.3–5.0)	–
Abdominal pain	6.2 (4.0–9.6)	2.3 (1.2–4.4)	6.5 (4.7–9.0)
Urinary symptoms	3.5 (2.2–5.7)	2.5 (1.3–4.8)	1.9 (1.4–2.6)
Constipation	3.5 (2.0–6.3)	1.6 (0.7–1.4)	1.1 (0.8–1.4)
Fatigue	2.9 (2.5–6.1)	1.4 (0.7–2.7)	2.2 (1.4–2.6)
Abdominal mass	–	5.4 (2.4–12.0)	24.1 (10.0–58.1)

Adapted from Olson et al. [8], Goff et al. [7], Lurie et al. [9]

bloating (OR 19.2 95 %, CI 9.9–37.5); abdominal pain (OR 5.5 95 %, CI 2.8–10.8); constipation (OR 5.5 95 %, CI 2.5–12.0).

One of the concerns regarding the Memorial study was that the controls were obtained through random digit dialing and were not necessarily women visiting a physician's office for a problem visit. Therefore, these controls may not represent a group that would likely have many complaints and may not be representative of patients that primary care physicians frequently see. To address this issue, researchers at the University of Washington did a case control study to evaluate symptoms typical of ovarian cancer in over 1,700 women presenting to a large primary care clinic [7]. Women were surveyed about the types of symptoms they had experienced over the prior year. In addition, they provided information about the frequency, severity, and duration of symptoms. The clinic patients were then compared as controls to a group of 128 women with pelvic masses who filled out an identical survey prior to surgery for an ovarian mass and before they knew whether or not their mass was malignant. Evaluation of the clinic patients in this study revealed that over 95 % of patients presenting to a primary care clinic will have a symptom that might be associated with ovarian cancer and 72 % will have recurring symptoms, with the most common being back pain, fatigue, and constipation. Another very interesting finding was that as women got older, most symptoms, except urinary symptoms, were less common and less severe. As women complete menopause and enter the postmenopausal period of their reproductive lives, many abdominal and pelvic symptoms seem to improve. It is also important for practitioners to be cautious about attributing symptoms to the process of aging.

When the investigators compared cases to controls, they found symptoms such as bloating, increased abdominal size, urinary symptoms, and pelvic and abdominal pain were found significantly more frequently in women with ovarian cancer than in those presenting to primary care clinics. The odds ratios for symptoms of cases as compared to controls are shown in Table 9.3. The symptoms with the most significant differences were bloating, difficulty eating, and pelvic/abdominal pain. One of the potential reasons that the odds ratios are so much lower in the Goff et al. study [7] than the Olson et al. study is that the control group used at the

University of Washington were patients visiting their primary care physician for a problem visit.

The study by Goff et al. also explored the presentation of symptoms in cancer patients versus controls [7]. Cancer patients typically reported that their symptoms occurred 20–30 times per month as compared to 2–3 times for the clinic population. Cancer patients rated their symptoms as more severe, and the symptoms were of recent onset. For instance, duration of symptoms was usually less than 3–6 months for cancer patients as compared to a year or more for the clinic controls. Evaluation of age found no difference in symptoms between pre- and postmenopausal cancer patients. The authors also noted that 44 % of women with ovarian cancer had a triad of bloating, increased abdominal size, and urinary urgency, as compared to only 8 % of clinic controls. So, while the types of symptoms that women with ovarian cancer experience are vague and frequently reported by women presenting to primary care clinics, the important distinction between cases and controls appears to be in the frequency, severity, and duration of the symptoms. Researchers from other institutions across the USA and in other countries have found remarkably similar findings [10–14]. Age of cancer patients has not been shown to affect symptom presentation. In addition, large population-based studies have identified the majority of ovarian cancer patients as experiencing significant symptoms prior to diagnosis [9, 15–18].

Goff et al. did a follow up case control study to establish a symptom index that might be useful in the early diagnosis of ovarian cancer [19]. In this study, there were 149 women with ovarian cancer who were surveyed about symptoms prior to surgical exploration, and controls consisted of 255 women in an ovarian cancer screening program and 233 women who were referred for pelvic ultrasound. All the cancer patients were surveyed before definitively knowing that they had cancer, and controls were chosen as they might have a heightened awareness of symptoms so that as much as possible, recall bias could be evened out between the two groups. Logistic regression was used to determine which factors independently predicted ovarian cancer in an exploratory group and then sensitivity and specificity were tested in a confirmatory group. The symptom index that was most predictive of a woman having ovarian cancer was having any one of six symptoms (bloating, increased abdominal size, difficulty eating, feeling full quickly, abdominal or pelvic pain) which occurred at least 13 times per month and were present for less than a year. The overall sensitivity and specificity was 70 and 86 %, respectively. The sensitivity for detecting early stage disease was 57 and 80 % for advanced stage disease. Retrospective analysis of the symptom index in 1,700 women who had been screened in the primary care clinic revealed that only 2.6 % tested positive. Of note, only 1.5 % of women over 50 screened positive on the SI. The specificity of the SI in women over 50 is 87.5 %.

While most studies report that the symptoms of early and advanced stage disease are similar, other investigators have found slightly different patterns of symptom presentation. In a population-based case control study evaluating 432 women with invasive ovarian cancer to 491 matched controls, symptom data was collected with retrospective interviewer-administered questionnaires (Table 9.3). The predictive

ability of symptoms were evaluated by comparing the area under the receiver operating curves (ROC) [9]. These investigators found that abdominal pain (ROC = 0.817), distended abdomen (ROC = 0.83), vaginal bleeding not associated with periods (ROC = 0.88), and palpable abdominal mass (ROC = 0.88) were significantly predictive of localized disease. The combination of this symptom index has a sensitivity of 74 % with a specificity of 71 %. Urinary symptoms had low predictive probability for either early or advanced stage disease. The combination of fatigue/loss of appetite and bowel symptoms was predictive of advanced stage disease. Researchers from CDC evaluated the SEER Medicare database for diagnosis and procedure codes in 3,250 women over age 65 with ovarian cancer [16]. They found that 81 % of women had visits for gastrointestinal, urinary, or gynecologic symptoms prior to diagnosis. Women presenting with gastrointestinal symptoms were more likely to have later-stage disease and longer time to key diagnostic tests than those with gynecologic symptoms. Because all the symptom codes were taken from billing records prior to the diagnosis of ovarian cancer, this significantly reduces the potential of recall bias.

One of the main concerns about symptom reporting has been the issue of recall bias [20]; however, investigators have conducted case control studies evaluating chart notes and claims data of ovarian cancer patients prior to their diagnosis so that recall bias is almost eliminated [15, 16, 21]. These studies also confirm that women with ovarian cancer are significantly more likely than controls to have target symptoms 3–6 months prior to diagnosis. Smith et al. evaluated the SEER Medicare database for 1,985 ovarian cancer patients, 6,024 breast cancer patients, and 10,941 non-cancer patients [15]. The prevalence of International Classification of Diseae-9 (ICD-9) billing codes were compared prior to the diagnosis date or reference date for non-cancer patients. Ovarian cancer patients were significantly more likely to have visits for target symptoms, including abdominal pain, abdominal swelling, and gastrointestinal complaints within 6 months prior to diagnosis. In a similar study, Hamilton et al. performed a chart review of 212 ovarian cancer patients and 1,060 controls and found that 85 % of cases had one of seven ovarian cancer symptoms documented in the medical records prior to diagnosis as compared to 15 % of controls [21]. Abdominal distension, urinary frequency, and abdominal pain were significantly associated with ovarian cancer even at 6 months prior to diagnosis. The positive predictive value of abdominal bloating was 2.5 % in this study.

Other investigators who have evaluated the symptom index developed at the University of Washington have found poor performance. In a retrospective study by Pavlik et al., only 6 of 30 patients (20 %) who had undergone surgery for ovarian cancer had a positive symptom index [22]. The authors did not provide information as to how long after surgery symptom information was collected. Rossing et al. also retrospectively surveyed women about symptoms prior to diagnosis and compare this to age-matched controls [18]. In this study, women were surveyed on average of 9 months following diagnosis. In this study, the symptom index was positive in 62.3 % of women with early stage disease and 70.7 % of those with advanced stage disease, but only 30 % of women with a positive symptom index became positive more than 5 months prior to their diagnosis. The authors felt that a 5-month improve-

ment in time to diagnosis would unlikely impact the overall outcome for women with ovarian cancer. In addition, the authors retrospectively calculated a positive predictive value and found it to be low, approximately 1 %. Because of the low positive predictive value the authors argue for a cautious approach to the use of symptoms to trigger an extensive medical evaluation for ovarian cancer. The low estimates of positive predictive values are not surprising given the frequency of these symptoms in the general population and the low incidence of ovarian cancer (40 per 100,000 women over age 50), but it does not mean that these symptoms should be ignored [23].

Currently, investigators at the University of Washington are conducting a large clinical trial using symptom-triggered screening for ovarian cancer. Women who screen positive on a symptom index (Table 9.4) are referred on for testing with CA125 and TVS. While the sensitivity of the symptom index is likely to be a significant weakness, symptom identification may be a low-cost method to improve rates of early detection in the general population, a group for which no screening test exists nor is recommended.

From a practical perspective, until we have a cost-effective screening test that can be used in women at average risk of ovarian cancer, it is important for women and practitioners to be aware of the symptoms associated with ovarian cancer. It is also important not to attribute symptoms typical of ovarian cancer to the process of getting older. Symptoms most typical of ovarian cancer include bloating, abdominal or pelvic pain, and difficulty eating. In some studies, urinary symptoms are also a common presenting symptom. When these symptoms occur at least 13 times per month and are of recent onset (6–12 months), then ovarian cancer should be considered as a possibility. While most women who have these symptoms will not have ovarian cancer, it is important that providers include ovarian cancer in their differential diagnosis (Table 9.5). This is especially true in older women as the incidence of ovarian cancer increased with age. The first step in evaluating these types of symptoms is to perform a thorough history and examination, including a pelvic and rectovaginal examination, to evaluate for the possibility of an ovarian abnormality as well as other conditions. Imaging such as transvaginal ultrasound, blood tests such as CA125, or additional diagnostic tests will be determined by the initial clinical evaluation. Critics have raised concerns that evaluation of symptoms will lead to unnecessary surgery; however, a recent clinical trial of over 2,000 women evaluated with symptoms screening followed by symptom-triggered transvaginal ultrasound and CA125 found that none of the screened patients underwent a laparotomy or even laparoscopy because of enrollment in a symptom screening program [24]. This is an important issue because in the recent report from the PLCO trial, investigators found that screening with annual TVS and CA125 did not reduce mortality rates for women who developed ovarian cancer. In addition, in those women who underwent surgery for a false-positive screen, the risk of major complications was 15 % [25].

Ultimately, the timely diagnosis of ovarian cancer will rely on clinical judgment and careful analysis of presenting symptoms within the context of a thoughtful dialogue between the patient and her physician [20]. The World Health Organization classifies ovarian cancer as a disease that would likely benefit from screening due to

Table 9.4 Symptom Index Questionnaire

Are you currently experiencing any of the following symptoms? Check the box Yes or No. If yes, also check the box for number of days per month and the box for the number of months you experienced each symptom.

Symptom Study Index for Ovarian Masses

	Have you had this symptom?		How many *days per month* did you experience this symptom?			How long did this symptom persist? (months)			
Symptom	No	Yes	<1–5	5–12	≥13	<1	1–6	6–12	≥12
Pain									
Abdominal/pelvic pain	□	□	□	□	□	□	□	□	□
Eating									
Feeling full quickly	□	□	□	□	□	□	□	□	□
Unable to eat normally	□	□	□	□	□	□	□	□	□
Abdomen									
Abdominal bloating or increased abdomen size	□	□	□	□	□	□	□	□	□

□ No symptoms

Table 9.5 Key steps to diagnosing ovarian cancer

Obtain careful history
Remember that ovarian cancer will mimic many gastrointestinal disorders
Both clinicians and patients can erroneously ascribe symptoms to other diseases or getting older
Perform a pelvic examination
Most pelvic masses are palpated on rectovaginal exam but are not palpable on abdominal exam
In a general physical examination, look for:
Ascites
Omental cake
Pleural effusion
Lymphadenopathy
Malnourished appearance (despite stable weight from increasing ascites)
Perform the following diagnostic studies if ovarian cancer is suspected:
Pelvic ultrasound (easiest way to assess ovaries and check for ascites)
Abdominal-pelvic CT scan (more expensive, but can evaluate for other pathology)
CA125 blood test (not recommended as a single test, since this tumor marker is not accurate in premenopausal women and 50 % of patients with stage I ovarian cancer will have normal CA125)
Prompt referral to a gynecologic oncologist if ovarian cancer suspected
Abnormal ovarian masses require surgical resection to establish diagnosis
Direct referral to gynecologic oncologist for surgery advised based upon published ACOG guidelines[a] (outcomes are improved when gynecologic oncologists perform surgery)
If cancer is found at surgery, comprehensive staging or surgical cytoreduction is required

[a]ACOG [1]

the substantial improvement in survival if disease is detected early [26, 27]. To date, no studies have shown that screening either high-risk populations or the general population has an impact on the morbidity or mortality of the disease. While there is active research in early detection, especially with biomarkers, currently in 2012 no national organizations or expert consensus panels recommend screening for the women at average risk. In fact, the American Congress of Obstetricians and Gynecologists recommends against population-based screening for ovarian cancer [28], and the US Preventative Services Task Force has assigned screening for ovarian cancer a "D" grade [29]. This indicates that there is fair evidence to recommend its exclusion from periodic health exams. The rationale is that more women are harmed from the false positives of screening than benefit from early detection.

Timely diagnosis of ovarian cancer is as important for elderly women as it is for younger patients. While age has been shown to be an independent predictor of overall survival in women with ovarian cancer, a significant number of elderly women are able to undergo surgical cytoreduction and intraperitoneal chemotherapy and experience overall survival similar to younger patients [30]. However, the volume of disease at the time of presentation is a very important prognostic factor for optimal cytoreduction, and elderly patients tolerate very aggressive cytoreduction procedures more poorly than younger women [30, 31]. Women over 75 with even one comorbidity have a 12.7 % risk of 30-day mortality following a primary cytoreductive surgery for women with advanced

stage ovarian cancer [31]. Therefore, diagnosing elderly women early enough that an optimal cytoreduction can be achieved without aggressive procedures such as bowel resection, diaphragmatic resections, or splenectomy is critical to improving outcomes. We now know that ovarian cancer is not a "silent killer," but clinicians must still listen carefully to their patients to avoid potentially harmful delays in diagnosis. Table 9.5 summarizes the key steps in diagnosing ovarian cancer regardless of age.

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Chapter 10
Ovarian Cancer: Surgical Considerations

Kara C. Long and Dennis S. Chi

Abstract Cytoreductive surgery (CRS) followed by platinum-based chemotherapy is the cornerstone of treatment for advanced epithelial ovarian cancer (EOC). While elderly patients are generally at an increased risk for perioperative morbidity, many studies demonstrate that the elderly are just as likely to benefit from aggressive standard of care treatment as are younger patients. Despite this, elderly patients with cancer are more likely to undergo substandard surgical management, resulting in poorer disease-specific and overall survival. In order to optimize the benefit of CRS while minimizing the risks of perioperative complications, patients must be carefully selected and prepared for surgery. The following chapter presents the current evidence regarding CRS in older patients and reviews important aspects of patient selection, preoperative preparation, intraoperative techniques, postoperative care, and management of complications in older patients with EOC.

Keywords Elderly • Ovarian cancer • Cytoreductive surgery • Perioperative care • Postoperative complication

Introduction

Age is one of the strongest risk factors for the development of epithelial ovarian cancer (EOC). As the population ages rapidly, so does the incidence of ovarian cancer in older women. Women over the age of 75 years make up approximately 25 % of new

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diagnoses and 40 % of deaths from ovarian cancer. Furthermore, elderly women more commonly present with advanced stage disease than their younger counterparts [1]. The management of advanced EOC in older women is complicated by the unique physical, functional, and psychosocial challenges facing this group of patients. This is especially relevant in the surgical management of older patients, where an individualized approach is crucial to optimizing outcomes and minimizing risk.

The upfront treatment of advanced EOC consists of primary cytoreductive surgery (CRS) followed by platinum-based chemotherapy. Optimal primary CRS (residual tumor ≤1 cm) has consistently been shown to confer a survival advantage. Improved response to adjuvant platinum-based chemotherapy, disease-free survival, and overall survival are all associated with optimal CRS. In theory, the elimination of bulky, poorly perfused tumor allows for more efficient delivery of chemotherapy to tumor cells. Additionally, it has been suggested that "debulking" tumor increases the proportion of rapidly dividing and therefore more chemosensitive, tumor cells. While "optimal" CRS is considered resection of all disease to ≤1 cm, the evidence demonstrates that each incremental decrease in tumor volume less than 1 cm results in improved outcomes [2]. Therefore, complete gross resection of all disease should be the goal of surgery. In order to achieve this ideal result, an extensive surgical effort is frequently required. This standard of care does not change based on a patient's age; however, extremes of age may be accompanied by unique circumstances, such as the desire to maintain fertility in the very young or the need to curtail treatment side effects in the very old. The acceptance of a potentially extensive and complex surgical procedure as part of the standard of care of a malignancy in an elderly patient is understandably daunting, but the survival benefit associated with primary CRS is well established.

As with many vulnerable populations, the elderly are more likely to undergo substandard surgical management and are less likely to be included in clinical trials than their younger counterparts [3–6]. This is due to strict eligibility criteria which frequently include comorbid conditions and functional status, as well as physician and researcher bias [7]. In a review of all patients excluded from ovarian cancer clinical trials, Harter et al. reported that the mean age of excluded patients was 66.7 years, as compared to 57.2 years in enrolled patients. These older patients underwent less extensive surgery and were more likely to have bulky residual disease after primary CRS [8].

Decreased physiologic reserve, increased medical comorbidities, and complicated social situations all contribute to the disparities in the care of older women with advanced EOC. While elderly patients are generally at an increased risk for treatment-related complications, many studies demonstrate that the elderly are just as likely to benefit from aggressive standard of care therapy as are younger patients. Moreover, many studies provide evidence that in properly selected elderly patients, perioperative morbidity and mortality after CRS for advanced EOC are not increased. This chapter will present the current evidence regarding the surgical management of older women with EOC, as well as review the important aspects of patient selection, preoperative preparation, intraoperative techniques, postoperative care, and management of common complications in older patients.

The Impact of Age: A Review of the Evidence

There is conflicting evidence in both the general surgery and gynecologic surgery literature on the impact of age on operative outcomes. Prospective studies are limited, and, as previously stated, the elderly are underrepresented in many clinical trials. There are inherent challenges involved in both performing and critically analyzing research on older patients. The medical comorbidities and complicated psychosocial issues facing elderly patients are extremely difficult to control for. These challenges, along with the lack of a standard definition of "elderly" in the literature, contribute to the difficulty of applying the available evidence to any one individual patient. Given these challenges and the conflicting current evidence, an individualized approach to the care of older patients with EOC is strongly recommended.

The elderly are more likely to be surgically undertreated than younger patients. A multicenter pattern of care analysis of 12,316 women with ovarian cancer was published through the American College of Surgeons Cancer Commission by Hightower et al. in 1994 [9]. They found that in addition to being more likely to receive care by non-gynecologic oncologists (an established predictor of poorer outcomes), older women underwent fewer surgical procedures, were less likely to undergo an optimal CRS and were less likely to receive adjuvant chemotherapy than their younger counterparts. Accordingly, older patients experienced significantly worse survival outcomes even after controlling for stage [9].

Some evidence shows that elderly women with EOC have increased perioperative complications and poorer overall outcomes than younger patients. Diaz-Montes et al. reported the results of a large population-based study of elderly women with ovarian cancer [10]. Women ≥80 years of age were more likely to receive care in a nonacademic center and had longer hospital stays than women less than 80 years old. They also reported that women 80 years and older had a 2.3-fold increase in 30-day mortality as compared to younger women. Another important finding in this study was that perioperative death was significantly higher in low-volume hospitals (centers performing ≤20 ovarian cancer cases per year), as compared to high-volume centers [10].

In contrast, there are a number of studies that demonstrate similar clinical outcomes among highly selected older patients with EOC. In 2007, Eisenhauer et al. from Memorial Sloan-Kettering Cancer Center reviewed 292 patients with advanced EOC; of these, 37 % were 65 years or older. They reported that women ≥65 years had similar rates of optimal CRS, clinical response to chemotherapy, progression-free survival, and overall survival as patients less than 65 years [11]. Similarly, Aletti et al. published two studies from the Mayo Clinic evaluating predictors for optimal CRS. In patients with stage III and stage IV EOC, there was no statistically significant difference in optimal cytoreduction rates based on age alone [12, 13]. In 2005, Sharma et al. performed a retrospective review of the safety and efficacy of CRS in women aged 65 and older. Of 140 patients with advanced EOC, 45 % were ≥65 years. Optimal CRS rates were similar among the older and younger groups, and there was no statistically significant difference in perioperative morbidity. Moreover, patients who underwent optimal CRS had significantly improved outcomes in all age groups [14].

Other studies highlight the prognostic significance of a complete gross resection in elderly patients with EOC. Langstraat and colleagues from the Mayo Clinic performed a retrospective analysis of 280 patients ≥65 years with advanced EOC undergoing primary CRS. They found that increasing age and residual disease was associated with a decreased overall survival; however, all patients (regardless of age) benefitted similarly when complete gross resection of tumor was achieved. In patients with 0 mm of residual disease, median overall survival was 5.9 years in patients 65–69 years, as compared to 5 years in patients ≥80 years ($P = .5516$). Creatinine, albumin, surgical complexity score, residual disease, stage, and age were all determined to be independent predictors of overall survival [15]. In 2010, Fotopoulou et al. reviewed 101 patients over the age of 69 years undergoing surgery for EOC. The majority (86.1 %) had stage III–IV disease, and complete tumor resection rate was achieved in 44.6 %. Postoperative mortality was 6 %, and the overall complication rate was 40.6 %, with a major postoperative complication occurring in 37.6 % of patients. The median overall survival was 33 months (95 % CI, 9.7–56.28). Patients with no gross residual tumor after CRS had significantly improved outcomes over patients with any residual tumor (5-year survival 70 % vs. 13 %, $P < 0.001$). Multivariate analysis showed that age >75 years, incomplete tumor resection, and absence of adjuvant chemotherapy all adversely affected overall survival. Of note, only 4.95 % of patients underwent a multivisceral approach when multivisceral involvement was present and 37.6 % did not receive any adjuvant chemotherapy. They concluded that despite the high rate of complications, complete resection of tumor conveys a significant overall survival benefit in patients aged 70 years or older [16].

In patients aged 80 years and older, the role and impact of CRS is also controversial. Uyar and colleagues performed a multi-institutional review of 131 patients over the age of 70 undergoing CRS for ovarian cancer. The rate of optimal CRS was 80 % and was associated with a significant improvement in overall survival. Within this cohort, patients 80 years and older were less likely to undergo surgery than patients age 70–79 years; however, those who did undergo CRS had similar rates of optimal results. Optimal CRS was the strongest prognostic factor for overall survival. Age was not independently associated with survival [17]. Cloven et al. reported a small retrospective series in 1999 of 18 women with ovarian cancer aged 80 years or older. While 88 % underwent primary surgery, only 25 % underwent optimal cytoreduction. However, overall survival was strongly associated with optimal CRS status [18].

In 2008, Moore et al. performed a retrospective analysis of 85 patients over the age of 80 years treated for ovarian cancer at the University of Oklahoma Health Sciences Center. In this cohort, 86 % had advanced disease and 70 % had at least one medical comorbidity. Primary CRS was performed on 80 % of patients, with radical resection required in 41 %. Of the patients who underwent primary or interval CRS, 74 % were optimal. Postoperative complications were extremely common, and 13 % of patients were unable to receive planned adjuvant chemotherapy. Perioperative death (within 60 days of surgery) occurred in 20 % of patients. Despite the high rate of optimal CRS in this group, the frequent postoperative complications

and high rate of perioperative death call into question the overall benefit of upfront CRS in patients over 80 years [19].

Individualization of Treatment: Selecting the Surgical Candidate

The goal of individualized treatment of advanced EOC is to maximize benefit while minimizing treatment-related complications. This becomes especially challenging in the surgical management of elderly patients, who at baseline may have functional limitations, decreased stress tolerance, and multiple comorbidities. It is well established in the gynecologic oncology literature that, whenever possible, an attempt should be made to resect all visible tumor prior to the initiation of adjuvant platinum-based chemotherapy [2, 20]. However, in patients with unresectable disease or in those who cannot tolerate CRS, neoadjuvant chemotherapy followed by a less extensive interval cytoreductive surgery is a reasonable option. In theory, this approach would allow for an easier and potentially less complicated resection of disease.

The role of neoadjuvant chemotherapy in advanced EOC was recently examined in a randomized trial by the European Organization for Research and Treatment of Cancer (EORTC), published by Vergote et al. in 2010. Primary CRS followed by adjuvant chemotherapy was compared to neoadjuvant chemotherapy followed by interval cytoreduction in women with advanced EOC. Patients were matched for age and other accepted prognostic factors. They reported similar overall and progression-free survival for each arm of the trial. Median overall survival in each arm was approximately 30 months. While this landmark study is the first randomized trial to examine neoadjuvant chemotherapy as compared to primary CRS, the relatively short median survival in both arms (as compared to other published results in similar patient groups) has led to doubts regarding the generalizability of these data [21].

Currently, there are no standard, accepted criteria for determining who is a candidate for upfront surgery and who is not. Each patient must be evaluated individually, and the risks and benefits of upfront CRS weighed carefully. In order to benefit from upfront CRS, a patient must have resectable disease and be medically fit to undergo all necessary surgical procedures required to achieve an optimal result. In order to identify patients at highest risk from primary CRS, Aletti and colleagues performed a multicenter study of 576 women with advanced EOC. In the majority of patients, CRS with low residual disease conferred a significant survival benefit, which outweighed the morbidity of surgery. However, a high-risk group of patients was identified and characterized by the following: age ≥75 years, plus high initial tumor dissemination or stage IV disease, plus poor performance status (American Society of Anesthesiology [ASA] score of ≥3) or poor nutritional status (serum albumin <3). These patients experienced a 63.6 % postoperative morbidity and limited survival benefit after upfront CRS [22]. In patients meeting these high-risk criteria, neoadjuvant chemotherapy is recommended.

In the majority of cases, however, surgical candidacy and resectability are less clear. Consultation with internal medicine, geriatrics, and cardiology is often necessary to determine whether or not a patient is fit for surgery. We recommend that in patients with extensive thoracic disease (as seen on preoperative CT or video-assisted thoracic surgery), extensive involvement of the mesentery of the small bowel, parenchymal liver disease, or unresectable portal disease, neoadjuvant chemotherapy should be considered.

Surgical candidacy is affected by preexisting medical comorbidities and in some patients with advanced EOC, by the disease itself. It is not uncommon for patients with advanced disease to present in an already weakened state due to their illness. Large-volume ascites, tumor burden, and impending bowel obstruction can lead to nausea, vomiting, decreased oral intake, and ultimately malnutrition. Patients with significant gastrointestinal disturbances should be evaluated preoperatively for the presence of a bowel obstruction. In chronically malnourished patients with a decreased serum albumin, it is not unreasonable to consider 2 weeks of total parenteral nutrition prior to the initiation of therapy. A bedside paracentesis to drain ascites can temporarily improve symptoms related to abdominal distention. Similarly, patients with large pleural effusions may require thoracentesis to temporarily alleviate symptoms of dyspnea. If the diagnosis or stage is unclear, ascites and pleural fluid can be sent for cytologic review. While symptom management is a very important part of caring for patients with EOC, expeditious initiation of treatment should remain the priority.

The lack of standard criteria for resectability, along with significant variations in practice patterns, results in notable discrepancies in the management of advanced EOC. To date, no prospective studies have examined the role of neoadjuvant chemotherapy based on chronologic age alone. However, current evidence consistently supports the positive impact of complete tumor resection on survival outcomes in elderly patients. The standard remains that whenever possible, an upfront attempt to resect all visible disease should be made in appropriate surgical candidates of all ages.

Preoperative Assessment and Preparation

The preoperative assessment is one of the most critical aspects of the surgical management of older women with advanced EOC, especially in those who may require extensive multiorgan resection. As in any patient with a suspected gynecologic malignancy, workup should begin with a careful history and physical exam including breast, gynecologic, and rectal exam. If a pelvic mass is found on physical exam, size, mobility, and extent of disease (sidewall and rectal involvement) should be carefully noted. Cervical cytology, mammography, flexible sigmoidoscopy or colonoscopy, and upper gastrointestinal evaluation can be utilized to rule out non-ovarian etiologies. Distention and a fluid wave on abdominal exam can indicate the presence of ascites. Similarly, abnormalities on lung exam can indicate the presence of pleural effusions. Serum tumor markers such as a CA-125, CEA, CA 19-9, LDH,

AFP, inhibin, and HCG can all aid in the preoperative assessment of a patient with suspected ovarian cancer.

Understanding the extent of disease preoperatively is especially important in older women with EOC who may require more complicated and extensive perioperative care. A complex adnexal or pelvic mass, peritoneal carcinomatosis, pelvic lymphadenopathy, and ascites all suggest a diagnosis of advanced disease. Transvaginal sonography, computed tomography (CT) scan of the abdomen and pelvis, pelvic magnetic resonance imaging (MRI), and positron emission tomography (PET) scan can all be used as tools to evaluate extent of disease. In cases of known advanced disease or in patients with shortness of breath, it is imperative to assess the chest (usually with a chest CT scan) for pleural disease, effusions, and enlarged mediastinal lymph nodes. Ultimately, surgical pathology will be necessary for determination of final stage and pathologic diagnosis.

In older women with ovarian cancer, a rigorous preoperative medical assessment is necessary to determine if a patient is suitable for a potentially extensive surgical procedure. With few exceptions, all elderly patients should undergo medical or geriatric clearance in the preoperative setting. Preoperative testing should include a complete blood count, basic metabolic panel, liver function tests, coagulation studies, and a serum albumin. An electrocardiogram should be performed, and any abnormalities followed-up by a cardiologist before surgical intervention. If a chest CT scan has not been done, a chest X-ray must be performed to rule out underlying lung disease. In patients with advanced disease or with any lower extremity swelling, venous Dopplers should be performed. Patients with advanced EOC have an extremely high risk of deep vein thrombosis (DVT). If a DVT is diagnosed, an inferior vena cava filter can be placed preoperatively to decrease the chance of pulmonary embolus. Consultation with anesthesiology prior to the day of surgery will help to foster a multidisciplinary and individualized approach to the patient; frequently, this practice will also expedite care on the day of surgery.

Standardized measures can facilitate communication among providers and help to identify patients who may be at increased risk. The *Preoperative assessment of cancer in the elderly* (*PACE*) is a tool designed to assess the physiologic reserve of older patients to assist in individualized cancer care. The PACE instrument is comprised of multiple previously validated tools including the comprehensive geriatric assessment (CGA), the Brief Fatigue Inventory (BFI), the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and the American Society of Anesthesiologists (ASA) grade. In 2007, Pope et al. reported the results of a prospective study designed to evaluate this instrument in elderly patients (over age 70) undergoing elective surgery. The PACE instrument was determined to be a reliable tool to aid in the assessment of functional capacity and health status in the preoperative setting [23]. The PACE instrument has also been evaluated as a predictor of postoperative outcomes. An instrumental activity of daily living score (<8), an abnormal PS (>1), and a moderate or severe BFI (>3) were associated with an increased risk of postoperative complications and extended hospital stay.

Preoperative consent discussion should include the patient's family or caregivers whenever possible. The potential need for extensive surgery, blood transfusion, creation

of a temporary or permanent ostomy, extended hospital stay, and subacute rehabilitation services at discharge should be clearly conveyed. In elderly patients with complicated psychosocial situations, preoperative consultation with social work can be extremely beneficial. Planning for postoperative care beyond the hospital setting eases hospital transitions and provides reassurance to patients and their family members.

Intraoperative Management

There are three major objectives of surgery for ovarian cancer: to obtain tissue for a definitive pathologic diagnosis, to determine stage, and to resect all visible disease (or to resect to less than 1 cm of disease when complete resection is not possible). Once a patient has been appropriately selected for surgical management, every effort should be made to achieve these goals. The evidence supports that optimal CRS is feasible and beneficial in elderly patients with advanced EOC [11–14].

Prior to the initiation of surgery, the nursing and anesthesia teams should be prepared for a potentially lengthy surgical resection; adequate vascular access and the availability of blood products for transfusion should be confirmed. Sequential compression devices for DVT prophylaxis should be in place prior to the initiation of anesthesia. The patient should be placed in the dorsal lithotomy position; this position allows for a more thorough exam under anesthesia and provides optimal access for a rectosigmoid resection and anastomosis if needed. A sterile Foley catheter should be placed in the urinary bladder; in cases in which an extensive pelvic dissection is expected, a two-way Foley catheter can be placed. During the case, the bladder can be retrograde filled to assess for injury.

If extent of disease or resectability is unclear, diagnostic laparoscopy can be performed initially to assess tumor burden and obtain tissue for pathologic assessment. Whether the initial approach is via laparotomy or laparoscopy, the first step upon entry into the abdomen should be careful assessment of tumor extent and location. All peritoneal surfaces should be examined with careful attention to the posterior cul-de-sac, the paracolic gutters, and the right diaphragm.

Staging

Patients with clinically early stage disease should undergo a comprehensive surgical staging procedure after frozen section pathologic assessment confirms gynecologic malignancy. The primary specimen should be removed with extreme caution to avoid spillage of tumor into the abdomen. Depending on the size of the mass, this can be accomplished using a vertical midline incision or an endoscopic bag during laparoscopy. Surgical staging should include peritoneal cytology, total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and paraaortic lymphadenectomy (up to the level of the renal vessels), and peritoneal biopsies from anterior/posterior cul-de-sac,

pelvic sidewalls, paracolic gutters, and bilateral diaphragms. Incomplete staging can lead to underestimation of tumor dissemination and, subsequently, undertreatment of disease; therefore, a systematic and thorough approach to staging is recommended.

Cytoreduction

The goal of primary CRS should be complete gross resection or optimal resection (<1 cm residual disease) when complete resection is not feasible. After initial intraoperative assessment, if resection of disease to less than 1 cm is not possible, the surgical effort should be aborted and the patient referred for neoadjuvant chemotherapy. To maximize exposure and access, a vertical midline incision (extending from pubis to xiphoid) should be made and a self-retaining retractor such as a Bookwalter or Omni should be placed. We recommend starting the resection in the upper abdomen, as this is frequently the limiting factor in suboptimal cases.

Omentectomy

The omentum is a frequent site of metastatic ovarian cancer. Resection of omental tumor (commonly referred to as an "omental cake") is a prudent first step during CRS, as it exposes the underlying abdominal cavity and provides tumor for frozen section diagnosis. Mobilization of the splenic and hepatic flexures may be necessary to safely resect extensive omental disease. In older patients who may have compromised tissue integrity, excessive traction on the omentum, which can cause tears and bleeding from the splenic capsule, must be avoided. While removal of the infracolic omentum is generally sufficient, a supracolic omentectomy may be necessary if tumor is present in the gastrocolic omentum. In order to maintain adequate perfusion to the transverse colon and watershed areas, the mesocolon and middle colic artery should be preserved. However, in cases where no plane exists between the tumor mass and the bowel wall, en bloc resection of the transverse colon and omentum can be considered.

Upper Abdomen

The liver, right diaphragm, Morrison's pouch, and peritoneum overlying Gerota's fascia are among the most common sites for metastatic ovarian cancer in the upper abdomen, partially due to the clockwise flow of peritoneal fluid in the abdominal cavity. The gallbladder, porta hepatis, celiac axis, left diaphragm, spleen, distal pancreas, and stomach can also be infiltrated with tumor. While challenging, the presence of disease at any of these sites does not represent an absolute contraindication to optimal or complete CRS.

Liver Mobilization

In order to adequately assess and treat disease in the right upper quadrant, the liver must be mobilized. Failure to mobilize the liver can lead to gross underestimation of disease volume in the right upper quadrant. The patient should be placed in reverse Trendelenburg position with the "RUQ up" (right upper quadrant up) and retractors adjusted to elevate the ribs, exposing the liver and right diaphragm. In order to maximize exposure through the midline incision, the xiphoid process can be resected. The free edge of the falciform ligament, which contains the round ligament, should be divided and tagged with a small clamp. Gentle downward traction on the falciform will improve exposure and control during liver mobilization. Using electrocautery, separate the falciform's attachment to the anterior abdominal wall in a cephalad fashion until the right and left coronary ligaments are visible (when the layers of peritoneum split laterally). Taking extreme caution to identify and avoid the right hepatic vein and inferior vena cava (IVC), continue to separate the right coronary ligament. We recommend staying adjacent to the liver surface during this dissection. This dissection can then be continued medially by dividing the lateral triangular ligament, until the bare surface of the liver is exposed. A combination of medial and lateral approaches can be extremely helpful during liver mobilization, especially in the setting of bulky disease. When the right posterior coronary ligament is completely free, the liver mobilization is complete. Gentle medial traction on the liver will then expose the right diaphragm, Morrison's pouch, and peritoneum overlying Gerota's fascia [24].

Diaphragm

The right diaphragm is a very common (and frequently underestimated) site of metastatic ovarian cancer. Tumor involvement can be superficial, with implants limited to the overlying peritoneum, or deeply infiltrative with tumor invading the underlying muscle of the diaphragm. At the level of the costal margin, the peritoneum should be incised and the edge grasped with a clamp. The peritoneal incision should be extended posteriorly using electrocautery. A combination of medial and lateral approaches may be necessary for a safe, efficient resection. The free edge of the peritoneum can be separated from the muscle of the diaphragm using alternating electrocautery and gentle, blunt dissection with a sponge stick while placing gentle downward traction on the peritoneal edge. In areas of deeply invasive tumor (or at the central tendon of the diaphragm), sharp dissection, electrocautery, or ablative techniques (such as the argon beam coagulator) may be required to free the tumor. Hemostasis can be achieved with electrocautery or a vessel-sealing device. After the resection is complete, it is important to inspect the muscle of the diaphragm for defects. Generally, defects can be repaired primarily using delayed absorbable figure of 8 sutures. Full-thickness resection of the diaphragm may be necessary in

areas of deep tumor infiltration. This can be accomplished using simple electrocautery, a vessel-sealing device, or an endo-GIA stapler. During medial diaphragm resection, the right hepatic artery and the right phrenic nerve are at risk for injury. The diaphragm can be closed using permanent (1-0 polypropylene) sutures in an interrupted, figure of 8 or running fashion. At the time of diaphragm closure, a red rubber catheter or chest tube can be used to evacuate any air, blood, or fluid that has accumulated in the pleural cavity. A chest tube placed intraoperatively can also be extremely useful in draining the postoperative pleural effusions that are common after extensive diaphragm stripping [24].

The left diaphragm can be approached in a similar manner after liver mobilization. In the setting of extensive tumor infiltration, an en bloc resection of the left diaphragm and other left upper quadrant structures (such as the spleen and distal pancreas) can be performed.

Liver Resection

Superficial implants on the liver capsule can be ablated using the argon beam coagulator, Cavitron Ultrasonic Surgical Aspirator (CUSA), or other device. In the setting of superficial parenchymal liver metastases, a liver wedge resection can be performed in conjunction with a hepatobiliary surgical consultant.

Splenectomy

To appropriately assess the spleen, pancreas, celiac axis, and porta hepatis, we recommend entry into the lesser sac. This can be accomplished by incising the posterior leaf of the omentum and reflecting the stomach and omentum anteriorly and medially. The patient is placed in the "LUQ up" (left upper quadrant up) position, and the retractors adjusted accordingly. As in many other cytoreductive procedures, a combination of anterior and posterior approaches for splenectomy may be necessary to achieve a safe and thorough resection. Taking caution to not injure the posterior wall of the stomach, the gastrosplenic ligaments and short gastric vessels should be divided. The distal pancreas can then be examined by gently lifting the spleen. After separating the splenorenal ligaments, identify the splenic vessels. The splenic artery should be isolated and doubly ligated using permanent sutures. We recommend ligating the splenic vein separately to allow for venous drainage and to prevent arteriovenous fistula. Once the vasculature is secured and hemostasis achieved, divide the remaining attachments including the inferior splenocolic ligaments, posterior and lateral lienorenal ligaments, and the splenophrenic ligaments. At the completion of the procedure, inspect all vascular pedicles carefully as any unidentified bleeding in the splenic bed can result in significant postoperative hemorrhage [24].

Distal Pancreatectomy

When omental tumor infiltration extends beyond the splenic hilum, it may be necessary to resect the distal portion of the pancreas. Generally, this is best accomplished by resecting the distal pancreas en bloc with the spleen. Incise the peritoneum overlying the inferior border of the pancreas (proximal to the tumor). Once the splenic vessels are secured, transect the distal pancreas with a TA or GIA stapler. The staple line should be reinforced using a running 2-0 permanent suture. A similar technique (with 2-0 or 3-0 sutures) can be used to oversew any defects noted in the pancreatic tail after dissection. Recognition and proper reinforcement of defects are critical, as an unrecognized injury to the pancreas can result in significant postoperative complications such as pancreatic leak, pancreatitis, and development of a pseudocyst. If desired, a drain left in the splenic bed can aid in the postoperative monitoring of the patient for pancreatic leak. We recommend keeping the drain in place until minimal output is noted and the patient is tolerating a regular diet [24].

Pelvis

Advanced ovarian cancer frequently presents with a large, conglomerate mass obliterating the pelvis and encompassing all of the pelvic viscera. In these cases, a complicated dissection with multiorgan resection is generally required. A modified posterior exenteration (MPE), or en bloc resection of the uterus, adnexa, rectosigmoid colon, and pelvic peritoneum, is one of the most frequently performed procedures during CRS for advanced EOC. This is best performed using a retroperitoneal approach, which optimizes exposure and facilitates a safe and efficient resection of tumor and pelvic viscera.

Open the pelvic sidewalls laterally and identify the ureters and pelvic vasculature. Identify and ligate the infundibulopelvic ligaments. Vessel loops can be used to tag both ureters. On the left, the lateral peritoneal incision can be extended along the white line of Toldt to mobilize the descending colon. During mobilization of the left colon, take care to preserve the left colic vessels in order to maintain adequate blood supply to the colon. The pararectal and paravesical spaces should be opened, and the ureters skeletonized from the pelvic brim to the tunnel of Wertheim. Divide the uterine vessels at the level of the hypogastric artery. The vesicouterine space can be developed by opening the peritoneum anteriorly. Occasionally, tumor infiltration into the bladder may obliterate this space, and full-thickness resection of the bladder wall will be required. The majority of bladder defects can be repaired primarily; however, care must be taken to avoid the trigone and ureteral orifices. The ureters should be unroofed from the bladder pillars and reflected laterally away from the specimen. Dissect the bladder off of the anterior vagina approximately 2–3 cm distal to the cervicovaginal junction. At this point, an anterior colpotomy can be made 1–2 cm distal to the cervicovaginal junction (this can be facilitated by placing a vaginal probe or sponge stick into the vagina). Extend this incision laterally, using

Heaney clamps to secure the vaginal walls. The vaginal angles should be secured using figure of 8 sutures, at which point the rectrovaginal septum can be safely entered by incising the posterior vaginal wall.

The degree of tumor involvement will dictate the extent of pelvic resection. A type 1 MPE involves resection of the pelvic peritoneum including the peritoneum of the posterior cul-de-sac, and a type 2 MPE involves resection of the rectosigmoid colon en bloc with the uterus and adnexa. For these resections, a GIA stapler can be used to transect the rectosigmoid colon 2–3 cm proximal to the area of tumor involvement. The mesentery of the sigmoid colon should then be incised and transected perpendicular to the long axis of the colon and the superior rectal vessel identified and carefully divided. After opening the pararectal space, gentle upward traction can be placed on the rectum, which can then be dissected off of the underlying presacral fascia using a combination of blunt dissection and electrocautery. Continue the dissection distal to the level of tumor involvement, elevate the specimen ventrally, and carefully clear away excess mesorectal fat. The rectum can then be transected using a TA stapler 2–3 cm distal to the area of tumor infiltration (with care not to injure the ureters and pelvic vessels). Rectal anastomosis can be accomplished using an end-to-end stapling technique. The anastomotic site should be tension-free, hemostatic, secure, and adequately perfused. Consider a diverting loop ileostomy if there are any concerns regarding the integrity or perfusion of the anastomosis. A postoperative anastomotic leak can be catastrophic, especially in older patients with decreased reserve and limited stress tolerance.

Bowel Resection

In addition to rectosigmoid resection, a transverse colectomy, ileocecal resection, extended right or left hemicolectomy, or small bowel resection may be necessary to achieve optimal cytoreduction. Mobilization of the colon is imperative to a safe resection. Incise the peritoneum along the white line of Toldt (along the paracolic gutters) and reflect the colon medially. By opening the lesser sac and transecting the gastrocolic ligaments, mobilization of the splenic flexure, hepatic flexure, and transverse colon can be facilitated. If further descent is desired, the inferior mesenteric vein can be ligated and divided inferior to the pancreas. Maintaining adequate blood supply is crucial to any colonic resection. In general, a GIA stapler can be used to transect the bowel, followed by an end-to-end or side-to-side tension-free anastomosis.

Lymphadenectomy

In patients with clinically early disease, we recommend a systematic staging pelvic and paraaortic lymphadenectomy up to the level of the renal vessels. In patients with grossly advanced disease (IIIC or IV), any grossly abnormal or enlarged lymph

nodes in the pelvis, abdomen, or chest should be removed. The removal of enlarged mediastinal lymph nodes is generally safe and feasible through the abdominal incision (with the assistance of a cardiothoracic surgical consultant if necessary). The utility of removing normal appearing lymph nodes in patients with advanced disease and complete gross resection of tumor is unknown and is left to the discretion of the operating surgeon.

Intraperitoneal Catheter Placement

Intraperitoneal (IP) catheters for delivery of adjuvant chemotherapy should be routinely placed in patients who achieve optimal CRS. Since removal of an IP catheter is fairly simple and can be performed in the clinic under local anesthesia, we recommend proceeding with placement during CRS even if doubts exist regarding the patient's candidacy for IP therapy. The catheter should be placed in the LUQ (or RUQ if more technically feasible) in the midclavicular line over the distal ribs. A 4-cm transverse skin incision should be made and carried down to the level of the fascia. A combination of blunt dissection and electrocautery can then be used to make a pocket just large enough to accommodate the port reservoir. Using a long, fine-tipped clamp, create a tunnel from the incision into the mid-abdomen; this is best accomplished under direct visualization while elevating the abdominal wall. Grasp the catheter tubing and draw it back through the tunnel into the incision, trim to the desired length, and attach to the reservoir as directed by the manufacturer. After the port is secured in place using delayed absorbable sutures and before the incision is closed, flush the system with heparinized saline and examine each component for patency and leaks.

Abdominal Closure

Meticulous closure of the abdominal wall is critical in decreasing postoperative wound complications. Women with advanced EOC are at high risk for the development of incisional hernias, especially in the setting of adjuvant intraperitoneal chemotherapy [25]. Older patients with compromised wound healing may be at an even greater risk for ventral hernias or fascial dehiscences.

The fascia should be closed with a continuous running delayed absorbable monofilament suture (such as #1 looped polydioxanone/PDS) with a suture length to wound length ratio of at least 4:1. Several randomized trials in the general surgery literature demonstrate that placement of the sutures 5–8 mm from the fascial edge (as opposed to 1 cm or more) results in lower rates of postoperative wound infections and hernias, potentially by decreasing the degree of tissue necrosis [26, 27]. Additionally, we recommend copiously irrigating subcutaneous tissue and meticulously ensuring hemostasis prior to closing the skin.

Postoperative Issues in the Elderly Patient

Decreased physiologic reserve and increased medical comorbidities make the elderly an especially vulnerable population in the postoperative setting, especially following extensive multiorgan CRS. However, the evidence remains conflicted regarding the impact of age on postoperative outcomes. The majority of the studies examining postoperative complications in the elderly are retrospective and therefore limited by substantial selection bias.

In 2006, Turrentine et al. published a review of surgical risk factors, morbidity, and mortality in elderly patients. A total of 7,696 surgical procedures were reviewed with a morbidity rate of 28 % and a mortality rate of 2.3 %. In patients over the age of 80 years, they noted a 51 % morbidity rate and a 7 % mortality rate. Surgical morbidity and mortality exhibited a linear relationship with increasing age. On further analysis, they determined that surgical risk factors and morbidity increased together until age 70, at which point morbidity increased with age independent of risk factors. Specifically, wound, renal, cardiovascular, and respiratory complications were associated with increasing age. In patients over the age of 80, preoperative transfusion, emergency operation, and weight loss were the strongest predictors of morbidity. Furthermore, emergency operation, increase in ASA score, and impairment of activities of daily living were associated with mortality in all age groups. They concluded that overall, increasing age was an independent risk factor for postoperative morbidity and mortality [28].

Other studies have failed to show an association between age and increased perioperative morbidity. Friedman and colleagues performed a case-control study examining perioperative complications following gynecologic surgery in women ≥80 years as compared to women aged 50–79 years. They found that while the older patients had a slightly longer length of stay, the overall perioperative morbidity and mortality were similar to those of younger patients. On further analysis of specific postoperative complications, they found that women ≥80 years were more likely to have sepsis, urinary tract infections, psychiatric disturbances, and fluid-balance-related cardiopulmonary issues [29]. Similarly, Ben-Ami et al. performed a review of women undergoing surgery for ovarian and uterine cancers. They also concluded that there was no increased rate of perioperative morbidity in the women aged 70 years and older [30].

Prevention is a key component of the postoperative management of elderly patients with EOC. Venous thromboembolism prophylaxis (with sequential compression devices and prophylactic dose anticoagulation), gastrointestinal prophylaxis (with a proton pump inhibitor or H2 blocker), pulmonary toileting, and assistance with early ambulation should be standard for all patients undergoing CRS. Specialized ancillary services play an integral part in the postoperative care of the elderly patient and should be considered an indispensible part of the cytoreductive team. Physical therapy, respiratory therapy, anesthesia/pain management, wound care specialists, enterostomal care specialists, social work, and case management all have important roles in the individualized care and rehabilitation of the elderly surgical patient. These specialized care teams are especially crucial in patients with medical comorbidities, baseline functional or cognitive limitations, and complicated, resource-poor social situations.

Postoperative Complications: Diagnosis and Management

The risk of postoperative complications after extensive CRS is extremely high. Prompt identification and management of these complications is an essential aspect of perioperative care, especially in elderly patients. Admission to the intensive care unit (ICU) may be required for fluid management and supportive care, especially in elderly patients. High-risk features for extended postoperative ICU admission include poor nutritional status (albumin <3.5), excessive fluid resuscitation, and age >63 years [31]. The following section covers some of the most frequently encountered postoperative complications after CRS for advanced EOC.

Cardiopulmonary

Fluid shifts, specifically extensive third spacing, are extremely common following CRS for advanced EOC, especially in the setting of large-volume ascites. While patients may have some clinical signs of fluid overload such as lower extremity edema and reaccumulation of ascites, they are generally quite intravascularly depleted, which is evidenced by low urine output, dry mucous membranes, and tachycardia. Renal perfusion should be closely monitoring by following urine output and serum creatinine. Diuretics should be used sparingly (if at all) and with great caution. Spontaneous diuresis ideally occurs within 3–4 days of surgery and is generally associated with an uncomplicated recovery. Failure to diurese spontaneously within 7 days of surgery may indicate an underlying infection or other significant intra-abdominal process.

Postoperative *pleural effusions* are extremely common in patients with ascites or in those who have undergone liver mobilization and/or right diaphragm peritonectomies [32]. Thoracentesis, chest tube, or drainage catheter placement may be necessary in the setting of symptomatic pleural effusions. Chest tubes placed intraoperatively should be continued until drainage output is <200 cc/day (on straight drain). *Pneumothorax* can also result from right diaphragm resection/peritonectomy. Performing a chest X-ray in the recovery room can assist in identifying patients with residual pneumothorax who may require closer follow-up. Dyspnea or hypoxia in the postoperative setting may indicate acute or worsening pneumothorax or effusions.

Hematologic

Prompt identification of *postoperative hemorrhage or coagulopathy* is critical, especially in older patients who may have limited stress tolerance at baseline. Monitoring of vital signs, blood counts, and coagulation profiles is the most crucial in the first 24–48 h after surgery, when the risk of an acute bleed is the highest. If a postoperative bleed is suspected, aggressive transfusion of blood products and transfer to the ICU should be initiated. Prompt reoperation should be considered in patients who remain unstable despite appropriate resuscitation.

Patients undergoing lengthy pelvic surgery for an advanced gynecologic malignancy are at an extremely high risk for postoperative *venous thromboembolism* (*VTE*). Shortness of breath, hypoxia, unexplained tachycardia, or lower extremity tenderness or edema (especially unilateral) should raise suspicion for a VTE, and workup should not be delayed. All patients should receive postoperative VTE prophylaxis with anticoagulation and sequential compression devices. Additionally, consideration should be given to discharge home with an extended prophylactic anticoagulation regimen (4–6 weeks).

Infectious

The presence of fever, leukocytosis, or other abnormality on physical exam within the first few weeks of surgery is highly suggestive of an underlying infection. Workup should include a complete blood count, blood and urine cultures, chest X-ray, and thorough physical exam with focus on all surgical incisions. CT scan can also be a valuable tool in diagnosing postoperative collections and abscesses. Hospital acquired pneumonia, urinary tract infection, wound infection, and intra-abdominal abscesses are all possible sources of infection after CRS. Elderly patients may also present with mental status changes in the setting of developing sepsis.

Surgical site infections are among the most common infections after CRS and frequently resolve with antibiotic treatment alone. However, wounds should be opened to facilitate drainage of underlying collections in the setting of frank purulent drainage, fluctuance, or infections that persist despite appropriate antibiotic therapy. Wet to dry dressing changes (2–3 times/day) can be performed until resolution of the infection, at which point a wound vacuum system can be placed. *Intra-abdominal or pelvic abscesses* should be suspected with unexplained leukocytosis, fever, prolonged ileus, or failure to diurese by postoperative day 7. Broad spectrum intravenous (IV) antibiotics and drainage (preferably by interventional radiology) are generally sufficient treatment for most abscesses.

Gastrointestinal

Some of the most devastating postoperative complications following CRS include *bowel injury* and *anastomotic compromise*; both can present with diffuse peritonitis, sepsis, or drainage of enteric contents from incisions and surgical drains. Any of these signs in a postoperative patient should prompt immediate workup and consideration of surgical exploration. However, these potentially catastrophic complications can also present with much more subtle, nonspecific findings such as unexplained fever, persistent leukocytosis, or prolonged ileus. In unstable patients with a suspected anastomotic leak, emergent reoperation with intestinal diversion is required. However, in stable patients without evidence of sepsis or peritonitis,

anastomotic leaks can occasionally be managed nonsurgically. In these patients, we recommend broad-spectrum IV antibiotics; drainage of collections; and, in selected cases of rectal anastomotic leak, endoscopic covered stent placement or repair.

A much more frequently encountered complication after CRS is *postoperative ileus*, especially in patients who require bowel resection, mobilization of the bowel, or extensive lysis of adhesions. While early postoperative refeeding is generally acceptable even after extensive CRS, patients with postoperative nausea and vomiting should be placed on immediate bowel rest. In the vast majority of cases, postoperative ileus will resolve with IV hydration, bowel rest, and nasogastric decompression. Limiting narcotics and fluid overload can also serve to decrease the incidence, severity, and duration of ileus. In patients with a prolonged ileus, imaging should be considered to evaluate for the presence of a *small bowel obstruction* (*SBO*). In these cases, nonsurgical management (IV hydration, nasogastric tube decompression, and bowel rest) is also generally effective; however, surgical intervention may be required in some cases. If a patient requires greater than 5–7 days of bowel rest, total parenteral nutrition should be considered.

After splenectomy or distal pancreatectomy, fever, nausea/vomiting, or unexplained leukocytosis may also suggest a *pancreatic leak*. A CT scan can be performed to assess for postoperative collections in the splenic bed, and if a LUQ surgical drain was left in place, monitoring output and drain amylase may assist in diagnosing a leak. In patients with a drain amylase >3× serum amylase, a leak should be suspected. When a pancreatic leak is suspected (high drain output, drain amylase >3× serum amylase), reasonable initial management includes bowel rest, IV hydration, continued drainage, and somatostatin to decrease gastric secretions [33].

Neuropsychiatric

The elderly are at a significantly increased risk for postoperative neuropsychiatric events, especially in ICU or step-down settings. Postoperative *delirium* should be promptly evaluated, and underlying causes, such as stroke, sepsis, alcohol withdrawal, and narcotic overdose, ruled out. Patients experiencing confusion postoperatively should be carefully monitored, as the risk of falls and other adverse events is extremely increased. It is prudent to have a low threshold for consulting neurology, psychiatry, or geriatrics.

The Impact of Age: Ethical Dilemmas

Physician bias is a significant factor in the disparate care of elderly patients with advanced EOC and in the underrepresentation of these patients in clinical trials [7–9]. The delivery of equitable and bias-free care should be a common goal among all gynecologic oncologists. However, the potential morbidity of extensive CRS must be

strongly considered in patients who may have a limited lifespan at baseline. Medicolegal concerns, the changing health care economy, and pressure from patients and family members all influence the management of older patients with advanced EOC.

The role of chronologic age in the surgical management of patients with EOC is poorly understood, and thus patients remain at risk for both under- and overtreatment. High-quality research involving the elderly must become a priority. Techniques to improve preoperative assessment of elderly patients and to minimize perioperative complications must be investigated. Furthermore, when possible, the eligibility criteria of clinical trials must be expanded to include elderly patients. Finally, understanding the important quality of life issues facing the elderly, especially after surgical treatments, is crucial in improving overall care.

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Chapter 11
Ovarian Cancer: Primary Chemotherapy

William P. Tew

Abstract Since primary (first-line) platinum-based chemotherapy is a potentially curative treatment in conjunction with a debulking surgery for newly diagnosed ovarian cancer, it is important to explore these options with all patients regardless of age. Careful consideration of the dosing and scheduling of chemotherapy is required in our older patients. Although few prospective trials dedicated to older patients with newly diagnosed ovarian cancer have been performed, there have been several papers outlining outcomes and options for older patients. In this chapter, we will review the current guidelines and evidence for various intravenous and intraperitoneal chemotherapy regimens.

Keywords Ovarian cancer • Primary chemotherapy • Neoadjuvant chemotherapy • Elderly patients

Ovarian Cancer

More than half of all patients diagnosed with ovarian cancer are older than 65 years of age. This ratio is expected to increase in the coming decades as our population ages and life expectancy improves [1, 2]. Due to inadequate screening tools and nonspecific symptoms, the vast majority of women with ovarian cancer present with advanced stages and curative treatment requires both aggressive surgery and chemotherapy.

Older patients with ovarian cancer are less likely to be offered standard cancer treatments, have poorer outcomes, and develop higher toxicity to treatment. In addition, advancing age is considered a risk factor for survival in ovarian cancer. Several

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groups reported at least a twofold increased risk of death in women older than 65 years of age [3, 4]. There have been various theories proposed to account for this survival disparity in older women, including (1) more aggressive cancer with advanced age, (2) inherent resistance to chemotherapy, (3) individual patient factors such as multiple concurrent medical problems, and (4) physician and health-care biases toward the elderly which lead to inadequate surgery, less than optimal chemotherapy, and poor enrollment in clinical trials [5].

Since primary chemotherapy is a potentially curative treatment in conjunction with a debulking surgery, it is important to explore these options with all patients regardless of age. However, careful consideration of the dosing and scheduling of chemotherapy is required in our older patients. Although few prospective trials dedicated to older patients with newly diagnosed ovarian cancer have been performed, there have been several papers outlining outcomes and options for older patients.

First-Line Chemotherapy

Ovarian cancer is one of the most chemotherapy-sensitive malignancies, and treatment has a strong impact on survival in the postoperative (first-line) settings. For newly diagnosed stage III and IV patients, the superior chemotherapy regimen has evolved over the past decades from cyclophosphamide-based regimens to a current standard: intravenous carboplatin (AUC5-6) and paclitaxel (175 mg/m^2) [6, 7]. Based on a variety of phase III trials employing this regimen following maximal cytoreduction, the expected progression-free and overall survival is as follows: stage III optimal (progression-free survival, PFS, 21–28 months, overall survival, OS, 52–57 months) and stage III suboptimal (PFS 18 months; OS 38 months).

The poor prognosis of many older women with ovarian cancer is partly due to the reduced use of standard chemotherapy. Reports have suggested that only half of women over the age of 65 years receive standard first-line platinum-based therapy, and the likelihood of receiving it decreased with age, independent on comorbidity [8]. Hershman's group found similar low-chemotherapy use – only about half of women with advanced ovarian cancer over age 65 were treated with platinum-based chemotherapy. However, survival improved by 38 % in the treated women, similar to the benefits described in randomized controlled trials among younger patients. The greatest benefit was seen when platinum was combined with paclitaxel [9].

In a SEER review, Sundareajan and colleagues found that older patients treated with any chemotherapy had actually increased in the years of 1992–1996. Eighty-three percent of patients received any chemotherapy treatment (single agent or combination regimens) within 4 months of diagnosis [10]. However, as age increased, the odds ratio of patients receiving chemotherapy dropped significantly. With 65–69 years as a reference, OR was 0.96 for ages 70–74, 0.65 for 75–79, 0.24 for 80–84, and 0.12 for ages 85+ years old. The disparities for the oldest patients were significantly observed in the nonwhite subgroup. Fear of excessive toxicity, patient preference, and unequal access to care were felt to be the major contributors to lack of chemotherapy use with advancing age.

In a more recent SEER review (2001–2005) of woman with ovarian cancer over 65 years old, Fairfield and colleagues found similar low chemotherapy use in the oldest

patient and low completion for all older patients [11]. Among 4,617 patients, 29 % received no chemotherapy, 25 % received partial course of chemotherapy, and 46 % completed all planned cycles of chemotherapy. Patients who were at greatest risk of incomplete chemotherapy were older than 75 years (OR 1.64) and/or had two or more comorbidities (OR 1.83). Interestingly, for those women who had any chemotherapy, there was no increase use in health services (hospitalizations, emergency room visits, or physician visits) for the oldest women (age 80 years or older) compared to the younger cohort.

Several strategies have been described to improve the tolerability of the first-line treatment including single-agent carboplatin, low-dose weekly schedules, and dose reductions [12–15]. The goal of each of these strategies is to reduce toxicity while maintaining efficacy.

In a series of 26 ovarian cancer patients older than 70 years (median 77), weekly carboplatin (AUC2) and paclitaxel (60 mg/m^2) on day 1, 8, 15 every 4 weeks demonstrated a favorable toxicity profile [13]. Patients had a high incidence of comorbidity (54 % with two or more) and dependence (31 % activities of daily living (ADL), 50 % instrumental ADL). Despite these barriers, only 11 % had high-grade toxicity: grade 3 heart rhythms, grade 3 increase of liver transaminases, and prolonged hematological toxicity. Grade 1 neuropathy was reported in four women. RECIST response rate was 39 %, and median overall survival was 32.0 months, which appears lower than expected compared to standard IV carboplatin and paclitaxel every 3 weeks.

A second retrospective study compared two cohorts older than 70 years who received carboplatin-paclitaxel either standard dosed (SD) or reduced dosed (RD) [15]. RD patients received carboplatin AUC 4-5 and paclitaxel 135 mg/m^2, while SD patients received carboplatin AUC 5-6 and paclitaxel 175 mg/m^2. RD patients ($n=26$) were significantly older than SD patients (median age 77.0 vs. 74.7, respectively, $p=0.014$). There were no differences in stage, comorbidity scores, cytoreductive status, or growth factor administration between cohorts. In the SD group, grade 3–4 neutropenia incidence was higher (54.1 % vs. 19.2 %; $p=0.002$), and women were more likely to experience cumulative toxicity and require treatment delays. Although performance status was lower in SD patients ($p=0.02$), on a multivariate analysis, only the administration of the SD regimen predicted toxicity ($p=0.008$). There were no differences in progression-free or overall survival between cohorts, although on multivariate, these data suggests that reduced-dose carboplatin/paclitaxel may be better tolerated but equally effective as the standard regimen in elderly ovarian cancer patients.

Single-agent carboplatin particularly in frail or the oldest patients (greater than 80 years) have been advocated by many oncologists, given the lack of reliable toxicity and efficacy data of doublet chemotherapy in the elderly population [12]. The results from the ICON 3 study are cited as a rationale; single-agent carboplatin was shown to have high efficacy and with attention to the subgroup analysis of those over 65 years (30 % of patients on study), carboplatin-paclitaxel did not significantly improve efficacy [16]. In addition, other studies have illustrated that the addition of paclitaxel significantly increases neutropenia, thrombocytopenia, infection, alopecia, and sensory neuropathy without clear efficacy advantages to carboplatin [14].

However, despite these thoughtful treatment modifications, several retrospective studies have suggested that elderly women who can tolerated cytoreductive surgery could (and should) receive combination platinum-taxane chemotherapy [17–20].

Our group reported a cohort study of 292 patients with stages IIIC–IV ovarian cancer who had their primary surgery at Memorial Sloan Kettering Cancer Center from 1998 to 2004 and subsequently began a platinum-taxane chemotherapy regimen [19]. 108 women (37 %) were older than 65 years old, and 184 (63 %) were younger than 65. Stage of disease, optimal cytoreduction rate, number of chemotherapy cycles, and chemotherapy regimen alterations were similar between groups. However, the older cohort had a lower median carboplatin (AUC) dose. Older patients achieved a clinical complete response with a similar frequency to those <65 (70 % vs. 79 %), similar rates of platinum sensitivity at 6 months (61 % vs. 65 %) and similar overall median survival (52 months vs. 55 months). However, selection bias in this "fit" population who can tolerate surgery and seek out a tertiary center can limit the results generalizability [19].

A second study reported on 148 consecutive women with gynecologic malignancies over the age of 70 years who were treated with chemotherapy between 1999 and 2000 in Italy [18]. The median age was 73 years (range 70–84, 37 % over 75 years). Most patients had ovarian cancer (70 %) and multiple comorbid conditions (80 %). Standard schedules were administered to 97 % of cases with 1,046 cycles of therapy administered (median, 6; range, 1–35, per patient). Most received platinum-combination chemotherapy regimens (72 %) rather than single agent (28 %). Toxicity was primarily hematologic, grade 3–4 (38 %). Only 7 % of women required discontinuation, and 17 % required treatment delays >7 days. From a subgroup analysis, those older than 75 years required the most drug delays and dose reductions. In addition, the number of patients receiving several subsequent lines of chemotherapy for recurrent cancer diminished: one regimen (57 %), two (33 %), three (6 %), and four (4 %). From these results, chronological age did not adversely influence the ability to receive first-line platinum-doublet treatment regimens.

A large retrospective analysis reported the outcome and toxicity differences seen in the 620 cohort of patients 70 year and older enrolled on GOG182, a phase III trial studying triplet-chemotherapy regimens for patients with newly diagnosed ovarian cancer [21]. Older patients had poorer performance status, lower completion rates of all 8 chemotherapy cycles, and increased toxicities, particularly grade 3+ neutropenia and grade 2+ neuropathy. Older women had significantly shorter overall survival (37 vs. 45 months, $p < 0.001$), consistent across all regimens and adjusted for major prognostic factors [21].

There is only one reported prospective therapeutic study of newly diagnosed ovarian cancer in older women in the United States. Only 12 patients were enrolled – highlighting the difficulty to accrue older patients onto clinical trials. In their report, Matulonis and colleagues illustrated that standard carboplatin (AUC 5) and paclitaxel (175 mg/m^2) can be administered to an older group of women (median age 82 years, range 75–86) [22]. Fifty percent of patients completed all six cycles with no dose reductions. Grade 3 or higher toxicities included febrile neutropenia (17 %), nausea (8 %), constipation (8 %), vomiting (8 %), obstipation (8 %), and hypoxia (8 %). Three patients died on study: one due to sudden death after cycle six, one from aspiration pneumonia, and one due to progressive cancer. Those patients who underwent primary debulking surgery and had less comorbidities and good performance status (0–1) were more likely to tolerate treatment.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NACT) is the delivery of chemotherapy prior to an aggressive debulking surgery. NACT use is gaining popularity in both the USA and Europe, particularly for older and frail patients. By shrinking cancer prior to surgery, several reports suggest that NACT increases the chance of an optimal debulking surgery (defined as <1 cm disease post-surgery) with less surgical morbidity and no significant effect on survival [23–29].

The definitive study of NACT was recently published from the European Organization for Research and Treatment of Cancer (EORTC) [28]. This prospective study randomized 632 patients with newly diagnosed stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer to either primary debulking surgery followed by six cycles of platinum-based chemotherapy or to three cycles of NACT platinum-based followed by an interval debulking surgery followed by an additional three cycles of platinum-based chemotherapy. Complete description of the chemotherapy used was not outlined in the manuscript. The two cohorts had similar baseline characteristics (age, performance status, histology type, grade, and stage). The median age was 62 years (25–86) in the primary surgery group and 63 years (33–81) in the NACT group. No subgroup analysis was reported based on older age.

This study concluded that NACT was not inferior to primary surgery, as the hazard ratio from death (intention-to-treat analysis) was 0.98 (90 % CI, 0.84–1.13, $p=0.01$ for non-inferiority) and the hazard ratio for progressive disease was 1.01 (90 % CI, 0.89–1.15) [28]. The median overall survival was 29 months in the primary debulking group and 30 months in those assigned to NACT. Complete resection of all macroscopic disease at primary or interval surgery was the strongest independent variable in predicting overall survival. The median outcome overall survival for those with no residual disease, those with 1–10 mm residual tumors, and those with >10 mm residual tumors was 45, 32, and 26 months, respectively, in the primary surgery group, and 38, 27, and 25 months, respectively, in the NACT group. Following this landmark study, NACT has been gaining wider acceptance as first option.

One criticism has been that the survival seen in primary debulk surgery group (OS 29–30 months) was much lower than expected, compared to prior phase III studies in this patient population (OS 38–57 months, dependent on surgical outcome) [30]. Potential confounders with the EORTC trial could be patient selection (higher comorbidities, higher surgical risk) and substandard surgery compared to prior studies.

In support of this critique, Chi and colleagues identified 316 patients who underwent primary treatment for advanced ovarian cancer from 9/1998 to 12/2006 at Memorial Sloan Kettering Cancer Center [31]. Study inclusion and exclusion criteria were identical to those of the EORTC trial. 285 (90 %) underwent primary surgery with a median age of 60 years (range 25–88). A much smaller cohort of only 31 (10 %) received NACT due to extra-abdominal disease, medical comorbidities, and/or advanced age (>85 years). Most had carcinoma of ovarian origin (248, 87 %), stage IIIC disease (249, 87 %), stage IV (36, 13 %), grade 3 tumors (237, 83 %), and serous histology (249, 87 %). The EORTC study had more stage IV patients (23 %) and less serous tumors (66 %).

For the primary surgery group, Chi reported that the optimal cytoreduction (≤1 cm residual) was achieved in 203 patients (71 %) and postoperative platinum-based chemotherapy was given to 281 of 285 patients (99 %) [31]. The median PFS and OS were 17 and 50 months, respectively, in the primary surgery group. For the 31 patients who underwent NACT, interval cytoreduction was performed on 28 (90 %), with no gross residual disease in 15 patients (54 %) and residual disease ≤1 cm in 24 patients (86 %). The median PFS for this group was 13 months (95 % CI, 8.6–16.4), and the median OS was 37 months (95 % CI, 13.4–59.8). A marked difference in overall survival was seen in this analysis compared the EORTC-NCIC study (50 months vs. 29 months) for primary debulking surgery, while the NACT outcomes were not as different (37 months vs. 30 months). The authors conclude that primary surgery should continue to be the preferred initial management for patients with bulky stages IIIC–IV ovarian carcinoma and NACT should be reserved for those who cannot tolerate surgery and/or when optimal cytoreduction is not feasible [31].

Elderly women, particularly those with high comorbidities and frailty, are at highest risk of surgical morbidity and may be the most appropriate candidates for NACT. In one retrospective study, Glasgow and colleagues from Yale University compared the outcomes in 104 women aged 70 years or older with advanced ovarian cancer who received NACT followed by surgery ($n=42$) and those who underwent primary surgery followed by the same platinum-based chemotherapy ($n=62$) at their institution [29]. Age, comorbidities, and preoperative ASA scores were similar in the two groups. Functional status or geriatric assessment variables were not reported. Compared to the primary surgery cohort, women who underwent NACT were more likely to have stage IV disease (57 % vs. 29 %, $p=0.0004$), lower baseline CA125 (1,305 vs. 1,757, $p=0.01$), serous histology (74 % vs. 53 %, $p=0.003$), and no visible residual disease after surgery (71 % vs. 28 %, $p<0.001$). NACT patients had reduced perioperative morbidity compared to the primary surgery group – less blood loss at surgery (435 ml vs. 773 ml, $p=0.01$), required fewer small bowel resections (0 % vs. 15 %, $p=0.009$), thromboembolic events (0 % vs. 10 %, $p=0.03$), and fewer hospital days (6.5 days vs. 11.7 days, $p=0.04$). There was no statistically significant difference in progression-free survival (median PFS 25 months vs. 19 months, $p=0.08$) or overall survival (median OS 25 vs. 39 months, $p=0.9$) in the NACT and primary surgery groups, respectively; however, the median survival was 14 months higher in the primary surgery group. Although this small single-center study has limitations given its retrospective design, it provides reassurance that NACT leads to less surgical morbidity without significant outcome differences in patients older than 70 years.

Guidelines are necessary to determine which patients are most suitable candidates for NACT. Aletti identified a high-risk group of women who do not appear to benefit from primary surgery, and this may be a suitable group of women best served with a NACT approach [32]. Risk features include stage IV disease, high initial tumor distribution (i.e., low likelihood of optimal debulking), poor performance status (ASA score ≥ 3), poor nutritional status (albumin < 3.0 g/dl), and older age (≥75 years). Although each patient plan must be individualized, these criteria are reasonable to use as guidelines for a NACT approach.

Intraperitoneal Chemotherapy

Cisplatin-based intraperitoneal (IP) chemotherapy has demonstrated significant survival benefit for patients with an optimally cytoreduction surgery (none or up to <1 cm residual disease) for stage III ovarian cancer and is a standard of care at most cancer centers [33–35]. Despite growing acceptance of its superior survival advantages, several concerns remain: technical difficulties (IP catheter placement and complications) and increased toxicities (renal dysfunction, neuropathy, hearing loss).

In the most recent IP study (GOG 172) reported by Armstrong, 39 % of the 205 women who received IP cisplatin-paclitaxel were elderly: 26 % (61–70 years), 12 % (71–80 years), and 1 % (over age 80) [35]. Their functional status was good (92 %, GOG performance status 0–1). However, regardless of age, less than 50 % of all patients were able to complete four or more cycles of the IP regimen due to toxicity. In a quality of life assessment, physical and functional well-being, and ovarian cancer symptoms were significantly worse in the IP arm, particularly before cycle four [36]. Patients in the IP arm also reported significantly worse abdominal discomfort and neurotoxicity 3–6 weeks ($P=0.001$) and 12 months ($P=0.003$) after completing IP treatment. However, the quality of life of both the IV and IP groups improved over time.

How does an oncologist apply these results to their older population? First, the major limitation to the study was that patients received IP cisplatin. By the age of 70, renal function may have declined by as much as 40 %, and this reduction in glomerular filtration rate (GFR) may lead to enhanced toxicity of drugs, particularly those with significant renal excretion, such as cisplatin [37–39]. On GOG172, patients were required to have a serum creatinine less than 1.2 mg/dl; however, creatinine clearance is a more sensitive marker for renal dysfunction and should be used [40]. The second limitation was the use of paclitaxel, as its drug clearance declines with age and its toxicities such as neuropathy and cytopenias heightens [41]. To improve tolerability, current GOG trials are exploring the elimination of the day 8 IP paclitaxel, substitute to IP cisplatin to carboplatin, substitute to IV paclitaxel to docetaxel and substituting all taxane to an IV weekly paclitaxel schedule.

Two studies have reported on the tolerability of IP chemotherapy in an older patient population.

O'Cearbhaill performed a descriptive analysis of 100 women older than 65 years who had an IP catheter placed with at primary surgery or at a second look surgery at Memorial Sloan Kettering Cancer Center [42]. Twenty-four percent had IP primary chemotherapy (front-line treatment after debulking surgery), and 76 % had IP platinum as consolidation therapy (after six cycles of IV platinum-therapy and a second look surgery). This was a healthy group of women (median performance status 90 %) with few comorbidities (median 2, range 0–6). In the IP primary therapy group, 54 % of patients were able to complete all six planned cycles of IP-IV chemotherapy, and 75 % completed at least four cycles. The IP-IV regimen was a modified version of GOG172: IV paclitaxel (135 mg/m^2 over 3 h) day 1, IP cisplatin (75 g/m^2) day 2, and IP paclitaxel (60 mg/m^2) day 8. In an intention to treat analysis, 100 patients with ovarian cancer younger than 65 were compared to this older cohort. There were no

significant differences in grade 3 or higher toxicity (17 % older vs. 21 % younger patients). However, the older patient required more treatment modifications: dose delays (13 % vs. 10 %, $p=0.51$), dose reductions (37 % vs. 20 %, $p=0.008$), and baseline dose reductions (21 % vs. 6 %, $p=-0.003$) in the older versus younger cohorts, respectively. Despite dose modifications, the older cohort had similar survival outcomes compared to the younger group. In the IP primary group, the median PFS was 1.9 years, and OS has not yet been reached; this was not a significant difference from the younger group (HR 0.91, CI 0.65–1.8, $p=0.6$). In addition, the multivariate analysis showed no significant differences in PFS by age group. The authors concluded that platinum-based IP chemotherapy could be safely administered in a selected older patient with adequate support and dose modifications.

Kothari and colleagues reported on 100 patients (86 % age < 70 years and 24 % age ≥ 70 years) who received IP chemotherapy at their institution from 2006 to 2009 [43]. They concluded similar findings as O'Cearbhaill. Older patients were less likely to complete all planned cycles of IP and required more dose modification but had similar survival and toxicity outcomes.

Clearly, we need prospective trials designed specifically for older patients with an emphasis of pharmacokinetics and toxicity to better screen this vulnerable patient group [44]. Until that time, IP chemotherapy should still be offered as an option to older women, particularly those with good functional status, adequate kidney and hearing function, and an understanding of the likelihood of higher toxicity compared to IV chemotherapy alone.

Conclusion

In order to improve the benefit and tolerability of cancer treatment, we must develop new geriatric-specific trials, better assessment tools, and encourage enrollment of older patients onto clinical trials. Age appears to be an important factor influencing treatment selection among women with ovarian cancer, and elderly patients may be inappropriately denied participation in research [45]. All standard treatment options for primary chemotherapy should be explored (IV carboplatin and paclitaxel, NACT or IP platinum-based therapy). To be mindful and respectful, one must define the goals of treatment to patients and their families (palliative vs. curative) as well as treatment toxicities. As the field of geriatric oncology evolves, guidelines will ultimately assist in these difficult decisions.

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Chapter 12
Relapse: Surgical Considerations and Secondary Cytoreduction

Sara M. Jordan and Robert E. Bristow

Abstract This chapter focuses on the survival benefit, selection criteria, and morbidity and mortality associated with secondary cytoreduction for recurrent ovarian cancer in the general population and the elderly. The goal of secondary cytoreduction is to improve overall survival by maximizing surgical tumor eradication in patients who demonstrate a complete clinical response to initial platinum-based chemotherapy. Retrospective studies consistently demonstrate a survival benefit associated with maximal secondary cytoreduction. Patient selection criteria should be individualized based on the patient's life goals, comorbidities and performance status, and availability of adjuvant therapy. Morbidity and mortality rates are comparable to those associated with primary cytoreduction. The role of secondary cytoreduction in the geriatric population is still evolving. In general, elderly are less likely to receive standard treatment for ovarian cancer, but research suggests that secondary cytoreduction can be both safe and feasible and advanced age alone should not be a contraindication to surgery.

Keywords Secondary cytoreductive surgery • Secondary cytoreduction • Recurrent epithelial ovarian cancer • Relapse • Elderly

Introduction

The majority of patients with ovarian cancer present with advanced disease, and while 80 % respond favorably to primary treatment, 50–60 % experience recurrence with subsequent death from their disease. According to the American Cancer

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Society, there will be 21,990 estimated new cases of ovarian cancer in 2011 resulting in 15,460 estimated deaths [1]. Although ovarian cancer continues to be diagnosed at a late stage, recent advances in therapeutics have resulted in improved overall survival. For patients with recurrent disease, the selective use of secondary cytoreductive surgery has been associated with improved survival outcomes.

The initial management of advanced-stage epithelial ovarian cancer is standardized—surgical cytoreduction followed by, or occasionally preceded with, platinum and taxane chemotherapy. Meigs, in 1935, was the first to describe the benefit of primary cytoreduction by demonstrating that patient response to postoperative radiation is directly correlated to the amount of pretreatment tumor removed [2]. In the mid-1990s, Hoskins more precisely quantified the inverse relationship between survival and amount of residual tumor [3].

Unlike the standardized primary management of ovarian cancer, the management of recurrent ovarian cancer continues to be debated. The term secondary cytoreduction was introduced by Berek in 1983 [4]. Theoretically, pharmacologic response can be improved by decreasing tumor volume prior to administering further chemotherapy. In the past 25 years, multiple studies have confirmed this theory by reporting improved overall survival after maximal secondary cytoreduction and adjuvant chemotherapy [5–14].

This chapter focuses on the survival benefit, selection criteria, and morbidity and mortality associated with secondary cytoreduction for recurrent ovarian cancer in the general population and the elderly.

Goal of Secondary Surgery Cytoreduction

Retrospective studies of secondary cytoreductive surgery for recurrent ovarian cancer consistently demonstrate an association between minimal residual disease and longer survival. While the observed survival benefit may potentially be influenced by selection bias, the results of these prior studies are compelling. Therefore, the aim of secondary cytoreductive surgery is to improve overall survival by maximizing surgical tumor eradication in patients who demonstrate a complete clinical response to initial platinum-based chemotherapy with disease-free interval of at least 6–12 months.

Terminology

The timing between completion of primary therapy and recurrence of ovarian cancer is related to individual tumor biology. Patients who show no response or have increased tumor volume during initial platinum treatment are considered to have refractory or progressive disease and have the worst prognosis. The prognosis is improved for patients who initially respond to platinum chemotherapy, but their survival is correlated with the length of their disease-free interval after completion

of treatment. Recurrence within 6 months is considered platinum-resistant disease and offers a worse prognosis than recurrence after 6–12 months or longer which is considered platinum-sensitive disease and is associated with the best prognosis.

The extent of residual disease after cytoreductive surgery is defined as follows: complete cytoreduction is removal of all macroscopic disease, optimal cytoreduction refers to residual disease of less than or equal to 1 cm greatest diameter, and suboptimal cytoreduction refers to residual of greater than 1 cm. This classification is important since many studies have described a continuum effect: the maximal diameter of residual tumor, up to a certain threshold (frequently described as 1 cm), is inversely related with overall survival (i.e., smaller residual disease correlates with longer survival). Some recent studies have suggested that the only true survival benefit is associated with complete secondary cytoreduction [6, 9].

Surgery performed after completion of initial treatment is classified according to the timing and intent of the surgery. Interval cytoreduction is surgery performed with the intent to remove disease that was initially considered unresectable after a patient has completed neoadjuvant chemotherapy. Second-look surgery is a means of surgically diagnosing persistent disease after completion of initial therapy when there is no clinical evidence of disease. Secondary cytoreductive surgery, discussed in this chapter, is a second surgical effort to maximize tumor reduction in patients who have completed primary treatment and who have platinum-sensitive recurrence after a disease-free interval of at least 6–12 months.

Surveillance

Surveillance practices to diagnose recurrent ovarian cancer are physician dependent. Most physicians examine patients every 3 months; however, history and physical exam alone is insufficient since patients typically present without symptoms and without palpable disease at the time of initial recurrence. For this reason, serum biomarkers are frequently monitored with the goal of diagnosing recurrence sooner than it would be diagnosed with history or physical exam alone. The most commonly used biomarker, CA 125, is frequently checked every 3 months, but this practice is controversial. The sensitivity of CA 125 is 77–94 % with a positive predictive value of 95–100 % [15]. In a small study of 39 patients with complete response to primary therapy, a relative doubling of CA 125 was significantly predictive of recurrence (OR 23.7, 95 % CI 2.9–192.5, $p=0.003$), as was an increase of CA 125 of 5 U/mL over nadir levels (OR 8.4, 95 % CI 2.2–32.6, $p=0.002$) and even more so 10 U/mL above nadir (OR 71.2, 95 % CI 4.8–999.9, $p=0.002$) [16]. A larger randomized trial, however, showed no survival benefit and worse quality of life when second-line therapy was initiated based on a rising CA 125 alone [17]. Other biomarkers used for ovarian cancer surveillance include OVA1 and HE4 with similar controversy.

The imaging modalities most commonly used to monitor for disease recurrence are computed tomography (CT) and positron emission tomography/computed tomography (PET/CT). CT sensitivity and specificity for diagnosing recurrence is

59–83 % and 83–88 %, respectively [18–20]. Small metastases, however, can be challenging to diagnose using conventional CT alone. In addition, disease recurrence can be masked by postoperative changes from prior cytoreductive surgery.

PET/CT is increasingly being used to guide optimal management of recurrent disease. The benefit of PET/CT over conventional CT was reported by Bristow et al. who evaluated 22 patients with ovarian cancer at least 6 months after completion of primary therapy with rising CA 125 and negative or equivocal conventional CT scans [21]. Using PET/CT, 18 of 22 patients were identified with greater than 1 cm of disease at the time of surgery. PET sensitivity and positive predictive value were found to be 83.3 and 93.8 %, respectively, compared to the lower sensitivity of conventional CT [21].

A retrospective cost-effective analysis of PET imaging was performed by Mansueto et al. who studied 32 consecutive patients with suspected recurrent ovarian cancer. All patients were imaged by both CT and PET/CT. Three strategies were evaluated: (1) CT only, (2) PET/CT for negative CT only, and (3) CT plus PET/CT. CT only detected 20/32 patients with recurrence, whereas PET/CT for negative CT detected 30/32 and CT plus PET/CT detected 29/32 positive patients. PET/CT for negative CT changed management in 31 % of cases, whereas CT plus PET/CT changed management in 62 % of cases. Combined CT plus PET/CT was found to be the most effective tool to guide management of patients with suspected ovarian cancer recurrence [22].

Magnetic resonance imaging (MRI) has also been suggested to improve diagnosis of recurrent ovarian cancer, specifically due to the enhanced resolution of soft tissue. The addition of MRI to CT, however, has not been shown to significantly improve diagnosis of recurrence [23]. In a study of 39 patients with suspected recurrent disease, MRI sensitivity was 67–83 %, specificity was 60–89 %, positive predictive value was 65–93 %, and negative predictive value was 47–83 % [24].

Based on these studies, recommended surveillance includes clinical exam and CA 125 every 3 months with CT scan every 6 months for 36 months. Thereafter, exam and CA 125 can be performed every 6 months with CT either discontinued or performed annually out to 5 years. A PET/CT is recommended for patients who have an elevated CA 125 and negative or equivalent CT and is also recommended to guide surgical management.

Survival Benefit Associated with Secondary Cytoreductive Surgery

A survival benefit associated with maximal secondary cytoreduction was first described by Berek et al. in 1983 [4]. This initial study described a heterogeneous group of 32 patients undergoing a repeat attempt at cytoreduction after relapse. There was a statistically significant increase of 20 months longer survival in patients with <1.5 cm residual versus only 5 months longer survival with >1.5 cm residual ($p<0.01$). Multiple studies since then have confirmed these findings.

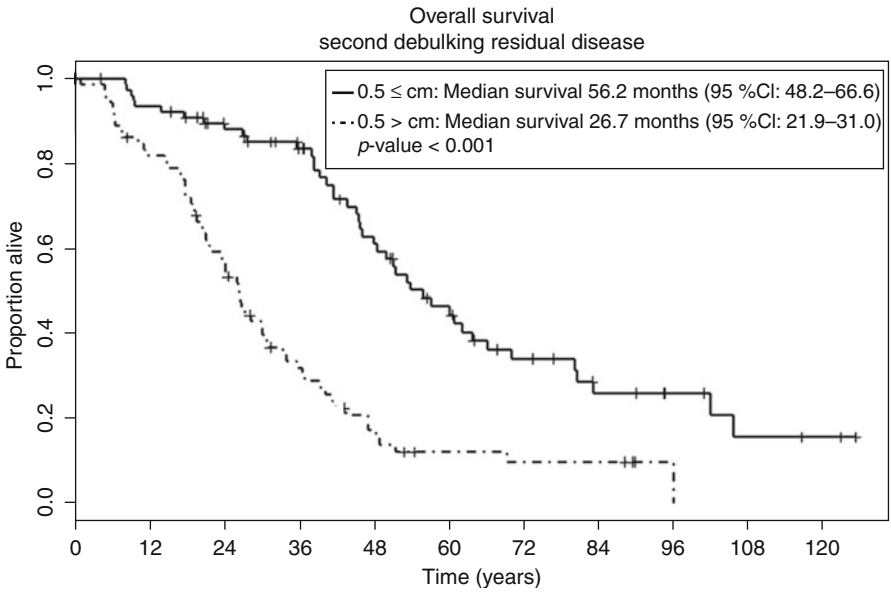

Fig. 12.1 Overall survival based on residual disease of ≤0.5 cm versus >0.5 cm (*Source*: From Ref. [8])

In a study by Eisenkop et al., 106 patients with clinical suspicion for recurrent ovarian cancer underwent secondary cytoreductive surgery [6]. Complete cytoreduction was achieved in 82 % of patients. Complete cytoreduction was associated with increased survival compared to any residual disease (44.4 months versus 19.3 months, respectively, $p = 0.0007$).

Scarabelli et al., in 2001, reported a similar survival benefit associated with complete secondary cytoreductive surgery [7]. In a prospective, although non-randomized, study of 149 patients with platinum-sensitive disease who underwent secondary cytoreductive surgery, 35.6 % had complete cytoreduction. Complete cytoreduction was significantly correlated with improved survival compared to residual of ≤1 cm (HR 2.65, 95 % CI 1.43–4.92) or residual >1 cm (HR 5.79, 95 % CI 2.99–11.21).

A study by Chi et al. from Memorial Sloan-Kettering Cancer Center in 2006 similarly evaluated extent of secondary cytoreduction and the association with overall survival [8]. Of the 153 patients who underwent secondary cytoreductive surgery, 41 % had complete cytoreduction with a total of 52 % who had ≤0.5 cm residual. Residual disease of ≤0.5 cm was a significant independent predictor of survival (56.2 months for ≤0.5 cm versus 26.7 months for ≥0.6 cm residual, $p < 0.001$). Figure 12.1 illustrates this association between residual disease and survival.

DESKTOP OVAR (Descriptive Evaluation of preoperative Selection KriTeria for Operability in recurrent OVARian cancer) was a landmark study published in 2006 [9]. This study represented the prospective combined experience of 25 institutions across Germany. Of the 267 patients enrolled, complete cytoreduction was achieved in 49.8 % of cases. Complete cytoreduction was associated with

significantly improved overall survival compared to any residual disease (median 45.2 versus 19.7 months; HR 3.71; 95 % CI 2.27–6.05; $p<0.0001$). The DESKTOP OVAR data confirmed that the goal for secondary cytoreductive surgery should be complete cytoreduction, rather than merely optimal cytoreduction.

A meta-analysis of 2,019 patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery in the collected literature between 1983 and 2007 was published by Bristow et al. [5]. This study confirmed that maximal tumor reduction is independently associated with increased overall survival. Optimal and complete cytoreduction were achieved in 70 and 50 % of patients, respectively. Each 10 % increase in complete secondary cytoreduction was associated with an increase in median post-recurrence survival of 3.00 months ($p=0.02$). The only other independent predictor associated with increased survival was year of publication. Each 1-year increase was associated with 1.00 month increase in overall survival ($p=0.01$).

Increasing tumor resection at the time of secondary cytoreduction was also confirmed to independently improve patient prognosis by Sehouli et al. [10]. This study concluded that overall survival is improved, not only by complete tumor resection but also by optimal tumor resection of less than 1 cm of residual disease. Of the 240 secondary cytoreductions, 54 % had complete cytoreduction, and 24 % had 0.1–1.0 cm residual. Survival was 42.3, 17.7, and 7.7 months for patients with complete tumor resection, 0.1–1.0 cm, and greater than 1 cm, respectively. The magnitude of the survival benefit is much greater the smaller the residual disease with maximal benefit associated with complete resection of disease.

Several other studies in the last few years have reported similar survival benefit due to increased cytoreduction at time of recurrence [11–14]. In these studies, optimal secondary cytoreduction has been associated with longer survival of 16–61 months compared to decreased survival after suboptimal secondary cytoreduction of only 8–27 months. The goal of secondary cytoreductive surgery should therefore be maximal removal of disease with complete resection when feasible.

Selection Criteria for Secdondary Cytoreduction

Despite the above data, it is important to appreciate that the survival benefit of secondary cytoreduction is limited to a subset of patients with recurrent disease. Patient selection for secondary cytoreductive surgery is critical and is based on both general prognostic factors as well as factors predictive of surgical outcome.

Variables Predictive of Overall Prognosis

Most experts agree that secondary cytoreductive surgery should only be considered for patients with recurrent platinum-sensitive ovarian cancer. In one of the few studies examining secondary cytoreductive surgery in patients with platinum-resistant disease, Morris et al. reported that patients with platinum-resistant disease did not have a survival benefit from secondary cytoreduction [25]. Optimal cytore-

Table 12.1 Variables predictive of improved overall prognosis

Residual disease after primary surgery
Long disease-free interval (>12–36 months)
Platinum-sensitive disease
Young age (<55 years)
Good performance status (GOG PS 3 or ECOG PS 2)
No medical contraindications to surgery
Patient acceptance of adjuvant chemotherapy postoperatively
Initial stage < IV
Optimal (<2 cm) primary cytoreductive surgery
Minimal ascites
Small tumor (<10 cm)
Few recurrence sites (≤1)
Recurrence limited to the pelvis
CA125 less than 250 U/mL
Few cycles of salvage chemotherapy (<6 cycles)
Secondary cytoreductive surgery prior to salvage chemotherapy

Source: From Refs. [6, 8–10, 14, 26–34]

duction was achieved in only 21 % of the platinum-resistant patients, and the majority of these patients had only an 8-month improvement in survival that was not statistically significant. Although there is no exact length of time to recurrence that dictates surgical versus nonsurgical management, it is known that longer disease-free interval (usually greater than 12–36 months) is associated with increased survival [6, 8, 26–29].

Treatment should be individualized and the criteria listed in Table 12.1 have been proposed to identify patients who may benefit from secondary cytoreductive surgery. Disease-free interval of >12 months is associated with improved survival (OR 0.51, 95 % CI 0.29–0.90) compared to a disease-free interval of 6–12 months (OR 0.92, 95 % CI 0.50–1.71) and a disease-free interval of <6 months ($p = 0.016$). Other variables significantly associated with improved survival are: optimal (<2 cm) primary cytoreductive surgery, young age (<55 years), favorable performance status (Gynecologic Oncology Group (GOG) 3 or Eastern Cooperative Oncology Group (ECOG) 2), no comorbidities precluding surgery, patient acceptance of adjuvant chemotherapy postoperatively, International Federation of Gynecology and Obstetrics (FIGO) stage at initial diagnosis < IV, ascites <500 mL, small tumor (<10 cm), few recurrence sites (<3), recurrence limited to the pelvis, CA 125 less than 250 U/mL, few cycles of salvage chemotherapy (<6 cycles), and secondary cytoreduction prior to salvage chemotherapy [6, 8, 10, 14, 26–34].

Variables Predictive of Secondary Cytoreductive Surgical Outcome

There is considerable overlap between variables predictive of surgical outcome and those associated with improved post-recurrence survival time. The first effort to describe variables predictive of optimal secondary cytoreduction was suggested by

Table 12.2 Significant variables associated with complete cytoreduction

Variable	
Performance status (ECOG)	0
	>0
International Federation of Gynecology and Obstetrics (FIGO) Stage	I/II
	III/IV
Residual after primary surgery (mm)	0
	>0
CA 125	<70
	>350
Ascites (mL)	<500
	≥500
Localized recurrence	Pelvis
	Other
Peritoneal carcinomatosis	No
	Yes

Source: Adapted from Ref. [9]

Berek in 1998 at the *Second International Ovarian Cancer Consensus Conference* [35]. Proposed criteria included disease-free interval >12 months after first-line therapy, potential for complete resection based on preoperative evaluation, favorable performance status GOG ≤ 3, and younger age <55, optimal primary cytoreductive surgery, small size of recurrent tumor ≤10 cm, few sites of recurrence ≤1, and surgery performed prior to chemotherapy [6, 10]. These criteria, although frequently used to triage patients, were based more on expert opinion rather than objective clinical data and patient selection criteria remained ill defined.

DESKTOP OVAR not only evaluated variables associated with improved overall survival but also factors that were independently predictive of surgical outcome [9]. These are listed in Table 12.2 and include the amount of residual tumor after primary cytoreduction (none versus any residual, OR 2.46, 95 % CI 1.45–4.20, $p < 0.001$), performance status (ECOG 0 versus >0; OR 2.65, 95 % CI 1.56–4.52, $p < 0.001$), FIGO stage at initial diagnosis I/II versus III/IV (OR 1.55, 95 % CI 0.85–2.82, $p = 0.036$), and absence of ascites greater than 500 mL (OR 5.08, 95 % CI 1.97–13.16, $p < 0.001$). These variables predicted complete resection in 79 % of patients with recurrent ovarian cancer.

Peritoneal carcinomatosis was initially described by Gadducci et al. as having a negative impact on survival [28]. In this study of 30 patients with recurrent ovarian cancer who underwent secondary cytoreductive surgery, complete resection was achieved in only 57 % of patients, but those patients undergoing successful surgery enjoyed the same survival benefit as patients with more limited disease and the same surgical outcome. DESKTOP I was a subgroup analysis of 125 patients in the DESKTOP OVAR trial, 74 % with no carcinomatosis and 26 % with carcinomatosis [36]. This trial confirmed that, as long as complete cytoreduction was achieved, peritoneal carcinomatosis was not independently associated with decreased survival. Those with no carcinomatosis had a significant survival advantage of 45.3 months versus 19.9 months for those without carcinomatosis ($p < 0.0001$); however, when patients with carcinomatosis underwent complete resection, their overall survival was equal to patients without carcinomatosis who underwent complete

resection (2 year survival 81 % versus 77 % for patients without and with carcinomatosis, respectively, $p = 0.96$). Therefore, as long as complete cytoreduction is achieved, carcinomatosis is not independently associated with decreased survival.

DESKTOP II published in 2011 was a randomized prospective validation study of DESKTOP OVAR conducted in 46 international centers with a variety of surgical experience [37]. This trial evaluated secondary cytoreduction in platinum-sensitive patients with (1) favorable performance status ECOG 0, (2) complete primary cytoreduction, and (3) absence of ascites >500 mL. Of the 516 patients enrolled, only those who met all three criteria were given a positive Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score. The primary endpoint was complete secondary cytoreduction. A total of 76 % of patients with a positive AGO score had complete cytoreduction versus 10 % with 1–10 mm residual and 14 % with >10 % residual. Thus, the AGO score became the first prospectively evaluated instrument to positively predict secondary cytoreductive surgical outcome.

An evidence-based model for patient selection for secondary cytoreductive surgery was proposed by Tian et al. in 2011 [38]. Over 1,000 patients with recurrent ovarian cancer were evaluated in 7 countries around the world. Complete cytoreduction was achieved in 40 % of patients and was associated with 6 variables: FIGO stage (OR 1.32, 95 % CI 0.97–1.80), residual disease after primary cytoreduction (OR 1.69, 95 % CI 1.26–2.27), disease-free interval (OR 2.27, 95 % CI 1.71–3.01), ECOG performance status (OR 2.23, 95 % CI 1.45–3.44), CA125 (OR 1.85, 95 % CI 1.41–2.44), and absence of ascites at recurrence (OR 2.79, 95 % CI 1.88–4.13). Patients were scored according to these variables, and those who fell into the lowest risk group had a 53 % chance of complete cytoreduction versus only a 20 % chance in the high-risk group (OR 4.55, 95 % CI 3.43–6.04). The sensitivity and specificity of this model was 83.3 and 57.6 %, respectively. This model may prove useful in the clinical setting to triage patients with recurrent ovarian cancer to secondary cytoreductive surgery prior to chemotherapy.

Morbidity Associated with Secondary Cytoreductive Surgery

Several studies have reported postoperative morbidity and mortality rates associated with secondary cytoreductive surgery. Based on the meta-analysis published by Bristow et al. [5], the mean operative time of 2,019 secondary cytoreductive surgeries reported in 40 studies was 4 h, and estimated blood loss was 600 mL, which is comparable to primary cytoreductive surgeries. From this meta-analysis, the incidence of significant postoperative morbidity was 19.2 % (range 0–88.8 %), and incidence of postoperative mortality was 1.2 % (range 0–0.5 %). These rates also are comparable to primary cytoreductive morbidity and mortality rates.

The postoperative morbidity and mortality from the 129 patients who underwent secondary cytoreductive surgery in the study DESKTOP II is listed in Table 12.3. The risk of secondary cytoreductive surgery includes common complications of surgery such as wound complications, ileus, urinary tract infection, or pneumonia

Table 12.3 Sources of SCRS morbidity and mortality

Postoperative morbidity	Percent of patients
Transfer to intensive care unit	52
Requirement for blood transfusion	44
Infection requiring antibiotics (including urinary tract infection, peritonitis, and pneumonia)	24
Second laparotomy (for bowel perforation, abscess, bleeding, and fistula)	11
Thrombosis	2
Other severe complications (including secondary wound healing, fistula, prolonged ileus)	8

Source: Adapted from Ref. [37]

and more serious complications such as bowel or bladder injury, fistula formation, blood transfusion, and risks of anesthesia or death.

The morbidity and mortality of secondary cytoreductive surgery in regard to the type of procedures performed were evaluated in several studies. Bristow et al. and Cliby et al. reported morbidity associated with rectosigmoid resection and diaphragm resection [39, 40]. A morbidity rate of 23.2 % (13/56 patients) and mortality 2 % (1/56 patients) was associated with rectosigmoid colectomy. The one death was due to an anastomotic leak and resulting abscess. Diaphragmatic resection was associated with a similar 2 % mortality rate (1/41 patients). These rates seem acceptable given the improved overall survival associated with maximal cytoreduction.

Perioperative morbidity and mortality associated with primary versus secondary cytoreductive surgery was compared by Woelber et al. [41]. In a study of 222 patients who underwent extensive cytoreduction (48 primary and 174 secondary) with similar range of surgical procedures, there were no significant differences in complication rates with 44 % complications after secondary cytoreduction versus 36 % after primary cytoreduction. Of those who had primary cytoreductive surgery, 48 % had <1 cm residual and 33 % had no residual compared to 82 and 58 %, respectively, for those who had secondary cytoreductive surgery. These findings again suggest that the morbidity with secondary cytoreductive surgery is comparable to that associated with primary cytoreductive surgery, and these rates are acceptable considering the survival advantage of maximal cytoreduction.

Patient selection and surgeon experience, however, are essential for maximizing the benefit from secondary cytoreduction and minimizing morbidity and mortality. Chemotherapy alone may have an equal survival benefit without the risk of surgical complications for certain patients. Obese patients with other comorbidities or poor performance status, for instance, would likely not tolerate a repeat extensive cytoreduction. In these cases, chemotherapy without repeat cytoreduction may be a safer alternative.

Secondary Cytoreduction in the Elderly

The role of secondary cytoreductive surgery specifically in the geriatric population is evolving. The specific selection criteria and associated survival benefit in this setting will need to be further addressed since this is a population that continues to grow in numbers. According to the United States Census Bureau, in 2010, there were 38.6 million adults over 65 years old which was 13 % of the country's population, and this number is predicted to increase to 20 % in 2030 [42]. The management of recurrent ovarian cancer in the elderly is important because ovarian cancer is a disease of the elderly with peak incidence in the eighth decade of life. Unfortunately, there is virtually no data to guide surgical management of recurrent disease in the elderly, so we are left with extrapolating data from the primary surgical setting.

Many surgeons previously believed that surgical cytoreduction was contraindicated in the elderly. A retrospective study by Alphs et al. in 2006, however, confirmed the benefit of optimal cytoreductive surgery in the elderly [43]. In this study, 78 elderly women with primary ovarian cancer were evaluated, and the association between perioperative characteristics and surgical outcome and survival was reported. Survival was 62 months after optimal cytoreduction versus 17 months after suboptimal cytoreduction ($p<0.001$). Age over 80, however, was found to be an independent predictor of decreased overall survival (HR 2.6, 95 % CI 1.51–4.41). Other predictors of survival were comorbidity index (HR 1.3, CI 1.07–1.58), serum albumin ≥3.7 g/dL (HR 0.6, 95 % CI 0.42–0.79), and surgery performed by a non-gynecologic oncologist (HR 2.0, 95 % CI 1.09–3.61) [43].

Despite the known importance of maximal cytoreduction, it has been demonstrated in multiple other studies in the primary setting that elderly are less likely to be optimally cytoreduced [44]. A retrospective review by Cloven et al. [44] of 18 patients over age 80 found that only 25 % had optimal cytoreduction and 75 % had admission to the intensive care unit with 13 % postoperative mortality. In the study by Alphs et al., age over 80 was found to be predictive of less optimal cytoreduction with 33 % optimal and 67 % suboptimal versus 57 % optimal and 43 % suboptimal in their younger counterparts (HR 2.7, $p=0.10$). Low serum albumin was also a significant predictor of suboptimal surgical outcome (OR 2.4, $p=0.04$). Body mass index (BMI), CA 125, comorbidity index, tumor size, and ascites were all nonsignificant [43]. In another study of octogenarians who underwent cytoreductive surgery, median length of stay was found to be 10 days versus 7 days for those patients under 80 years; cost of care was $76,760 versus $52,649 and 30-day mortality was 5.4 % versus 2.4 %, respectively [45].

In general, elderly are less likely to receive standard ovarian cancer treatment. While some researchers have suggested that this is due to increased medical comorbidities associated with older age [46], others found that the extreme elderly had a decreased chance of receiving surgery or combination chemotherapy despite equivalent comorbidities [47].

The surgical complication rate in elderly compared to younger patients was published by Chereau et al. in 2011 [48] This was a French study that evaluated 172 patients between 2001 and 2009, 143 who were under age 70 and 29 who were over

age 70. There was no difference between older and younger groups in terms of FIGO stage, time of surgery, surgical procedure, and rate of optimal resection. Patients greater than 70 years old had less peritoneal surgery ($p<0.001$), less diaphragmatic surgery ($p=0.006$), and less pelvic ($p=0.02$) and para-aortic (0.003) lymphadenectomy, but no there were no differences in pre- or postoperative complications and no difference in disease-free survival ($p=0.08$), although overall survival was better in under 70 years old ($p=0.002$).

Some researchers have suggested that differences in outcome are independently attributable to age [49, 50], but others suggest that there are other factors such as advanced stage, tumor cytoreducibility, and comorbidities are frequently worse in patients with advanced age leading to the differences in outcome. In a retrospective analysis of 175 patients who were optimally cytoreduced and stratified according to age (younger or older than 70), it was found that complication rates and survival were similar between both groups [51]. Aggressive cytoreductive surgery was concluded to be both safe and feasible in the elderly, and advanced age alone should not be a contraindication to surgery. There are no specific studies of the impact and feasibility of secondary cytoreduction in the geriatric population, but it can be inferred that the same selection criteria for secondary cytoreductive surgery should be used for the elderly as is used for the general population provided that performance status is good.

Few studies have been reported regarding tertiary cytoreduction in the case of recurrent ovarian cancer. In 2004, Leitao et al. demonstrated a survival advantage with complete cytoreduction in the tertiary setting with 36.3 and 10.6 month survival for ≤0.5 and >0.5 cm residual disease after tertiary cytoreduction [52]. A study from Memorial Sloan-Kettering Cancer Center was published in 2010 similarly suggesting that complete cytoreduction in the tertiary setting may prolong survival [53]. Further studies need to be performed to address the issue of tertiary cytoreduction. In patients with multiple recurrences of disease that remains platinum-sensitive, multiple repeated attmepts at debulking may be considered, provided performance status is adequate and additional adjuvant treatment options are available.

Surgical Approach

Evidence suggests that maximal cytoreduction is necessary to improve survival in all age groups. In order to accomplish maximal tumor removal, one must take into account the surgeon's comfort level and experience with maximal cytoreduction. In cases where the surgery is beyond the scope of the surgeon, a collaborative approach has been recommended [8]. A review of 20 cases of recurrent ovarian cancer that were managed collaboratively with surgical oncologists was published by Burton et al. in 2011. This represented 15 % of the secondary cytoreductive surgeries at a single institution. The 5-year survival rate following joint surgical effort was 45 % with median postsurgical survival of 42 months [54]. The non-collaborative rates were not reported in this study. The surgical approach is highly dependent on the surgeon's experience with extensive cytoreduction. Experienced surgeons would

likely not require a collaborative approach, whereas those with less experience may consider collaboration.

Maximal secondary cytoreduction frequently requires complex surgical procedures. The surgeon should be familiar with the following procedures: diverting colostomy with mucous fistula or end colostomy, rectosigmoid colectomy, peritoneal resection, diaphragm resection, hepatic resection, partial pancreatectomy, gastrocolic ligament resection, resection of the distal urinary tract, and extensive lymphadenectomy. Ultimately, the goal is to minimize morbidity and achieve maximal cytoreduction in order to prolong survival.

Future Direction

In conclusion, multiple retrospective studies have demonstrated that maximal secondary cytoreduction improves survival in patients with ovarian cancer. Patient selection criteria for secondary cytoreductive surgery should be individualized based on the patient's life goals, comorbidities and performance status, and availability of adjuvant therapy. Current studies are limited by heterogeneous populations of patients, difficulty collecting information regarding postoperative treatment, absence of prospective randomized trials, differences in defining optimal surgery, and difference in surgical experience. Future prospective studies are needed to validate the value of optimal, not only complete, cytoreduction in the setting of recurrent ovarian cancer. GOG 213 is a prospective multiinstitutional randomized study evaluating the benefit of secondary cytoreduction in recurrent ovarian cancer patients. This is a phase III randomized study of adjuvant Carboplatin and Paclitaxel with versus without Bevacizumab and/or secondary cytoreduction in patients with platinum-sensitive recurrent ovarian epithelial cancer. If the benefit of maximal secondary cytoreduction is confirmed in the general population, a future study is needed to extrapolate this benefit to the geriatric population.

DESKTOP III is a randomized phase III trial evaluating patients with a first recurrence of platinum-sensitive ovarian cancer [55]. Patients with a disease-free interval of 6–12 months versus >12 months after first-line platinum therapy are currently being randomized to either cytoreduction or no cytoreduction, with recommended additional platinum chemotherapy for both groups. Patients are being included if they have a positive AGO score and disease that appears completely resectable by the surgeon. The primary objective is overall survival. Secondary objectives include progression-free survival, quality of life, rate of complete tumor resection, complication rates of surgery, and analysis of surgical characteristics and chemotherapy. This will be the first randomized trial to include AGO score to triage patients for secondary cytoreductive surgery.

These are the first randomized phase III trials aimed to demonstrate a survival benefit due to maximal secondary cytoreduction for patients with platinum-sensitive ovarian cancer recurrence. Results from these studies will likely encourage increased surgical management in properly selected patients with recurrent platinum-sensitive epithelial ovarian cancer.

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Chapter 13
Ovarian Cancer Relapse: Experimental Therapies

Melina Shoni and Ursula A. Matulonis

Abstract Epithe ovarian cancer has the highest mortality of all gynecologic cancers with an estimated 22,280 cases diagnosed in 2012 in the United States and 15,500 deaths [1]. For women between the ages of 60 and 79 years of age, ovarian cancer is the fifth leading cause of cancer death following lung, breast, colorectal, and pancreatic cancer [1]. Survival improvements for newly diagnosed ovarian cancer have reached a plateau using upfront surgery followed by platinum- and taxane-based chemotherapy. Thus, investigational efforts with new therapeutic agents are underway in an effort to overcome platinum- and chemotherapy-resistant cancer and ultimately improve survival. Insights into the molecular biology of ovarian cancer through mechanisms such as The Cancer Genome Atlas Project have identified potential therapeutic targets [2]. Efficacy, toxicities, and drug metabolism related to targeted therapies in the elderly patient with ovarian cancer are not available, and thus, data on the risk-benefit ratio of targeted therapies in this age group are mainly derived from studies in non-gynecologic cancers. This chapter reviews the available targeted therapies for the management of ovarian cancer and outlines the application of newer biologic agents in elderly patients with recurrent ovarian cancer.

Keywords Ovarian cancer • Elderly • Targeted therapies • Relapse • Management

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Abbreviations

HTN	Hypertension
RF	Renal failure
FDA	Food and Drug Administration
ATE	Arterial thromboembolic event
VTE	Venous thromboembolic event
GIP	Gastrointestinal perforation
TKI	Tyrosine kinase inhibitor
IV	Intravenous
PFS	Progression-free survival
OS	Overall survival
PLD	Pegylated liposomal doxorubicin

Elderly Patients with Ovarian Cancer

Many studies have demonstrated that women diagnosed with ovarian cancer at age older than 65 years have a poorer overall survival compared to their younger counterparts; however, not all studies have corroborated this finding [3–9]. In the studies that have documented poorer outcome in older patients, this observation has been attributed to several factors which include possible increased biological aggressiveness of ovarian cancer in older patients, less aggressive treatment offered to these patients, inability of older patients to tolerate treatment because of comorbidities, and impaired drug clearance [10–16]. A prospective study of patients ≥70 years of age given standard intravenous (IV) carboplatin and paclitaxel regimen for newly diagnosed Müllerian tumors demonstrated that chemotherapy was better tolerated by patients who had a PS of 0 or 1 and had fewer comorbidities compared to patients who were a poorer surgical risk and had a PS of 2 or greater. These results suggested that medically screened and appropriate older patients should have access to platinum- and taxane-based chemotherapy [17]. In a population of women with recurrent platinum-sensitive ovarian cancer using a multivariate analysis, all of the following were all independently associated with survival: number of disease sites (>1 vs. 1), performance status at recurrence (2–3 vs. 0–1), recurrence-free interval (6–12 months vs. >12 months), and age at recurrence [18].

Age-Related Considerations for Targeted Therapies in Ovarian Cancer

Insights into cancer pathogenesis have yielded new classes of agents that interfere with biologic processes in tumor cells and their microenvironment and are crucial for tumor growth, progression, and survival [19]. The targeted therapies that are of

Table 13.1 Selected therapies of interest for ovarian cancer

Therapies of interest and in clinical testing
Anti-angiogenic agents
Epidermal growth factor family inhibitors (EGFR, ErbB2, ErbB3)
PI3kinase pathway inhibitors
Hedgehog inhibitors
Antifolate drugs
PARP inhibitors
Aurora kinase inhibitors
Immunotherapies

specific interest in ovarian cancer and are in active study are listed in Table 13.1. Currently, no targeted therapies have been FDA approved for use in ovarian cancer. In addition, with respect to elderly patients with ovarian cancer, no age-specific analyses concerning efficacy and tolerability of molecularly targeted agents have been reported. Although the elderly constitute more than 45 % of all ovarian cancer patients, their enrollment in randomized controlled trials is poor, and selection bias arising from the enrollment of elderly with better performance status and minimal comorbidities may also call into question the applicability of existing data to real-world elderly patients [20–28]. Multiple causes including physician-, patient-, and study-specific-related factors likely account for poor accrual of older ovarian cancer patients onto clinical studies.

Theoretically, by selectively targeting a well-defined molecular pathway that spares normal cells, targeted therapies can provide specific antitumor effect with comparatively less toxicity; however, off target effects of these agents have led to significant toxicities not only in the elderly but in all ages [29, 30]. Furthermore, pharmacokinetic variability of targeted agents based on age-related physiological decline has not been assessed yet and is based on the drug's established biologic targets and the patient's functional status. For example, absorption of oral agents may be affected by the following in the elderly: decreased splanchnic blood flow, reduced gastric motility, decreased renal blood flow and glomerular filtration rate, and coadministration of CYP inhibitors or inducers that could alter the pharmacokinetics of agents metabolized by cytochrome P450 enzymes [29]. Treating clinicians must review potential interfering medications that the patient is taking prior to embarking on targeted therapies [29, 31, 32].

Targeted Therapies Under Investigation in Ovarian Cancer

Anti-angiogenic Agents

Anti-angiogenics are the most widely studied targeted agent in ovarian cancer. The rationale of anti-angiogenic agents in ovarian cancer is derived from the angiogenesis dependence of cancer development and the contribution of tumor-upregulated

proangiogenic factors, including vascular endothelial growth factor (VEGF) family, fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs), and angiopoietin, which drive new vessel formation [33, 34]. In addition, VEGF-receptor (VEGFR) family signaling pathways give rise to protumorigenic transduction cascades [35, 36]. In preclinical models, overexpression of VEGF leads to a survival advantage for transformed cells of the ovary [37]. In addition, some observational studies have demonstrated that serum VEGF levels correlate with extent of cancer and outcome [38–40].

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds all isoforms of VEGF receptor ligand VEGF-A and is the most studied anti-angiogenic therapy in ovarian cancer [41]. Bevacizumab has been tested in patients with newly diagnosed ovarian cancer combined with chemotherapy as well in the recurrent setting both as a single agent and combined with chemotherapy (Table 13.2). Bevacizumab was tested as a single agent in two separate studies of recurrent ovarian cancer, and both trials demonstrated activity of bevacizumab in both platinum-resistant and platinum-sensitive cancers. Both of these studies used bevacizumab at a dose of 15 mg/kg IV once every 3 weeks. In Burger et al., 62 patients with either recurrent platinum-resistant or platinum-sensitive (up to 12 months platinum-free interval) ovarian cancer were enrolled who had received up to 1 prior line of therapy for recurrent cancer [42] (Table 13.2). In this study, the response rate was 21 %, 6 month progression-free survival (PFS) rate was 40.3 %, median PFS was 4.7 months, and overall survival (OS) was 16.9 months. Observed toxicities included 9.7 % grade 3 hypertension (HTN), 22.6 % grade 2 proteinuria, 1.6 % grade 3 venous thromboembolism, and no episodes of gastrointestinal perforation (GIP) occurred. In a separate study that enrolled patients with platinum-resistant ovarian cancer who had received 2 or 3 prior lines of therapy and had cancer progression through either topotecan or pegylated liposomal doxorubicin (PLD), bevacizumab demonstrated an overall response rate of 15.9 %, median PFS of 4.4 months, OS of 10.7 months, and 6 month PFS rate of 27.8 % [43] (Table 13.2). Because of an 11.4 % rate of GIP, the study was closed early. Risks for GIP in this study included receipt of >2 lines of therapy in the recurrent setting; bowel wall thickening on radiographic imaging or bowel obstruction was also identified as potential risk factors, but these were not statistically significant. Other grade 3 and 4 toxicities included 9.1 % HTN and 15.9 % proteinuria. Three bevacizumab-related deaths occurred: 1 episode each of myocardial infarction/cerebrovascular ischemia, GIP, and convulsion/hypertensive encephalopathy. Several other prospective single-arm phase II studies have tested bevacizumab in combination with other chemotherapy agents as well as other targeted biologic agents [44–51].

Observed activity of single-agent bevacizumab in the recurrent ovarian cancer setting has led to several randomized phase III studies in both newly diagnosed as well as recurrent ovarian cancer patients. In the newly diagnosed setting, Gynecologic Oncology Group (GOG) study 218 and ICON-7 demonstrated prolongation of PFS with bevacizumab administered concurrently with the standard carboplatin/paclitaxel regimen and continued as single-agent consolidation therapy but no overall survival improvement was seen [52, 53]. GOG study 218 was a double-blinded

Table 13.2 Selected bevacizumab studies in ovarian cancer

Study	Accrual	Patient population	Treatment regimens	Primary endpoint	Results
Single-agent studies in patients with recurrent ovarian cancer					
GOG 170D [42]	62	Platinum sensitive or resistant, 1–2 prior lines, PFI < 12 month	Single-agent bev 15 mg/kg every 3 weeks	6 month PFS and RR	21 % ORR 40.3 6 month PFS rate 4.7 month median PFS
AVF2797 [43]	44	Platinum resistant, 2–3 prior lines	Single-agent bev 15 mg/kg every 3 weeks	RR	15.9 % ORR 27.8 % 6 month PFS rate 4.4 month median PFS
Randomized studies in newly diagnosed ovarian cancer					
GOG218 [52]	1873	Newly diagnosed stage III or IV	1. C/P/placebo plus maintenance placebo 2. C/P/bev plus maintenance placebo 3. C/P/bev plus maintenance bev Bev dose 15 mg/kg q3week	PFS	PFS arm 3: 14.1 month PFS arm 1: 10.3 month (HR 0.717, $p < 0.0001$). OS not different
ICON7 [53]	1528	Newly diagnosed (1) stage I or IIA and clear cell or grade 3 tumors or (2) advanced stage IIB to IV	1. C/P 2. C/P/bev plus maintenance bev Bev dose 7.5 mg/kg q3week	PFS	PFS arm 1: 17.3 month PFS arm 2: 19.0 month (HR 0.81, $p = 0.0041$) OS not different
GOG 252 (NCT00951496)	Targeted accrual of 1500	Newly diagnosed stage III or IV	1. IV C/P 2. IP C/P 3. IP Cis/3 h P/day 8 IP C. All arms contain bev during chemotherapy and maintenance Bev dose 15 mg/kg every 3 weeks	PFS	Study ongoing

(continued)

Table 13.2 (continued)

Study	Accrual	Patient population	Treatment regimens	Primary endpoint	Results
GOG 262 (NCT01167712)	Targeted accrual of 625	Bev (optional) 15 mg/kg q3 weeks	1. C/P 2. C/weekly P Bev is optional for both arms	PFS	Study ongoing
Randomized studies in patients with recurrent ovarian cancer					
OCEANS [55]	484	1st recurrence, platinum-sensitive cancers, i.e., >6 months PFI	1. C/G/placebo + M Placebo 2. C/G/bev (15 mg/kg q3w) + M Bev	PFS	1. PFS 8.4 month 2. PFS 12.4 month PFS HR 0.484, $p<0.0001$ No differences in OS
AURELIA [56]	361	Platinum-resistant ovarian cancer (≤6 months after ≥4 cycles of platinum-based therapy)	1. Weekly P 2. Weekly topo or 3. PLD All arms with or without bev. Patients on the bev arm may opt to continue bev as maintenance. Bev dose could be either 10 mg/kg q2 weeks or 15 mg/kg q3 weeks	PFS	Median PFS was 3.4 months in the non-bev arm and 6.7 months in the bev-containing arm (HR 0.48, $p<0.001$)

Abbreviations: *ORR* overall response rate, *PFS* progression-free survival, *Bev* bevacizumab, *PFI* platinum-free interval, *C* carboplatin, *P* paclitaxel, *G* gemcitabine, *Topo* topotecan, *PLD* pegylated liposomal doxorubicin

placebo-controlled study that enrolled 1873 patients with optimally or suboptimally debulked advanced FIGO stage III or IV ovarian cancer [52]. Patients were randomized in a 1:1:1 ratio to 1 of 3 treatment arms: group 1 (control), carboplatin AUC 6, paclitaxel 175 mg/m^2, and placebo every 3 weeks × 6 cycles, followed by maintenance placebo every 3 weeks for an additional 16 cycles; group 2, carboplatin AUC 6, paclitaxel 175 mg/m^2, and bevacizumab 15 mg/kg every 3 weeks × 6 cycles, followed by maintenance placebo for 16 weeks; and group 3, carboplatin AUC 6, paclitaxel 175 mg/m^2, and bevacizumab 15 mg/kg every 3 weeks, followed by maintenance bevacizumab 15 mg/kg every 3 weeks for 16 weeks. Statistical analyses compared each of the bevacizumab-containing arms to the control arm; group 2 was compared to group 1, and group 3 was compared to group 1. When group 2 was compared to group 1, no significant benefit in PFS was seen (median PFS 10.3 months control vs. 11.2 months treatment, HR 0.908, $p = 0.080$). Group 1 compared to group 3 revealed a statistically significant improvement in PFS for group 3 versus group 1 (median PFS 10.3 months control vs. 14.1 months treatment, HR 0.717, $p < 0.0001$). No OS benefit has been noted in any of the groups, and OS was 39.3 months in group 1, 38.7 months in group 2, and 39.7 months in group 3. The bevacizumab-containing arms demonstrated higher toxicities with GI fistula and GIP rates of 2.8 and 2.6 % on the bevacizumab arms (groups 2 and 3, respectively) compared to 1.2 % in group 1. The GI events occurred mostly during the chemotherapy portion of treatment rather than during maintenance. HTN was also higher in the bevacizumab arms; grade 2 or higher hypertension rates of 16.5 and 22.9 % were observed in groups 2 and 3, respectively, compared to 7.2 % in group 1.

The second upfront study testing the addition of bevacizumab to carboplatin and paclitaxel chemotherapy, called ICON7, enrolled 1528 women with newly diagnosed ovarian cancer [53]. Patients were randomized 1:1 to receive either carboplatin AUC 6 and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles or carboplatin AUC 6 and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles, with the addition of bevacizumab 7.5 mg/kg every 3 weeks and continuing for an additional 12 cycles of maintenance therapy [53]. Bevacizumab or placebo was started at cycle 2 of carboplatin and paclitaxel. Differences between GOG 218 and ICON7 included that GOG 218 was double-blinded and the dose of bevacizumab was lower in the ICON7 study compared to GOG 218 (7.5 mg/kg every 3 weeks vs. 15 mg/kg every 3 weeks). In addition, eligible patients in ICON7 included FIGO stage I/IIA (grade 3), IIB/C, III, and IV, whereas GOG 218 included only stage III and IV patients. Improvement of PFS in ICON7 was observed in the bevacizumab group with median PFS of 17.3 months in the control arm and 19.0 months in the treatment arm (HR 0.81, $p = 0.0041$) [53]. OS was not significantly different between the two arms (median OS not reached in either arm; HR 0.81, $p = 0.098$). Increased adverse events in the bevacizumab treatment arm included HTN, bleeding, and arterial and venous thromboembolic events. GIP was also higher in the bevacizumab arm although the rate of GIP was overall low at 1.3 %. Both GOG 218 and ICON7 examined benefit of bevacizumab based on age (<60 year, 60–69 year, and >70 year of age) but did not find any differences based on age with respect to benefit of bevacizumab; toxicities based on age were not reported in either study. The European Medicines Agency has approved

the use of bevacizumab for the frontline treatment of advanced ovarian cancer in the European Union, but this drug is not FDA-approved in the United States [54].

Two additional upfront studies that are designed to examine different chemotherapy strategies (i.e., IP and dose-dense chemotherapy) have incorporated bevacizumab, but these studies were not designed to investigate the benefit of adding bevacizumab to upfront chemotherapy for newly diagnosed ovarian cancer patients. GOG 252 has completed accrual and enrolled patients with stage II, III, or IV cancer, either optimally (≤1 cm residual cancer) or suboptimally (>1 cm residual cancer) cytoreduced. Patients were randomized to one of three chemotherapy arms all of which contained bevacizumab followed by maintenance bevacizumab therapy (clinicaltrials.gov number NCT00951496). The three arms in GOG 252 are (1) IV carboplatin AUC 6 d1 and IV paclitaxel 80 mg/m^2 d1, 8, and 15; (2) IP carboplatin AUC 6 d1 and IV paclitaxel 80 mg/m^2 d1, 8 and 15; or (3) IV paclitaxel 135 mg/m^2 over 24 h d1, IP cisplatin 75 mg/m^2 d2, and IP paclitaxel 60 mg/m^2 d8. The other trial is GOG 262 which limited eligibility to suboptimally debulked stage III or stage IV patients and randomized patients to one of two arms: (1) IV carboplatin AUC 6 and IV paclitaxel 175 mg/m^2 d1 or (2) IV carboplatin AUC 6 d1 and IV paclitaxel 80 mg/m^2 d1, 8, and 15 (clinicaltrials.gov number NCT01167712). Although GOG 262 has completed formal enrollment, the study continues to enroll patients as part of a translational study that is examining tumor perfusion and use of radiographic imaging as a biomarker for early detection of response or nonresponse. In GOG 262, the use of bevacizumab is optional, and patients and their doctors have the option of receiving bevacizumab or not receiving bevacizumab given with chemotherapy and then followed by maintenance bevacizumab until time of disease progression or intolerable toxicity.

Two phase III studies have been completed that tested bevacizumab in recurrent ovarian cancer. The OCEANS study tested bevacizumab in combination with carboplatin and gemcitabine in patients with recurrent platinum-sensitive ovarian cancer [55] (Table 13.2). The primary endpoint of this study was PFS, and 484 women who had received no prior therapy for recurrence were randomized to receive either carboplatin AUC 4 day 1 and gemcitabine 1,000 mg/m^2 days 1 and 8 with bevacizumab 15 mg/kg or placebo given IV every 3 weeks. Median PFS was 8.4 months in the chemotherapy-alone arm and 12.4 months with the addition of bevacizumab (HR 0.484, $p < 0.0001$). Response rates were 57.4 % in the control group and 78.5 % in the bevacizumab arm ($p < 0.0001$). OS was not different between the groups. But this data is not yet mature. Toxicities were higher in the bevacizumab-treated arm including HTN, proteinuria, bleeding, and thromboembolic events. GIP did not occur in either arm, but two patients developed GIP after completing bevacizumab. GOG 213 is another study that is testing bevacizumab in the platinum-sensitive setting; this study is testing the roles of secondary cytoreductive surgery and bevacizumab in combination with carboplatin and paclitaxel in platinum-sensitive recurrent ovarian cancer (NCT00565851); this study is ongoing.

The second phase III study evaluating bevacizumab in recurrent ovarian cancer was done in the platinum-resistant setting. The AURELIA study is a randomized, open-label, two-arm study that evaluated the efficacy and safety of bevacizumab

when added to chemotherapy versus chemotherapy alone in patients with platinum-resistant ovarian, fallopian tube or primary peritoneal cancer [56]. Chemotherapy selection was performed by the treating physician, and patients were randomized to receive chemotherapy (PLD, topotecan, or weekly paclitaxel) with or without bevacizumab (10 mg/kg IV 2 – weekly or 15 mg/kg IV 3 – weekly). Patients received study treatment until disease progression, toxicities, or withdrawal of consent. Patients on the chemotherapy-alone arm could cross over to bevacizumab monotherapy upon progression. The primary endpoint of the study was PFS, and the study accrued 361 patients. Median PFS was 3.4 months in the group not receiving bevacizumab and 6.7 months in the group receiving bevacizumab (HR (95 % CI): 0.48 (0.38–0.60), ($p=0.001$)) [56]. OS is not mature.

Currently, studies evaluating the impact of bevacizumab on the elderly with ovarian cancer do not exist, and the best measures are currently derived from nonovarian cancer randomized clinical trials and their age subgroup meta-analyses [29, 57, 58]. Neither bevacizumab's pharmacokinetics nor pharmacodynamics appear to fluctuate significantly based on age [59]. A pooled analysis of five metastatic colon, breast, and lung cancer trials showed that concurrent administration of bevacizumab with chemotherapy increased the risk of arterial thromboembolic events (ATEs) compared to chemotherapy alone (HR 2.0; $p=0.031$), and this risk correlated with prior ATEs ($p < 0.001$) or age ≥ 65 years ($p=0.01$). Patients carrying both risk factors were at significantly higher risk if they were not taking concurrent aspirin (22.9 % bevacizumab arm vs. 3.4 % control arm; $p=0.03$) [60]. The observational community-based analysis BRiTE showed identical ATE risk between the <65 years and 65–74 years age groups (~1.5 %) with a significantly higher ATE rate in patients aged ≥75 years (4.1 %) [61]. In a recent SEER-Medicare database review of stage IV colorectal patients, combination chemotherapy with bevacizumab was associated with a higher risk of stroke (4.9 % vs. 2.5 %, respectively; $p<0.01$) and GIP (2.3 % vs. 1.0 %, respectively; $p<0.01$) compared to patients not receiving bevacizumab [62]. Cardiac and venous thromboses were not increased with bevacizumab [62]. In elderly patients with non-small cell lung cancer receiving carboplatin and paclitaxel combined with bevacizumab, the three drug combination had higher rates of neutropenic fever, hemorrhage, nausea, anorexia, and HTN in the elderly receiving bevacizumab, and at least one grade 3 or higher toxicity was noted in 87 % of elderly compared to 70 % of younger patients ($p=0.001$) [63].

Other anti-angiogenic agents that interfere with circulating VEGF have been studied in ovarian cancer. Aflibercept (VEGF-Trap) interferes with circulating VEGF and is a fusion protein that combines the Fc portion of human IgG1 with the principal extracellular ligand-binding domains of VEGFR. Single-agent aflibercept demonstrated an 8 % response rate in patients with platinum-resistant recurrent ovarian cancer and has also been compared to placebo to control ascites [64, 65]. Gotlieb et al. tested the efficacy of aflibercept versus placebo for treatment of refractory ascites in patients with recurrent ovarian cancer as well as safety evaluation [65]. Patients were randomized to either placebo or aflibercept 4 mg/kg IV every 2 weeks; mean time to repeat paracentesis was significantly longer with aflibercept than with placebo (55 vs. 23.3 days ($p=0.0019$). However, the frequency of fatal

gastrointestinal events was higher with aflibercept (3 episodes of GIP) than with placebo (one intestinal fistula) [65].

Single-agent tyrosine kinase inhibitors (TKIs) have also been tested in recurrent ovarian cancer, and these agents are listed in Table 13.3 [66–74]. These agents have included sunitinib (targets VEGFR, c-Kit, PDGFR, RET, and FLT-3), cediranib (targets VEGFR, c-Kit), sorafenib (targets VEGFR, c-Kit, RAF, and PDGFR-beta), pazopanib (targets VEGFR, PDGFR, and c-Kit), ENMD2076 (targets VEGFR and aurora A), and cabozantinib (targets VEGFR and c-MET). BIBF1120 (targets VEGFR, PDGFR, and FGFR) and vandetanib (targets VEGFR2, VEGFR3, EGFR, and RET) have been tested in randomized phase II studies [75–78]. None of these agents has been tested with respect to impact of age on either efficacy or toxicities. Toxicities of the TKIs have included hypertension, fatigue, diarrhea, other gastrointestinal toxicities such as nausea and vomiting, hand-foot syndrome, myelosuppression, and proteinuria [79].

Sunitinib has been tested in several phase II studies [68–70]. One recent publication tested two different dosing schedules with the primary endpoint of the study being objective response rate [70]. Eligible patients included recurrent platinum-resistant ovarian cancer who had previously received up to three prior chemotherapies. Two schedules were compared: arm 1 (50 mg sunitinib daily orally for 28 days followed by 14 days off drug); and arm 2 (37.5 mg sunitinib administered daily continuously). There were 6 observed responders in arm 1 (16.7 %) and 2 responders in arm 2 (5.4 %). The median PFS (arm 1:4.8 months vs. arm 2:2.9 months) and OS were similar in both groups as were toxicities.

Cabozantinib (XL184) has been tested in recurrent ovarian cancer demonstrating a 29 % confirmed partial response rate in platinum-resistant or platinum-refractory ovarian cancer and 40 % response rate in platinum-sensitive cancers [73]. A phase II randomized discontinuation study of cabozantinib in 70 patients was performed in patients with either platinum-refractory, platinum-resistant, or platinum-sensitive cancer; cabozantinib starting at 100 mg PO q day as a lead in stage was administered for 12 weeks followed by tumor staging [74]. For patients attaining a partial or complete response, cabozantinib was continued. If stable disease was achieved, patients were then randomized 1:1 to either cabozantinib or placebo, and treatment was unblinded at the time of disease progression. An initial response of disease progression led to patients being removed from study. Eighteen percent of patients with platinum refractory, 22 % with platinum-resistant cancer, and 28 % of patients with platinum-sensitive response had a partial response to XL184. Two grade 5 events occurred (both after the lead-in stage): 1 episode of enterocutaneous fistula and 1 episode of GIP.

BIBF1120 (nintedanib) is an oral anti-angiogenic TKI with activity against VEGFR, PDGFR, and FGFR, and an ongoing phase III randomized, placebo-controlled, double-blinded study is testing whether the addition of BIBF1120 in addition to carboplatin and paclitaxel compared to carboplatin and paclitaxel alone will improve PFS (primary endpoint) in patients with newly diagnosed ovarian cancer (clinicaltrials.gov identifier NCT01015118). Eligibility includes patients with newly diagnosed stage IIB-IV ovarian cancer, and patients need to have undergone upfront

Table 13.3 Selected single-agent phase 2 studies of TKIs in recurrent ovarian cancer

Agent tested	Eligibility	ORR	6 month PFS rate	Median PFS	Notable toxicities
Cediranib [66]	Both platinum sensitive and resistant	17 %	17 %	5.2 month	46 % grade 3 HTN 24 % grade 3 fatigue 13 % grade 3 diarrhea
Sorafenib [67]	Platinum resistant or sensitive (up to 12 months PFI)	3.4 %	24 %	2.1 month	19.7 % grade 3 dermatologic 14 % grade 3 metabolic 1.4 % grade 3 HTN 25 % grade 2 GI
Sunitinib [68, 70]	Platinum resistant or sensitive	3.3 %	NR	4.1 month	10 % grade 3 for each: granulocytes, platelets, hemoglobin Fatigue, diarrhea, hand-foot
	Platinum resistant	17 % using 50 mg/day × 28 days and 1 week off (arm 1)	NR	Arm 1: 4.8 months	1.6 % versus 4.3 % ≥ grade 3 platelets (arm 1 vs. arm 2).
		5 % with 37.5 mg PO daily (arm 2)		Arm 2: 2.9 months (NS)	<1 % ≥ grade 3 hand foot and fatigue for both arms.
Pazopanib [71]	Both platinum sensitive and resistant	18 %	17 %	NR	8 % grade 3 ALT elevation 11 % grade 3 fatigue 11 % grade GGT elevation 8 % grade 3 diarrhea
ENMD2076 [72]	Platinum resistant	7 %	19 %	NR	Grade 3 hypertension (46 %) Grade 3+ fatigue (24 %) Grade 3+ diarrhea (13 %) 1 Grade 4 CNS hemorrhage

(continued)

Table 13.2 (continued)

Agent tested	Eligibility	ORR	6 month PFS rate	Median PFS	Notable toxicities
Cabozantinib (XL184) [73]	Platinum sensitive and resistant	40 % platinum sensitive 29 % platinum resistant	NR	NR	Toxicities ≥ grade 3: 12 % PPE syndrome 7 % diarrhea 5 % fatigue 5 % vomiting 3 % HTN

ORR overall response rate, *PFS* progression-free survival, *NR* not reported, *HTN* hypertension, *PFI* platinum-free interval, *GIP* gastrointestinal perforation, *GI* gastrointestinal, *PPE* palmar plantar erythrodysesthesia

debulking surgery or have planned interval cytoreduction; planned accrual is 1,300 patients. BIBF1120 has also been tested in the recurrent setting in a randomized, double-blind, phase II trial of BIBF1120 (250 mg q2d) versus placebo in ovarian cancer patients in at least second remission [77]. Although this trial was not statistically powered to directly compare the two arms, the 36-week PFS rate was achieved in 16.3 % of patients receiving BIBF1120 maintenance therapy versus 5.0 % on placebo maintenance (HR 0.65; $p < 0.06$). The proportion of patients with any grade 3 or higher toxicities was similar between the groups (34.9 % for BIBF1120 vs. 27.5 % for placebo; $p < 0.49$).

Vandetanib (inhibits VEGFR2, VEGFR3, EGFR, and RET) was tested in a randomized phase II study of docetaxel and vandetanib versus docetaxel alone in SWOG S0904 in patients with platinum-refractory, platinum-resistant, and platinum-sensitive recurrent ovarian cancer [78]. Patients were randomized to either docetaxel 75 mg/m^2 IV once every 3 weeks versus docetaxel 75 mg/m^2 once every 3 weeks plus vandetanib 100 mg PO daily; 131 patients were enrolled. Patients on the docetaxel-alone arm upon progression were crossed over to vandetanib alone. Median PFS for the docetaxel plus vandetanib arm was 3.0 months and docetaxel-alone arm was 3.5 months (HR 0.98 (80 % CI:0.75–1.27)). Median OS was 14 months (combination arm) versus 12 months (docetaxel alone) (HR 0.84 (80 % CI:0.56–1.28)).

Other anti-angiogenic drugs that have different mechanisms of action compared to bevacizumab and TKI's are also being investigated in ovarian cancer. AMG 386 is a novel investigational peptide-Fc fusion protein that mediates antiangiogenic effects by potently and selectively inhibiting the interaction of angiopoietin-1 and angiopoietin-2 with Tie2 [80, 81]. A randomized phase II study of AMG 386 combined with weekly paclitaxel for the treatment of recurrent ovarian cancer showed longer median PFS for patients receiving AMG 386 compared to placebo (7.2 vs. 4.6 months; $p = 0.165$) [82]. The toxicity profile of AMG386 differs from other VEGF inhibitors with peripheral edema, hypokalemia, and thromboembolism being the most common adverse events, whereas significant HTN has not been reported [82]. Several studies of AMG386 combined with chemotherapy are underway in both the recurrent as well as newly diagnosed ovarian cancer setting. TRINOVA-3 is a double-blinded, placebo-controlled phase III study of AMG386 or placebo in combination with paclitaxel and carboplatin for the treatment of newly diagnosed stage III or IV ovarian cancer (clinicaltrials.gov identifier NCT01493505); accrual is planned for 2,000 patients. In addition, two phase III studies are testing AMG386 in recurrent ovarian cancer. TRINOVA-1 is an ongoing phase III study of weekly paclitaxel +/− AMG386 in patients with recurrent ovarian cancer with a platinum free interval of <12 months; the primary endpoint of this study is PFS, and planned accrual is 900 patients (clinicaltrials.gov identifier NCT01204749). TRINOVA-2 is a phase III randomized, double-blind study of PLD plus AMG386 or PLD plus placebo in women with recurrent partially platinum-sensitive ovarian cancer (<12 months platinum-free interval) or platinum-resistant epithelial ovarian, primary peritoneal or fallopian tube cancer (NCT01281254); planned accrual is 380 patients.

Other agents being tested include ombrabulin, a vascular disrupting agent, which is being studied in a double-blind, placebo-controlled, randomized study in patients with platinum-sensitive recurrent ovarian cancer in combination with carboplatin and paclitaxel (NCT01332656).

Epidermal Growth Factor Receptor (EGFR) Inhibitors

Aberrations of EGF receptor family (EGFR, ErbB2, ErbB3, and ErbB4) are found in epithelial ovarian carcinomas, and multiple agents exist that target these receptors [83–86]. Table 13.4 lists examples of EGFR family inhibitors that have been tested in ovarian cancer as well as agents currently in active studies. To date, the overall clinical impact of EGFR family inhibitors when used as single agents in unselected recurrent ovarian cancers has been poor [87–94]. In addition, chemotherapy as well as hormonal therapies has been combined with EGFR family inhibitors in single-arm phase II studies [95–102]. Randomized phase II studies in unselected patients have been negative thus far [103–105]; however, other studies are underway that are attempting to identify predictive biomarkers for response (NCT01447706). Data on EGFR inhibitor pharmacokinetics, efficacy, and safety in elderly ovarian cancer patients is not available.

PI3K-AKT-mTOR Pathway Inhibitors

The PI3K-AKT-mTOR pathway is a complex signal transduction cascade which is involved in a variety of important physiological functions [106]. Upstream, the PI3K family is influenced by a number of membrane receptor tyrosine kinases comprised of EGFR, PDGFR, and IGFR. Downstream, PI3K activates serine/threonine kinase AKT which in turn mediates signaling involving multiple effectors, including the mTORC1 complex. Deregulated PI3K-AKT-mTOR pathway is an essential step for the initiation and maintenance of tumorogenic phenotypes [106]. The most commonly described pathway abnormalities include genetic aberrations of *PIK3CA* and AKT, functional loss of the tumor suppressor gene PTEN, as well as those affecting upstream receptor tyrosine kinases [106]. Recent data has demonstrated that PI3kinase is amplified in high-grade serous ovarian cancer (HGSC), while somatic mutations are present in clear cell cancer of the ovary, suggesting that PI3kinase inhibitors may have a therapeutic role in ovarian cancer [2, 107–109]. There are several inhibitors targeting different parts of the PI3kinase pathway, and their precise role in the treatment of ovarian cancer is still being determined. The mTOR inhibitor, temsirolimus (IV 25 mg weekly), was investigated in a phase II GOG trial of heavily pretreated women with measurable recurrent Müllerian cancer [110]. The overall response rate was 9.3 %, and the 6 month PFS rate was 24.1 %. In order to preselect patients for improved responses to a PI3kinase pathway

Table 13.4 Selected studies of EGFRs inhibitors in ovarian cancer

Generic name	Drug name	Study	Phase	Treatment	RR (%)	SD (%)	Median PFS
Trastuzumab	Herceptin	Bookman et al. [90]	II	Trastuzumab	7.3	39	2 month
Pertuzumab	2C4	Gordon et al. [91]	II	Pertuzumab	4.3	6.8	1.5 month
		Makhija et al. [103]	II	Pertuzumab + G	13.8	NR	2.9 month
		Kaye et al. [104]	II	Pertuzumab + CT versus CT alone	60.6 % P58.7 % CT alone	NR	34.1 weeks P versus 31.3 weeks CT alone (ns)
Cetuximab	Erbitux/IMC-C225	Secord et al. [97]	II	Cetuximab + C	For EGFR+:34	For EGFR+:31	9.4 month
Matuzumab	EMD72000	Seiden et al. [92]	II	EMD72000	0	21.7	NR
MM-121	MM-121	NCT01447706	II	MM121 + P, ongoing			
Canertinib	CI-1033	Campos et al. [93]	II	Canertinib	0	26–34	NR
Erlotinib	Tarceva/OS-774/ CP-358774	Gordon et al. [87]	II	Erlotinib	6	44	NR
		Hirte et al. [102]	II	Erlotinib + C	57	13	NR
Gefitinib	Iressa/ZD1839	Schilder et al. [88]	II	Gefitinib	4	14	2.2 month
		Posadas et al. [89]	II	Gefitinib	0	37	NR
		Wagner et al. [95]	II	Gefitinib + Tamoxifen	0	28.5	NR
		Mavroudis et al. [96]	I and II	Gefitinib + Oxaliplatin + Vinorelbine	23.8	NR	4.1 month
Lapatinib	Tykerb/GW 572016	Garcia et al. [94]	II	Lapatinib	0	16	1.8 month
		Kimball et al. [100]	I	Lapatinib + C	27	27	NR

CT chemotherapy, *C* carboplatin, *G* gemcitabine, *NR* not reported

inhibitor, a phase II study of MK2206, an AKT inhibitor, is underway in patients with PTEN loss or a somatic mutation in any gene members of the PI3kinase pathway (NCT01283035).

Hedgehog (Hh) Pathway Inhibitors

The Hedgehog (Hh) signaling pathway represents a crucial process implicated in cell growth and differentiation during embryo-fetal development [111, 112]. Hh signaling status is mainly determined by the triad of ligand (Sonic Hh, Indian Hh, Desert Hh, or fly Hh homologue), transmembrane protein patched 1 (PTCH1), and transmembrane G-coupled protein, smoothened (SMO). In the absence of a ligand, PTCH1 inhibits SMO keeping the pathway inactive; when the ligand binds to PTCH1, SMO suppression is lost resulting in downstream signaling and activation of Gli Hh transcription factors [113]. This pathway has seen increased interest in ovarian cancer therapeutics by the discovery that ligand-independent/PTCH1-downregulated activation of Hh signaling may represent a potential driver of neoplasia in a significant portion of epithelial ovarian cancers [113, 114]. The oral SMO inhibitor GDC-0449 was tested as maintenance therapy in a phase II randomized, placebo-controlled study in patients as maintenance therapy in patients with recurrent ovarian cancer in second or third complete remission [115]. The primary endpoint was investigator assessed PFS, and 81 % of patients were in second remission at study entry. Median PFS was 5.8 months for placebo and 7.5 months for GDC-0449 (HR 0.79 (95 % CI, 0.46–1.35)) [115]. Hh expression was not detected in most submitted archival tissues.

Folate Receptor (FR) Inhibitors

Alpha folate receptor (α-FR) is a membrane-bound protein that provides cellular growth advantage by transporting folates intracellularly via receptor-mediated endocytosis. While α-FR is largely absent from normal tissue, over 70 % of primary and 82 % of recurrent ovarian tumors overexpress FRs thus providing a potential therapeutic strategy for ovarian cancer treatment [116–118]. FRs may allow for a high-affinity tumor-specific target for antifolate agents such as anti-α-FR antibodies (e.g., farletuzumab), conjugating chemotherapeutic agents (e.g., EC145), and antifolate antineoplastic agents (e.g., pemetrexed).

Farletuzumab is a humanized IgG1 monoclonal antibody that targets α-FR [119]. When administered in heavily pretreated patients with platinum-resistant ovarian cancer, 80 % of them experienced grade 1 or 2 AEs, mainly mild hypersensitivity reactions (60 %), fatigue (48 %), and diarrhea (16 %), but no myelotoxicity, neurotoxicity, or other grade 3+ toxicities were recorded [119]. Phase II studies of this agent are underway. EC145 is a folic acid/desacetylvinblastine monohydrazide

conjugate that binds with high affinity to folate receptors [120, 121]. EC145 has been tested in a randomized phase II study that evaluated PLD with or without EC145 in women with recurrent platinum-resistant ovarian cancer [122]. The addition of EC145 to PLD demonstrated an increase in median PFS (overall 21.7 vs. 11.7 weeks, $P=0.031$; FR positive tumors 24 vs. 6.6 weeks, $p=0.018$), and a phase III study is currently underway (122, NCT01170650). Pemetrexed is a multi-target antifolate agent that exerts its action by disrupting folate-dependent enzymes that are essential for purine and pyrimidine biosynthesis [123]. Single-agent pemetrexed has been evaluated in two studies in recurrent platinum-resistant ovarian cancer; Vergote et al. examined two doses (500 and 900 mg/m^2), and overall response rates were 9.3 % versus 10.4 % for the 500 mg/m^2 dose and 900 mg/m^2 dose resp. [124]. The lower dose had a preferable toxicity profile [124]. The GOG tested 900 mg/m^2 of pemetrexed demonstrating a 21 % response rate in platinum-resistant ovarian cancer, and a median PFS of 2.9 months [125]. When pemetrexed (500 mg/mg^2 given once every 3 weeks) was combined with either carboplatin AUC 5 or 6 in patients with platinum-sensitive relapse, overall RR ranged from 32.8 up to 51.1 %, while median PFS ranged from 7.6 to 9.4 months [126, 127].

PARP Inhibitors

Considerable interest has been generated regarding the use of poly (ADP-ribose) polymerase (PARP) inhibitors in ovarian cancer. PARPs represent a family of enzymes involved in base-excision repair (BER), a vital pathway for the repair of DNA single-strand breaks [128–130]. Deregulated BER pathway results in the accumulation of unrepaired single-strand breaks that are consequently converted to double-strand breaks. Physiologically, the latter are repaired primarily by means of the error-free homologous recombination (HR) pathway, key components of which are the tumor-suppressor proteins BRCA1 and BRCA2 [128–130]. Defective HR pathway results in interruption of DNA replication and eventually in cell apoptosis via p53-dependent or p53-independent mechanisms [131–134]. The concept of synthetic lethality results by combining the events of BER and HR in cancers in germline BRCA1 or BRCA2 mutations or possibly "BRCAness" phenotype attributed to functional loss of BRCA proteins [135, 136]. Several PARP inhibitors are currently in development (see Table 13.5).

Olaparib is a potent oral PARP inhibitor that has undergone the most extensive investigation of all known PARP inhibitors in ovarian cancer thus far. Initial phase I testing of olaparib using doses from 10 mg PO daily 2 out of 3 weeks up to 600 mg BID dosed daily continuously demonstrated a maximally tolerated dose (MTD) of 400 mg BID daily [137]. Clinical benefit was demonstrated in 12 of 19 patients who were BRCA carriers with ovarian, breast, or prostate cancer. Olaparib has demonstrated single-agent activity in germline BRCA-deficient ovarian cancer as well as in HGSC patients who do not harbor a germline BRCA1 or BRCA2 mutation likely because of the loss of BRCA function from deletion, somatic mutations, or

Table 13.5 PARP inhibitors in clinical development

PARP inhibitor	Company	Route
Olaparib (AZD2281)	Astrazeneca	PO
AZD2461	Astrazeneca	PO
Veliparib (ABT888)	Abbott	PO
MK4827	Tesaro	PO
Rucaparib (AGO14699) (PF-01367338)	Clovis	IV, PO
BMN673	BioMarin	PO
CEP9722	Cephalon	PO

methylation [138, 139]. Phase II studies have demonstrated overall response rates up to 41 % in patients with germline BRCA1- or BRCA2-associated cancers and 24 % in sporadic high-grade serous cancers using the MTD dose of olaparib of 400 mg BID (capsule formulation) [138, 139]. Toxicities of olaparib have included fatigue, nausea, vomiting, and decreased appetite. Age-related efficacy and toxicities of olaparib in ovarian cancer patients are not known.

Table 13.6 shows the completed and ongoing randomized studies of olaparib in ovarian cancer. Olaparib has been compared to PLD in patients who have recurrent ovarian cancer, a known germline BRCA mutation, and have never received PLD [140]. Patients were randomized 1:1:1 to PLD, olaparib 200 mg BID daily or olaparib 400 mg BID daily. Median PFS was 6.5 months (95 % CI, 5.5–10.1 months), 8.8 months (95 % CI, 5.4–9.2 months), and 7.1 months (95 % CI, 3.7–10.7 months) for olaparib 200 mg, olaparib 400 mg, and the PLD groups, and there was no significant differences in PFS for the combined olaparib doses versus PLD (HR 0.88, 95 % CI 0.51–1.56, $p=0.66$). There were no observed OS benefit for any of the three arms either.

Olaparib has also been explored as maintenance therapy in women with recurrent platinum-sensitive HGSC who completed platinum-based chemotherapy and achieved a clinical remission [141]. Following completion of platinum-based chemotherapy, patients were randomized to either placebo or olaparib 400 mg BID daily in this double-blinded study with PFS as the primary endpoint. Median PFS was statistically significantly different in the two groups; the PFS of patients receiving olaparib was 8.4 months compared to 4.8 months for patients receiving placebo (HR 0.35 (95 % CI 0.25–0.49, $p<0.00001$)), and OS was not significantly different between the two groups.

A recently presented phase II randomized study compared carboplatin and paclitaxel chemotherapy with and without olaparib in patients with platinum-sensitive recurrent ovarian cancer [142]. One hundred and sixty two patients were enrolled and median PFS was the primary endpoint. Treatment consisted of olaparib (200 mg bid, d1 – 10 out of 21 days), paclitaxel 175 mg/m^2 IV on day 1, and carboplatin AUC 4 IV on day 1 with olaparib 400 BID maintenance versus carbolatin AUC 6 and paclitaxel 175 mg/m^2 IV. Median PFS was 12.2 months for patients receiving olaparib and 9.6 months for those patients not receiving olaparib (HR = 0.51, 95 % CI 0.34–0.77 ($p=0.0012$)). OS data is not yet mature.

Table 13.6 Randomized trials of olaparib

Study	Patients	Treatment	Primary endpoint	Results
Kaye et al. [140]	All BRCA germline mutation carriers, $N=97$	Olaparib 400 BID Olaparib 200 BID PLD 50 mg/m^2	PFS	No difference among arms for PFS; 6.5 month (200 mg dose), 8.8 month (400 mg dose), and 7.1 month (PLD)
Ledermman et al. [141]	High-grade serous cancer, $N=265$	Olaparib 400 mg BID versus placebo for maintenance therapy	PFS	8.4 month (olaparib) versus 4.8 months (placebo) ($p<0.001$); interim OS NS
Oza et al. [142]	Platinum-sensitive, recurrent ovarian cancer, $N=162$	Olaparib (200 mg BID, days 1–10/21) + carbo (AUC 4) + Pac (175 mg/m^2) + olaparib maintenance versus carbo (AUC 6) + Pac (175 mg/m^2)	PFS	Median PFS 12.2 versus 9.6 months (olaparib versus non-olaparib), $p=0.0012$
NCT01116648	Platinum-sensitive, recurrent ovarian cancer	Cediranib 30 mg q day + olaparib 200 mg BID versus olaparib 400 mg BID	PFS	Ongoing

Olaparib is now being tested together with other biologic agents. A phase I study assessed oral olaparib (100, 200, and 400 mg) twice daily with IV bevacizumab (10 mg/kg IV) every 14 days in 12 patients with advanced solid tumors [143]. The combination was generally well tolerated with drug-limiting toxicities. Recently, another phase I study investigating the combination of olaparib and the oral VEGFR2 inhibitor cediranib in recurrent ovarian or triple-negative breast cancer reported a 56 % unconfirmed response rate [144]; a randomized study of olaparib plus cediranib versus olaparib alone in patients with platinum-sensitive recurrent ovarian cancer is currently ongoing (NCT01116648). In addition, olaparib is being combined with the PI3kinase inhibitor BKM120, and this study should be underway later in 2012 (NCT01623349).

Aurora Kinase Inhibitors

Aurora kinases are cell-cycle-dependent regulators of mitotic spindle formation, centrosome maturation, chromosomal segregation, and cytokinesis [145]. Of the three aurora kinases, A, B and C, the aurora A gene amplicon and its overexpressed protein kinase are frequently found in epithelial ovarian cancer cells indicating involvement in tumorigenesis [146, 147]. Pan-aurora inhibition with tozasertib (MK0457) showed anticancer activity in a preclinical orthotopic model of ovarian cancer [148]. The orally active aurora kinase inhibitor alisertib (MLN8237) achieved a 10 % response rate among 31 unselected patients with platinum-resistant or platinum-refractory disease [149]. An ongoing study of weekly paclitaxel with or without MLN8237 is currently underway. The rationale for this study includes the following: (1) blocking of aurora kinase signaling enhances antitumor activity of taxanes in ovarian cancer models, (2) aurora A activity can help to protect cells from taxane-induced apoptosis through activation of Akt, and (3) targeting the mitotic apparatus through two separate mechanisms of action (i.e., MLN8237 and paclitaxel) may lead to increased anticancer efficacy [150–152].

Immunotherapy

The hypothesis that immunotherapy could be an effective treatment option for ovarian cancer stems from specific immunogenic features demonstrated by ovarian cancer; this topic has been previously reviewed by others [153–156]. Immunotherapies have been tested in ovarian cancer, and other studies are also underway. Abagovomab which is a murine monoclonal anti-idiotypic antibody against CA125 was tested in randomized phase II study using a 2:1 randomization as maintenance therapy following initial platinum-based chemotherapy for newly diagnosed advanced ovarian cancer [157]. There was no prolongation of PFS using

abagovomab compared to placebo when used as maintenance therapy. Ipilimumab, anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) antibody, was tested in a limited number ($n = 11$) of ovarian cancer patients, and three patients had evidence of antitumor activity, and three additional patients had stable disease ≥2 months [158]. One patient has had ongoing radiographic and CA125 response since 2003 [158]. These observations have led to further investigation of ipilimumab in ovarian cancer (clinical trials.gov number NCT01611558). Age-dependent responsiveness of immunotherapies in ovarian cancer and toxicities specific to the elderly are not yet known.

Other Targeted Agents and Future Directions

Insights into other targeted agents for ovarian cancer have arisen from molecular analyses such as the TCGA [2]. The TCGA demonstrated that pathways such as Rb, NOTCH, and FOXM1 signaling pathways are aberrant in HGSC suggesting that testing inhibitors of the NOTCH and FOXM1 signaling pathways in HGSC has rationale. With further molecular characterization of the different histologic subtypes of epithelial ovarian cancer (HGSC, high-grade endometrioid, low-grade tumors (serous and endometrioid), clear cell, and mucinous cancers) through somatic mutation profiling, identification of amplified genes, and further characterization based on expression profiling, additional targets for development of future therapies will be identified. In addition, biomarkers need to be identified to help predict effectiveness and perhaps toxicities of the various targeted therapies. As personalized medicine progresses, combination therapies will be necessary to target the multiple identified aberrant pathways that are responsible for cancer progression in patients.

Conclusions

At present, and contrary to other malignancies, FDA approval has not been obtained for any targeted agent yet in ovarian cancer. However, in the setting of ongoing clinical trials, elderly women should certainly be encouraged to participate in clinical studies as long as they meet eligibility. With few exceptions and to date, targeted agents appear to exhibit similar efficacy and safety across age subgroups and different cancers. It is challenging, though, to derive generalized interpretations from subset analyses of nonovarian malignancies and thus, clinical studies should be designed to cover the question of efficacy and tolerability in the elderly population. Careful monitoring from both a pharmacokinetic and toxicity standpoint is necessary in all age groups in order for elderly patients to derive maximal treatment efficacy and maintain a satisfactory quality of life.

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Chapter 14
Management of Recurrent Ovarian Cancer in Older Women

Nuria Romero and Franco Muggia

Abstract Data on the treatment of recurrent ovarian cancer in the elderly has relied mostly on selected pilot studies. The largest study, ICON4 analyzes the elderly subset and does suggest that patients over 65 benefit from treatment with carboplatin + paclitaxel when the disease is categorized as platinum-sensitive as compared to single agents or other combinations. When the disease is platinum-resistant, preliminary results of the AURELIA study indicate that bevacizumab adds to the effect of chemotherapy, and this may also be applicable to the elderly. Nevertheless, there are a number of considerations relating to co-morbid conditions, adherence to treatment, and drug interactions that may pose a challenge in any one elderly individual undergoing chemotherapy treatments. Detection of early recurrences may be important, but this has not been studied specifically in an elderly population.

Keywords Ovarian cancer • Relapse • Management • Pharmacology • Pharmacokinetics

Introduction

There is a growing awareness of the high incidence of gynecologic cancer in women 70 and older. All three most common sites of origin of gynecologic cancers: uterine cervix, endometrium, and ovary (usually including also fallopian tube and peritoneal primaries of mullerian epithelial origin) represent a major challenge for practicing physicians including geriatricians and oncologists. Other tumors that are mostly confined to younger populations, such as germ cell tumors, stromal tumors, and gestational

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trophoblastic malignancies will not be covered. This chapter will therefore concentrate on the management of the malignancies that are most common in older women. Nevertheless, some of the guiding principles herein described, may also apply to infrequent tumors such as vulvar and vaginal cancers (usually considered together with cervical neoplasias) and the rare uterine sarcomas. After describing general issues in management of ovarian cancer recurrences, we shall comment on general principles of screening and prevention – areas that are of considerable emerging interest since few guidelines have been worked out specifically for an older population.

General Issues in Drug Treatment

The essential principles of approaching cancer treatment in the elderly according to stage do not differ substantially from those applicable to younger patients. The roles of surgery or radiation may be curtailed if comorbid conditions exist and/or if logistics in post-interventional care pose obstacles. Moreover, age-related organ function declines require special attention to avoid potential risks of certain chemotherapy regimens, as further elaborated below.

Changes in Pharmacokinetics

- *Absorption*. Atrophy of the intestinal mucosa and decreases in gastrointestinal motility, splanchnic blood flow, and secretion of digestive enzymes all can contribute to a decreased rate of drug absorption in elderly adults [1]. Although absorption of orally administered drugs may be affected, the magnitude of such changes does not justify dose modification based upon age. However, adherence among the elderly may be compromised by comorbidities impeding access, by an increased number of prescribed medications for multiple comorbid conditions, by decreased social support, and by the increased incidence of memory problems in this population [2].
- *Metabolism*. Decline in hepatic volume and hepatic blood flow has been described [3]. As a result, drug metabolism and elimination may be slowed, potentially exposing patients to higher drug concentrations for longer periods of time. Although these changes are not of sufficient magnitude to require routine dose modification in elderly individuals, concurrent hepatic impairment due to liver metastases or other comorbid conditions may necessitate dose adjustments.
- *Distribution*. In the elderly people population, the fat content doubles from approximately 15–30 % of body weight, while intracellular water decreases, leading to more prolonged half-lives of lipid-soluble drugs [1]. In addition, decreases in plasma albumin and red blood cell concentration are often present with aging, and this can affect the pharmacokinetics of agents that are bound to albumin or erythrocytes [4]. On the other hand, decline in bone marrow reserve, places older patients at greater risk for chemotherapy-related cytopenias [5].

- *Excretion*. Decrease of glomerular filtration rate (GFR) can result in higher peak drug levels and more prolonged exposure to chemotherapy, causing excessive toxicity with agents that are dependent upon renal excretion for their clearance [6]. Loss of muscle mass increases with age, making the serum creatinine concentration alone a less reliable marker of GFR in elderly patients. The Wright formula has been found more accurate and precise than the Calvert formula in calculating the carboplatin dose in an elderly population [7]. However, guidelines adopted by groups such as the Gynecologic Oncology Group for carboplatin dosing include safeguards that minimize overdosing elderly and obese individuals (Appendix). Additional attention should be paid to fluid management, because volume depletion can lead to severe reductions in the presence of an already compromised renal function.

Medical Comorbidities

Elderly patients are more likely to have comorbidities that in turn will influence the type of treatment offered and may have an adverse impact on survival. However, chronologic age does not reliably predict physiologic decline, and it is essential to individualize treatments.

Some of the most common conditions are renal impairment, diabetes mellitus, hypertension, gastrointestinal problems, and heart disease. Contributing to age-related abnormalities are the increased risk of coronary disease, valvulopathies, decrease in ventricular compliance, stroke, and peripheral vascular disease. Such risk should be considered not only when potentially cardiotoxic drugs are being used but also with treatments that must include premedications such as glucocorticoids or require omission of anticoagulant measures that may potentially confer added risks of cardiac decompensation and/or complications.

Polypharmacy

At least 90 % of older patients use at least one medication, and the average is at least four medications per patient [8]. This fact increases the likelihood of harmful drug interactions, particularly for agents that are metabolized through the cytochrome P450 system. Furthermore, due to the large number of medications used, compliance with prescribed therapies becomes an important issue [9] to be taken into account when devising the most appropriate treatment regimens.

General Issues in Management of Ovarian Cancer

Advanced age has been recognized as a prognostic factor for ovarian cancer. Based on data from the Surveillance, Epidemiology, and End Results (SEER) program

database, women younger than 30 years have 5-year survival rate of 78.8 % compared with 58.8 % for those aged between 30 and 60 years and 35.3 % for those aged 60 and older [10]. These data were also evident in the analysis of more than 1,800 patients performed by the Gynecologic Oncology Group showing that age is an independent prognostic factor [11]; similar results were observed in European population-based studies [12–14].

The reason for the apparent decrease in survival with rising patient age is not clear, but one factor may be undertreatment. Analysis of retrospective series have linked inferior results with other associated adverse prognostic factors such as the lower rate of optimal initial debulking surgery in the elderly patient population and less frequent use of paclitaxel [15–17] . These findings reinforce the need to obtain prospective evidence for the management of ovarian cancer in the elderly [18].

Surgical Treatment

An analysis of chemotherapy clinical trials from the Gynecologic Oncology Group (GOG) suggests that advancing age was associated with larger volumes of residual disease after cytoreductive surgery [19]. Since outcomes in older patients that undergo aggressive cytoreduction are similar to younger patients [20–22], it is important to adequately prepare them for surgery and seek surgeons with skills to achieve whenever possible optimal cytoreduction.

Retrospective data about perioperative risks in the elderly undergoing ovarian cancer surgery have been conflicting. Selected series suggest that outcomes are worse than for younger patients [23, 24], and in a large population-based observational study, the elderly (≥80 years) had 2.3-fold higher 30-day mortality than younger women [25]. Recently, a review of the American College of Surgeons on 8,781 oncology patients demonstrated that patients 75 or older (20.7 % of the cohort) had higher operative mortality, a greater frequency of major complications, and more prolonged hospital stays [26]. Minimally, invasive procedures have the potential to alter the rate of complications.

Predictive factors for surgical outcomes have been examined retrospectively associating worse outcome with major comorbidity, surgical rather than gynecologic oncology specialty, insufficient PACE (Preoperative Assessment of Cancer in the Elderly) and lower albumin levels; these results need to be validated [27, 28]. Also, studies need to address whether laparoscopic techniques and the extent by which referrals to the appropriate specialists alter outcome.

Neoadjuvant Treatment

A retrospective multivariate review comparing neoadjuvant chemotherapy versus primary cytoreduction was performed in elderly women diagnosed with ovarian cancer.

There were no significant differences in both groups: similar surgical and chemotherapy-related complication rates and comparable survival were found to those aged 80 or older and those aged 65–79 [29]. Although one trial by the EORTC [30] suggests neoadjuvant chemotherapy may be non-inferior to initial surgery in patients who are unlikely to undergo optimal cytoreduction, this is insufficient rationale for avoiding surgery in an elderly woman presenting with stage III ovarian cancer. In fact, the best results in the neoadjuvant trial were obtained in those patients in either arm who were able to achieve optimal cytoreduction either initially or after neoadjuvant chemotherapy.

Chemotherapy Treatments

The Southwest Oncology Group analyzed data on 16,396 patients showing that only 9 % of cancer patients older than 75 years were included in registration trials submitted to the US Food and Drug Administration (FDA) evaluating new cancer therapies [31]. Much of the available evidence originates from subanalysis or retrospective studies, so the conclusions must be interpreted with caution. However, even for established regimens such as carboplatin + paclitaxel, there is underrepresentation of older women in most series. Moreover, delayed initiation and early discontinuation of chemotherapy has been described in elderly people, associated with increased mortality [32]. The chemotherapy schedule should be chosen depending on the features of each patient, and this oncologic principle is essential in the treatment of fragile patients.

The Arbeitsgemeinschaft Gynekologische Onkologie (AGO) report on 103 patients older than 70 years (13 % of the overall population) showed no differences between elderly and younger patients in paclitaxel, carboplatin, and cisplatin chemotherapy tolerance, except for febrile neutropenia [33]. A more liberal use of G-CSF support may be considered in patients 70 or over receiving these regimens. However, in a cohort study on 292 patients (37 % older than 65 years) with stage III or IV ovarian cancer that received a platinum + taxane combination after initial surgery, similar treatment tolerance, tumor response rate, progression-free survival and overall survival were observed in younger and older patients [34]. A retrospective multivariate analysis based on two consecutive studies ($n = 83$, $n = 72$) with patients older than 70 years was performed by the GINECO group to determine the feasibility of two chemotherapy regimens: carboplatin + cyclophosphamide (CC) and carboplatin + paclitaxel (CP) in elderly patients with advanced ovarian carcinoma. Although the two populations differed in some aspects, 75.6 % in the CC group and 68.1 % in the CP group completed six courses, with similar completion rates and survival curves [35].

With an aim toward improving chemotherapy tolerance in this subgroup of older patients, two studies were performed in 2008 with modified schedules. In one of them, 26 women with advanced ovarian cancer receiving carboplatin (AUC 2) + paclitaxel (60 mg/m^2) weekly up to six cycles demonstrated a favorable toxicity profile [36]. The second one, a retrospective multicenter analysis of 100 patients that received reduced dose (carboplatin AUC 4–5 and paclitaxel 135 mg/m^2), also

showed a better tolerance in elderly patients while showing similar efficacy as the standard-dose regimens [37].

Treatment of Platinum-Sensitive Recurrent Disease

A carboplatin-based doublet in an elderly patient with potentially platinum-sensitive disease should be considered bearing in mind the comorbidity and the toxicity profile of the planned treatment and the tolerance of the preceding therapy. In particular, if the patient received prior taxane treatment, the presence of any residual neuropathy should be ascertained. In addition, cumulative myelosuppression is likely to be observed early. In fact, baseline counts may document neutrophil counts below 1,500/mm^3 (usually, a finding without any clinical implications except that unfortunately it may exclude patients from protocol studies) and platelets below 150,000 – this last finding does indicate that dose reductions may be in store as one begins another round of carboplatin. Recognizing increasing marrow intolerance during retreatment (e.g., treatment upon recurrence), trialists have employed a starting dose of carboplatin at AUC 5 and given every 4 weeks – in contrast to the usual dosing in first-line. A subgroup analysis from the CALYPSO study comparing CP with carboplatin + pegylated liposomal doxorubicin (PLD) showed no obvious difference in this attenuated treatment tolerance among patients older than 70 years than among younger ones, except for greater frequency of neuropathy exceeding grade 2 [38]. Thus, the lower dose-intensity of carboplatin on retreatment is common practice, whether the patient is elderly or not. It should be noted that paclitaxel attenuates the platelet toxicity of carboplatin, so marrow tolerance at AUC 5 was somewhat less for the carboplatin + PLD than carboplatin + paclitaxel. On the other hand, the PLD-containing doublet seems to provoke lesser carboplatin allergic reactions – a problem that may be expected to be more significant in the elderly, since ventricular tachyarrhythmias and death have resulted from such events.

An Italian multicenter retrospective study in the recurrence setting has described a poor outcome of elderly patients with platinum-sensitive ovarian cancer, with a response rate of 67.2 % in younger versus 46.5 % in elderly ($p = 0.0004$). When the treatment was analyzed, less frequently secondary surgical cytoreduction and combination chemotherapy was observed in the older population [39]. These data, however, were from an Italian registry series from 2000 to 2002 that frequently utilized single platinum agents for recurrence. With the ICON4 results demonstrating that the addition of paclitaxel to carboplatin confers a survival advantage over platinum therapy alone or given in combinations in common use at the time (such as CAP: cyclophosphamide-Adriamycin (doxorubicin)-cisplatin), carboplatin + paclitaxel and carboplatin + gemcitabine and not single agents have become the standard treatment regimens for platinum-sensitive recurrences [40]. Therefore, this inferior efficacy reported above for older patients enrolled in Socrates may not be relevant.

Since ICON4 was a composite of various regimens comparing paclitaxel added to carboplatin or cisplatin versus the platinums as single agents or in non-taxane combinations (so-called conventional treatment), one needs to be cautious on subset analyses even within this largest of phase III studies for recurrent ovarian cancer that enrolled 802 patients. Nevertheless, patients over 65 made up about 30 % of enrolled subjects, and there is a trend ($p = 0.08$) favoring a positive interaction with age in diminishing the hazard ratio (HR) for progression-free survival in patients receiving paclitaxel plus platinum versus conventional treatment [40]. In fact, the HR for the patients over 65 is the strongest favoring the paclitaxel + platinum (HR about 75 %, and confidence intervals not overlapping 1.0). These results support the use of the carboplatin + paclitaxel combination for recurrent disease in the elderly vis-à-vis other choices, with the exception of carboplatin + PLD that had not undergone evaluation.

Treatment of Platinum-Resistant Recurrent Disease

Chemotherapy

Once the disease is shown to be platinum-resistant, single-agent is most often employed. PLD has gradually become the agent of first choice in this setting, and it is relatively safe in elderly patients without any history of myocardial dysfunction. The cardiotoxic potential of PLD is considerably less than the "free doxorubicin," and cumulative effects have only rarely led to clinical events, and usually because there has been prior exposure to the non-pegylated formulation. However, because there is little information on the use of PLD in the presence of low baseline ejection fraction or known heart disease, some caution must be exerted if such conditions are present. Gemcitabine, docetaxel, topotecan, etoposide, pemetrexed, or vinorelbine are other chemotherapeutic options for the treatment of platinum-resistant recurrences. However, there are no studies specifically addressing tolerance in the elderly with gynecologic cancers. Nevertheless, certain precautions need to be emphasized: docetaxel is more likely to be associated with febrile neutropenia, and its use often requires either dose attenuation, granulocyte growth factor support, or both. Pemetrexed must be given with great caution in the presence of renal dysfunction with creatinine clearances below 50 ml/min. In addition to chemotherapy, bevacizumab is now part of the therapeutic armamentarium.

Antiangiogenic Therapy

Bevacizumab has recently been shown to improve progression-free survival in first-line treatment of ovarian cancer, and patients at higher risk of progression may be the ones to benefit the most [41]. In the recurrence setting, the GOG was the first to show efficacy

among a number of other biological studied in ovarian cancer. Prompt adoption of the drug for patients after multiple regimens led to early cessation of a trial complicated by bowel perforations or fistulas in five patients. Experience at MD Anderson, on the other hand, showed that it had a strong record of safety, but in time, after a dose of 15 mg/kg every 3 weeks, proteinuria and hypertension became present in up to 40 % of patients. Other problems that have been reported included posterior reversible encephalopathy syndrome [42]. Comorbid conditions in the elderly might preclude use of bevacizumab or inhibit its use. Reports in patients with colon cancer indicate a higher risk of arterial thrombotic events with bevacizumab-containing regimens in older patients relative to younger patients [43], but another series did not duplicate these findings [44, 45]. As experience is accumulating, several safety questions arise: (1) might a lower dose be preferable, (2) is it possible to prevent hypertension with more aggressive treatment, and is its presence a marker of efficacy, and (3) is there an advantage in using this drug sequentially or in combination? These questions may be even more pressing in the elderly, and its exploration may be particularly worthwhile, since the drug has some advantageous features relative to chemotherapy. Moreover, the AURELIA study results presented at the May 2012 American Society of Clinical Oncology (ASCO) meeting reported delays in disease progression when bevacizumab was added to either paclitaxel, pegylated liposomal doxorubicin or topotecan versus either of the agents by themselves –thus encouraging use of combined treatments.

Hormone Therapy

Hormone therapy plays little or no role in the treatment of ovarian cancer, although it is a particularly attractive option for the treatment of elderly people with advanced or recurrent endometrial cancer. Accumulated experience with a variety of hormonal regimens suggests that between 15 and 30% of women with uterine cancers respond to hormone therapy, with progestins among the agents most often used [46–48]. The likelihood of response has been correlated with three main features: low-grade histology, expression of estrogen and/or progesterone receptors (ER/PR), and a long treatment-free interval between initial diagnosis and the development of metastases (usually in the lung). Responses are most often partial and measured in months, but some patients may remain progression-free survival for years [49]. Tamoxifen has been used in uterine cancer but is mostly effective when given in regimens alternating with progestins, with response rates of approximately 30–35 % [50–52]. Activity with aromatase inhibitors in advanced endometrial cancer has been reported, but just a few studies in the literature have been published [53, 54]. Because of their negligible effect on weight gain and absent predisposition to edema and thromboembolism, these drugs are often used in lieu of progestins. Is any of this information extrapolatable to ovarian cancer, when the tumors are strongly ER/PR positive and of the endometrioid variety? Future studies need to explore these treatments further. Tamoxifen has been studied by the GOG, and in a small phase III study showed a survival advantage over thalidomide. Because of increasing likelihood of throm-

boembolic disease with advancing age, interest in aromatase inhibitors has increased. These agents, however, carry with them some adverse events in patients who have diminished bone density or have problems with arthralgias and joint stiffness.

General Considerations Regarding Patient Communication

The disclosure of a diagnosis of cancer is complex, particularly in elderly for reasons related to the wishes of the family, fear of discouraging the patient, or the patient's inability to understand this information. Conversely, there is a lack of adequate geriatric expertise and care in oncology precluding adequate expertise among physicians leading them to treat older people frequently as a single homogeneous group. It is important that caregivers be sensitive to an individual's view about cancer. In particular, a study did find that a large proportion of older oncologic patients are willing to talk about their cancer [55]. Involvement of family members in making decisions for parents or spouses is often a key element, but the view of the patient herself in these decisions must not be overlooked. An oncologist's role in lessening the anxiety relating to cancer treatment (often based on prior experience with relatives or friends) has often been emphasized. However, there is less awareness of the important role an oncologist has in making the appropriate dose adjustments and in understanding supportive care issues that accompany the delivery of treatment. In particular, while supportive care has made steady strides in avoiding febrile complications and improving accompanying nausea and emesis, anything that is indiscriminately applied also runs the risk of producing added problems such as insomnia, constipation, aggravation of diabetes, among others. Many of these issues contribute to treatment acceptance by elderly patients.

Conclusions

In summary, the data support using similar drug regimens for recurrent ovarian cancer in older patients to those in general use. However, dose attenuations as described above often require more study before wide adoption, and use of G-CSF may be more reasonable in an older population (carboplatin and paclitaxel does not usually require accompanying use of G-CSF). Cisplatin use is likely to pose additional problems in the elderly and has limited if any role in treatment of recurrences: overall subjective intolerance and depression, preexisting renal disease, intolerance to excess hydration, and auditory and vestibular dysfunction are among the risks for additional complications to occur. In the presence of preexisting neuropathy, one might consider substituting docetaxel for paclitaxel (but this requires further study in an elderly population) or by pegylated liposomal doxorubicin based on the results of the CALYPSO study – drug supply problems are currently limiting adoption of these results. Neuropathy is a cause of greater concern in the elderly who may

already be compromised in their ability to walk, who suffer from nocturia, and have enhanced risks of fracture. Nevertheless, ICON4 gave a positive signal for improved results for the carboplatin + paclitaxel doublet compared to other salvage regimens in patients over 65 years old. Bevacizumab's adverse effects on blood pressure may pose problems to a greater extent in an elderly population, and additional data are needed about its safety and its relation to dose and comorbidities. In the future, it will be imperative to move beyond experience to clinical trials data so that we can best address the optimal treatment of elderly patients with recurrent ovarian cancer.

Appendix (From C. Aghajanian for Gynecologic Oncology Group, January 2012)[1]

Carboplatin Dose Calculation Instructions

The Cockcroft-Gault formula will be used in GOG trials.

Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.

A carboplatin calculation tool is available on the GOG website (Web Menu, Tools).

Dosing of Carboplatin

The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE grade 2 (serum creatinine >1.5 × ULN) or toxicity requiring dose modification, the dose of carboplatin *will not* need to be recalculated for subsequent cycles but will be subject to dose modification for toxicity as noted in the protocol.

At the time of dose modification, if the patients age has changed (the patient has had a birthday), the site can use the current age.

In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a *minimum value of 0.7 mg/dl*.

For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the preoperative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

[1] Reprinted with permission from GOG Statistical Center, Elm & Carlton Streets, Buffalo, NY 14263-0001.

Calvert formula:

$$\text{Carboplatin dose}(\text{mg}) = \text{Target AUC} \times (\text{GFR} + 25)$$

Note: The GFR used in the Calvert formula should not exceed 125 ml/min.

$$\textit{Maximum}\ \text{carboplatin dose}\ (\text{mg}) = \text{Target AUC}\ (\text{mg/ml} \times \text{min}) \times 150\ \text{ml/min}.$$

The maximum allowed doses of carboplatin are:

AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\text{Creatinine clearance}(\text{ml/min}) = \frac{[140 - \text{Age}(\text{years})] \times \text{Weight}(\text{kg}) \times 0.85}{72 \times \text{serum creatinine}(\text{mg/dl})}$$

Notes:
Weight in kilograms (kg):
Body mass index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
Adjusted weight should be used for estimation of GFR for patients with *BMI of greater than or equal to 25*.
Adjusted weight calculation:

$$\text{Ideal weight}(\text{kg}) = \left(\left(\left(\text{Height}(\text{cm}) / 2.54\right) - 60\right) \times 2.3\right) + 45.5$$

$$\text{Adjusted weight}\ (\text{kg}) = \left((\text{Actual weight} - \text{Ideal weight}) \times 0.40\right) + \text{Ideal weight}$$

The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).
At the time of a dose modification for toxicity:
If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

Moreover, the AURELIA study results presented at the May 2012 American Society of Clinical Oncology (ASCO) meeting reported delays in disease progression when bevacizumab was added to either paclitaxel, pegylated liposomal doxorubicin or topotecan versus either of the agents by themselves –thus encouraging use of combined treatments.

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Chapter 15
Treatment of Endometrial Cancer in the Geriatric Patient

Kathleen N. Moore

Abstract Despite the fact that endometrial cancer is predominantly a disease that occurs in elderly women, little is known about best practices for therapy when endometrial cancer develops in the "oldest old" patients greater than the age of 80 or in patients with age-associated comorbidities. Treatment of endometrial cancer in these populations is a challenge as surgery is indicated in the vast majority of cases, and there are no validated screening tools to assess a patient's fitness for endometrial cancer surgery. Patients with endometrial cancer not uncommonly require adjuvant therapy in the form of hormones, radiation, chemotherapy, or a combination thereof, but little information exists regarding best practices in an elderly patient and outcomes. This chapter aims to summarize the challenges and options surrounding the care of elderly patients who present with endometrial cancer.

Keywords Endometrial cancer • Geriatric patients • Comorbidity • Adjuvant therapy • Surgery • Chemotherapy

Introduction

The elderly population, typically defined as greater than 65 years of age, is the most rapidly growing age bracket in the United States (US). The US Census estimates that by the year 2020, there will be over 54 million people living in the USA over the age of 65 (13.5 %) and that by 2040, this will have increased to over 80 million persons (20.4 %) [1]. Within this growing population, the subpopulation of persons living beyond age 80 is also increasing. In 2020, approximately 2.2 % of persons will be greater than 80 years of age, and this percentage will double by 2050 [1].

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Along with this growth in the elderly population, comes an increased prevalence of cancer diagnosis. Cancer is recognized as a disease of the elderly with over 50 % of new cases being diagnosed after age 65 and over 70 % of deaths from cancer occurring in this same age group [2–4]. Endometrial cancer, which is predominantly a disease of postmenopausal women, should be expected to increase in prevalence with an increasingly aged population.

In the USA in 2011, there will be over 46,000 new cases of endometrial cancer and over 8,000 deaths. Among these cases, almost 25 % will be diagnosed among women older than 75 years but 50 % of deaths due to endometrial cancer will occur in this age demographic [5, 6]. This discrepancy between incident cases and mortality has been variably ascribed to three factors: (1) that elderly women have inherently more aggressive endometrial cancer than their younger counterparts, (2) that elderly women receive less aggressive interventions for their endometrial cancer than their younger counterparts, and (3) that age itself is an independent poor prognostic marker for endometrial cancer.

In a recent surveillance, epidemiology and end results analysis of over 37,000 women with endometrial cancer, Wright et al. confirmed some of these beliefs in women over the age of 80. Of the 37,718 women, 5,289 (14 %) were age 80–84 and 3,446 (9.1 %) were age 85 or greater. In looking at primary therapy offered, 95 % of women <70 underwent a hysterectomy of some sort while only 2/3 of patients ≥80 underwent hysterectomy. The rates of lymph node dissection were 43 % for those women age 65–69, 37.5 % for those women age 80–84, and 25 % for those women ≥85. His analysis also found that older women were less likely to receive either vaginal brachytherapy or external beam radiation therapy as adjuvant therapy following hysterectomy. This trend held true for those women found to have advanced stage disease as well. Most concerning is the finding that cancer-specific mortality also increased with age with women age 80–84 (HR 1.53) and women > age 85 (HR 1.89), both more likely to die of their endometrial cancer than women age 65–69 [4].

The Wright analysis confirms what many believe, that elderly women with endometrial cancer do not receive the same primary and adjuvant therapies received by their younger counterparts with negative effects on disease-free survival. This discrepancy in treatments given is in large part based on a belief that elderly patients are too frail to undergo standard therapies. Balducci and Extermann describe aging as a loss of entropy or functional reserve and of fractality or the ability to coordinate activities and negotiate the environment [7]. This paired with increasing medical comorbidities with age creates a perception of increased risk inherent to treating the elderly with the same standard surgical, radiation, and chemotherapeutic interventions [8].

Unfortunately, these perceptions are likely to persist given the fact that elderly patients are very poorly represented on clinical trials – including those for endometrial cancer, the published data on treatment of endometrial cancer in the elderly is all retrospective in nature and finally – we have no agreed-upon definition for "elderly." Despite these limitations, we will use this chapter to summarize what we know about treatment of endometrial cancer in an elderly population and give recommendations for future improvements.

Clinically Early Stage Disease

For patients who present with disease clinically limited to the uterus (or small volume cervical involvement), the standard of care is removal of the uterus and cervix with/without ovaries and with/without lymph node dissection. The first decision faced by the treating physician and patient is "can we operate?"

Surgery Versus No Surgery

There are no prospective trials in endometrial cancer validating a preoperative algorithm by which a patient's ability to tolerate surgery may be addressed. Such algorithms are currently under study in other malignancies and include the "pre-operative assessment in elderly cancer patients (PACE)" assessment, the comprehensive geriatric assessment (CGA), as well as evaluations of accumulated frailty characteristics [9–11]. The CGA is a tool that has been well validated as a predictor for morbidity and mortality for several chronic diseases in clinical settings but has not, as of yet, been validated for preoperative assessment [9]. The accumulated frailty assessment was performed in patients >65 undergoing elective procedures and who were going to require postoperative intensive care unit admission. It measured baseline frailty characteristics preoperatively (burden or comorbidity, function, nutrition, cognition, geriatric syndromes, and extrinsic frailty). The primary outcome measure was discharge to an institutional care facility, and they found that one in three of these patients required discharge to an institutional care facility after major surgery. There were several indices that were most predictive of need for institutionalization most centered in the domains of function or dependence [11]. While this outcome measure is of extreme importance to an elderly woman and her physician considering surgery, this study looked at a high-risk population (expected ICU stay) and is probably not as representative of the hysterectomy and associated procedures performed for endometrial cancer. The PACE assessment incorporates elements of the CGA, an assessment of fatigue and performance status as well as an anesthesiologists assessment of risk into a 20-min assessment. This tool has been prospectively assessed in elderly patients (>70 years) undergoing an elective surgery for breast (47.2 %), gastrointestinal (31.3 %), genitourinary (15.4 %), and other (6.1 %) cancers. The outcomes of interest were 30-day morbidity, mortality, and hospital stay. The components of the PACE associated with a 50 % or more increase in postoperative morbidity included poor health related to disability, fatigue, and performance status, and the authors concluded that it was feasible and suitable for generalized preoperative assessment of elderly patients [9].

Interest in incorporating these preoperative measures to remove the "age bias" in under-treating elderly patients is increasing, and in the future, these assessments will likely be routine. The data for endometrial cancer to date has decisions based on surgery or no surgery made by the assessment of the treating physician.

For patients deemed poor surgical candidates for any sort of surgery, palliative interventions would include (1) symptom control only or (2) use of hormones. Treatment alternatives would include use of primary radiation. The use of hormones (if tolerated by the patient) can be very effective in reducing bleeding and in some cases, treating the cancer itself for several years – especially in cases of grade 1 endometrioid cancers. Progestational agents have been most widely studied and can be administered in oral, parenteral, or intrauterine delivery. The initial response rates to progestational therapy are reported as 58–100 %, but long-term outcomes are less certain [12–16]. Recurrence may occur in up to 50 % of patients, and many publications recommend every 3-month endometrial sampling as surveillance for recurrence [14]. The majority of research involving use of progestational agents for treatment of endometrial cancer has involved patients interested in fertility preservation as opposed to those who cannot undergo surgical intervention or radiation; so the best regimen for this, more vulnerable population is still not well defined.

Primary radiation therapy can be a curative alternative for patients who are poor surgical candidates by virtue of age or medical frailty. Studies have evaluated use of primary radiation in both stage I and II patients who received both combination of external pelvic radiation and intracavitary radiation as well as intracavitary radiation alone. Five-year survival for grade 1 tumors ranged from 72 to 85 %, for grade 2 tumors from 59 to 68 %, and for grade 3 from 31 to 53 %. Local recurrence was documented in 0–36 % which is not to dissimilar from grade-by-grade recurrence risk post hysterectomy [17–20]. The type of radiation selected is decided based on the fitness of the patient to undergo radical radiation with a combined external and intracavitary approach vs. a more palliative intracavitary approach alone. Coon et al. described the variety of intracavitary applicators available (to include modified Heyman capsules, two channel "Y" applicators, multiple channel Bauer applicators, tandem and ovoids, and vaginal cylinders). His recommendation is for use of the "Y" applicator given its advantage of covering a larger uterine width. His 10-year report on 49 medically inoperable patients who were treated with the "Y" applicator either in combination with external beam (20 Gy in 5 fractions) or as primary modality (35 Gy in 5 fractions) found only 3 recurrences and 5-year cause-specific survival of 87 %. Overall, all cause survival at 5 years was only 42 % emphasizing the competing morbidities in these patients [21].

Type of radiation selected should be per the treating centers standard of care, but one can see the acceptable outcomes in terms of survival using a primary radiation approach in medically inoperable patients.

Surgical Staging Versus No Staging

For patients whose medical comorbidities preclude even consideration of full surgical staging, a variety of options are available. The most common alternative is to offer a simple hysterectomy via the vaginal route if possible. The use of vaginal hysterectomy as compared to abdominal hysterectomy for clinically stage I patients

has been evaluated and found to reduce hospital stays and result in less blood loss and fewer severe perioperative complications such as perioperative mortality. The observed survival of patients undergoing vaginal hysterectomy compared to abdominal hysterectomy does not appear to differ [22].

The decision to surgically stage a patient with endometrial cancer whom the surgeon feels is medically fit enough to undergo hysterectomy, oophorectomy, and lymph node dissection should be based on the surgeon's standard practice. The decision to stage or not stage is a controversial one with excellent arguments on both sides. Proponents of surgical staging point to certain knowledge of the lymph node status and the ability to tailor adjuvant therapy based on nodal status. There are also suggestions that lymph node dissection may be therapeutic, although this has not been validated in large trials [23, 24]. Detractors of surgical staging point to two recently published international trials which demonstrated no survival benefit associated with lymph node dissection [25, 26]. Further, the decision to offer adjuvant therapy or not in clinically stage I patients is more and more based on the uterine factors described in GOG 99 and PORTEC-1 and 2. Patients who fall into high-intermediate risk categories in these studies are offered adjuvant radiation regardless of lymph node status, and this treatment reduces this risk of recurrence from ~25 to 14 %. This further brings the necessity of lymph node dissection to question. The decision to stage or not stage should be based on the experience of the operating surgeon, fitness of the patient for a more lengthy surgery, and how the information gathered will change postoperative recommendations as discussed above.

Adjuvant Therapy Versus None

Use of adjuvant therapy and the type of adjuvant therapy is another area where there is no "standard of care" or "standard approach" despite some fairly compelling phase III data. Referring back to GOG 99 and PORTEC-1, we can see that in both a staged stage I and an unstaged clinically stage I population, these studies identified a subgroup of patients for whom the recurrence risk without therapy was unacceptably high and for whom adjuvant therapy, in this case external beam pelvic radiation, was indicated and demonstrated improvement in terms of recurrence risk. In GOG 99, this subgroup was deemed high-intermediate risk and was identified by a combination of age and the presence of grade 2 or 3 histology, presence of lymph vascular space invasion, and outer third myometrial invasion. For patients who were 70 years of age or older, only one risk factor was needed to fall into this high-intermediate risk group. These patients had a 27 % risk of recurrence with no additional therapy, and this was reduced to 13 % with the addition of adjuvant radiation [27]. Similarly, PORTEC-1 looked at clinical stage I patients who were randomized to no additional therapy vs. adjuvant external beam radiation and also identified a subgroup of patients for whom the risk of local recurrence was 3.7 % with no additional therapy and reduced to 4.2 % with adjuvant radiation. Identified risk factors were similar to those in GOG 99 with invasion >50 % of myometrium, age > 60 years and

Table 15.1 Pathologic findings for stage I/II patients reported in six published series on the elderly

Variable	Moore [8]	Fleming stage I/II [30]	Alektiar stage I/II [31]	Moscarini stage I/II [32]	Siento [33]	LaChance stage I [34]
N	65	106	84	68	67	151
Age	>80	>75	>70	>70	>65	>75
Staged	69 %	63 %	10 %	54 %	100 %	
Stage I	65 %	88 %		94 %	64.6 %	100 %
Stage II	15 %	12 %		6 %	8.4 %	
>50 % DOI	45 %	14 %	71 %	25 %	43.8 %	32 %
LVSI	31 %	NR	21 %	NR	NR	NR
Grade 1	26 %	49 %	85 %[a]	18 %	25 %	12 %
Grade 2	28 %	40 %		57 %	41.7 %	46 %
Grade 3	46 %	16 %	15%[b]	25 %	33.3 %	42 %
UPSC/CC						22 %

[a]85 % refers to grade 1 and 2

[b]15% refers to grade 3 and aggressive histology

grade 3 histology. Patients were felt to be at high-intermediate risk for recurrence if they had two of three risk factors [28]. PORTEC-2 enrolled just those patients felt to be at high-intermediate risk by PORTEC-1 criteria and randomized them to external beam pelvic radiation vs. intracavitary vaginal cylinder brachytherapy. Rates of distant metastases were similar (5.7 % vs.8.3 %) as were rates of local-regional failure 2.1 % vs. 5.1 %, respectively, establishing vaginal cylinder as an acceptable alternative to external beam pelvic radiation [29].

Table 15.1 outlines the pathologic findings for stage I/II patients reported in 6 published series on the elderly. Looking at just those five studies who reported on patients age 70 or older, between 15 and 88 % of patients would be designated as high-intermediate risk by GOG 99 criteria by virtue of grade alone. Twenty-one to thirty-one percent would qualify by combination of age and LVSI alone. Applying the PORTEC-1 criteria where two risk factors are needed, one is given for age > 60 and then 15–46 % would qualify based on grade 3 histology and 14–71 % would qualify based on depth of invasion >50 %. A large proportion of elderly patients end up falling into this high-intermediate risk category regardless of the model applied and would appear to benefit from adjuvant therapy.

Despite this evidence for benefit in both staged and unstaged patients, elderly patients still receive far less adjuvant therapy than their younger counterparts. Based on SEER data, patients age 80 were 20 % less likely to be treated with vaginal brachytherapy and those age 85 and older were 28 % less likely. For external beam pelvic therapy, patients age 80–84 were 33 % less likely to receive this adjuvant therapy and those older than 85 were 59 % less likely to receive external beam pelvic therapy [4]. This finding may be due to some patient refusal of adjuvant therapy but also certainly is due to a belief that elderly patients will tolerate postoperative radiation poorly. There are retrospective reports that suggest elderly patients (in these reports defined as >65) have reduced overall and disease-free survival following

hysterectomy and adjuvant radiation with no mention made of increased toxicity [35, 36]. Alektiar et al. evaluated a cohort of stage I and II patients who all underwent hysterectomy followed by adjuvant radiation and found that pelvic control for patients given intravaginal radiation was 88 % and for those receiving external beam pelvic radiation was 90 %. More importantly, the 5-year actuarial rate of ≥grade 3 complications was only 3 %, and this remained unchanged in the group >age 70 [31]. Finally, in a cohort of patients treated with radiation for pelvic malignancies on EORTC trials, there was no age related early or late toxicity difference seen among the 1,619 patients included [4, 37].

Clearly, there is more work and education needed to further elucidate which elderly patients would truly benefit from adjuvant therapy and then convincing patients and physicians that adjuvant therapy is a safe intervention for this population.

Advanced Disease

Local-Regional Spread of Disease

For patients, regardless of age, the standard of care for patients with local regional spread of disease is a moving target. This population of patients have either FIGO stage IIIa (tumor invades the uterine serosa or adnexa), stage IIIC1 (pelvic lymph node involvement), or stage IIIC2 (para-aortic lymph node involvement) [38]. Knowledge of this pathology implies that the patient was fit enough to undergo at least a hysterectomy and bilateral salpingo-oophorectomy with or without lymph nodes. Treatment options include radiation alone, chemotherapy alone, or a combination of chemotherapy and radiation. These patients were included on GOG 122 which randomized patients to either whole abdominal radiation or treatment with doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 × 7 total cycles with one additional cycle of cisplatin given. Here, chemotherapy was found to be superior to the use of whole abdominal radiation although this study included both patients with local regional spread as well as intraperitoneal (stage IV) disease. On subgroup analysis, the death hazard ratio of chemotherapy relative to that of radiation was 0.47 for stage IIIA and 0.75 for those with nodal disease indicting superiority of chemotherapy over radiation even in these groups [39]. There were more pelvic recurrences reported in the chemotherapy group relative to those in the radiation group which has prompted efforts to combine chemotherapy and radiation in this population. GOG 184 treated patients with local-regional spread of disease (the study had been initially open to stage IV but was closed to this group early in the study) to volume-directed radiation followed by a planned six cycles of doxorubicin 45 mg/m^2 and cisplatin 50 mg/m^2 vs. the same plus the addition of paclitaxel 160 mg/m^2. The addition of paclitaxel did not improve outcomes but did add to toxicity. In the doxorubicin/cisplatin arm, almost 83 % of patients completed all six cycles of chemotherapy following radiation reflecting acceptable tolerance of this regimen [40].

Whether or not the addition of radiation to chemotherapy is necessary in this population is unclear but currently under study via GOG 258 which compares paclitaxel and carboplatin × six cycles vs. volume-directed chemo-radiation followed by four cycles of paclitaxel and carboplatin. Results of this study are eagerly anticipated to finalize the standard of care for this population.

In terms of elderly patients, GOG 122 had only 14 % of randomized patients age 70 or older ($n=78$) and GOG 184 had 20 % ($n=82$), and adverse events were not analyzed separately for these patients.

Stage IV Disease

Treatment of stage IV disease (disease spread to intraperitoneal structures or distant metastases) is difficult in any patient but is especially difficult in an elderly patient. For those patients with metastases to organs not amenable to surgical resection, with rare exception, the treatment of choice is chemotherapy with either paclitaxel and carboplatin or doxorubicin and cisplatin day 1, followed by paclitaxel day 2, and neulasta day 3. For patients with surgically resectable disease, the decision is whether to attempt cytoreduction or not. Surgical cytoreduction has not been studied in an elderly endometrial population, and it has not been evaluated in a general endometrial population in any manner other than retrospective series. There have been no phase III trials allowing for evaluation of the effect residual disease has on outcome as there has been in ovarian cancer because in all but one of the phase III chemotherapy trials (GOG 122), advanced and recurrent patients were allowed, so we find a large population of patients who start with measurable disease. There is some proof or principle for cytoreduction if we look at GOG 122 and GOG 184 (chemotherapy + radiation) vs. the GOG chemotherapy-only studies (GOG 107, 139, 163, and 177). In GOG 122, all patients had <2 cm of disease on study entry and median progression-free survival was 38 months [39]. In GOG 184, again patients had to have <2 cm of disease and most had no measurable disease. Median progression-free survival had not been reached in this study with over 4 years of follow-up among those who are alive and disease-free [40]. This is compared to GOG 107, 139, 163, and 177 – all of which evaluated chemotherapy in an advanced/recurrent measurable disease population. Here, median survival ranged from 9.0 to 15.3 months [41–44]. Again, this comparison is somewhat polluted by the inclusion of recurrent patients, about half of whom would have received radiation in the past, but the effect of residual disease is suggested here.

There have been many single institution, retrospective studies which attempt to demonstrate the benefit of cytoreductive surgery in a stage IV population with overall survival ranges from 19 to 34 months for patients who achieve less than 1 cm of residual disease [45–49]. A case–control analysis by Landrum et al. compared patients with stage IV endometrial cancer who underwent cytoreductive surgery followed by chemotherapy to stage IIIc ovarian cancer patients who underwent a similar series of treatments. While the patients with endometrial cancer had inferior

outcomes when compared to their matched ovarian cancer counterparts on multivariate analysis, only residual disease <1 cm was predictive of survival in endometrial patients suggesting a benefit to cytoreduction in this population [50].

The ability of elderly patients to tolerate aggressive cytoreduction has only been studied in ovarian cancer patients and only in retrospective series with highly variable conclusions likely based on the selection criteria used at each institution to select patients for surgery or for a neoadjuvant approach [51–56]. Wright et al. evaluated the National Inpatient Sample to identify women who underwent surgery for ovarian cancer between 1998 and 2007. In a series of over 28,000 women, he evaluated morbidity and mortality based on age, number of radical procedures performed, and clinical characteristics and found that age was major predictor of postoperative morbidity. Compared to women less than 50 years of age, women over 80 had a baseline rate of complications of 10.2 % vs. 18 % with no radical procedures, and this increased to 23.7 % vs. 33 % for women who had two or more procedures. In addition, the rate of "non-routine discharge," i.e., discharge to a nursing home or facility increased with age and radicality of procedures from 0–2 % in women <50 with 0, 1, or 2 procedures to 30–49 % in women >80 with 0, 1, or 2 radical procedures [57]. This high cost of surgery (in terms of morbidity) for elderly patients with ovarian cancer can be justified by the presence of an effective adjuvant chemotherapy which appears to be more effective following radical surgery. For elderly endometrial cancer patients, who may have more medical comorbidities than their ovarian counterparts and for whom a similarly effective adjuvant chemotherapy has not yet been identified, this level of morbidity and institutionalization may be harder to justify, but decisions must be made based on the individual patient with age as just one deciding factor.

The use of progestational agents in the setting of advanced/recurrent disease is another active option with less toxic side effects than systemic cytotoxic therapy. The use of oral medroxyprogesterone or megestrol acetate has been studied in several prospective trials, and response rates of 11–25 % have been reported. While the duration of responses is relatively short, there are patients who do achieve disease stabilization for more than 12 months. These patients typically have more well-differentiated tumors, but responses have been reported across all grades making a trial of progestational therapy a valid option [58–62].

Conclusion

Age is a well-recognized prognostic factor for many malignancies including endometrial. The effect of age on outcome is multifactorial and likely includes some inherent increase in baseline biologic aggressiveness of these tumors paired with increased medical comorbidity conditions and underutilization of standard of care therapies.

Ideally, patients who present with clinical stage I/II disease will be offered at least hysterectomy with/without lymph node dissection based on the treating physician's

standard practice for treatment of endometrial cancer. For those patients with significant medical comorbidities, variation in this standard may include attenuation of the surgical plan, use of primary radiation therapy, or use of hormonal intervention.

Further validation of preoperative assessment tools will assist surgeons in making objective decisions on who is a surgical candidate for standard therapy and who requires some variation from standard.

Discussion of treatment for elderly patients with advanced disease is complicated by the lack of an agreed-upon standard of care. For patients with local-regional spread of disease options include radiation alone, chemotherapy alone, and a combination of the two. Which of these options provides the best outcome for patients in general has not yet been decided and then how best to modify these options for the elderly patients is currently left to the best practices of the treating physician.

For patients with distant or intraperitoneal spread of disease, again, the role of surgery in general is not agreed upon, and it is therefore difficult to give recommendations for an elderly population. In terms of adjuvant therapy, chemotherapy and hormonal therapy are both options. For elderly patients with endometrioid tumors, response rates can be as high as 30 % making this intervention a valid option. For those patients with more poorly differentiated/serous/clear cell tumors, chemotherapy is the standard option for therapy with most choosing paclitaxel and carboplatin at appropriate dose levels based on history of radiation and baseline performance status [63–65].

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Chapter 16
Treatment of Advanced Stage and Recurrent Endometrial Cancer in Elderly Women

Nita Karnik Lee and Gini F. Fleming

Abstract Most women who develop endometrial cancer are postmenopausal and over 40 % are over the age of 65. As the population ages, the burden of endometrial cancer is likely to increase. Age remains a poor prognostic factor with older women often presenting with higher stage and adverse pathology features with subsequent higher recurrence risk and worse survival. Though there is limited data on direct efficacy and toxicity for elderly patients, many significant trials in gynecologic oncology have naturally included older women. Treatment options for elderly women in the advanced and recurrent setting include combination chemotherapy, hormonal therapy, radiation therapy and combined treatment modalities. Balancing the comorbid conditions in the elderly population with treatment tolerance remain challenging for the treating oncologist.

Keywords Endometrial cancer • Advanced stage • Elderly • Radiotherapy • Chemotherapy

Introduction and Epidemiology

The majority of women diagnosed with endometrial cancer are postmenopausal with a median age of 61. According to United States population Surveillance Epidemiology and End Results (SEER) tumor registry data (2004–2008), the age distribution of endometrial cancer incidence is as follows: 45–54 years old (19.3 %), 55–64 (32.1 %), and 65–85+ (40.8 %). As seen in Fig. 16.1, in women younger than 65, only 28 % will be present with advanced disease (stage III or IV), while in contrast in women greater than 75 years of age, 43 % will have advanced disease at presentation [1]. In addition to more often presenting in advanced stages, older

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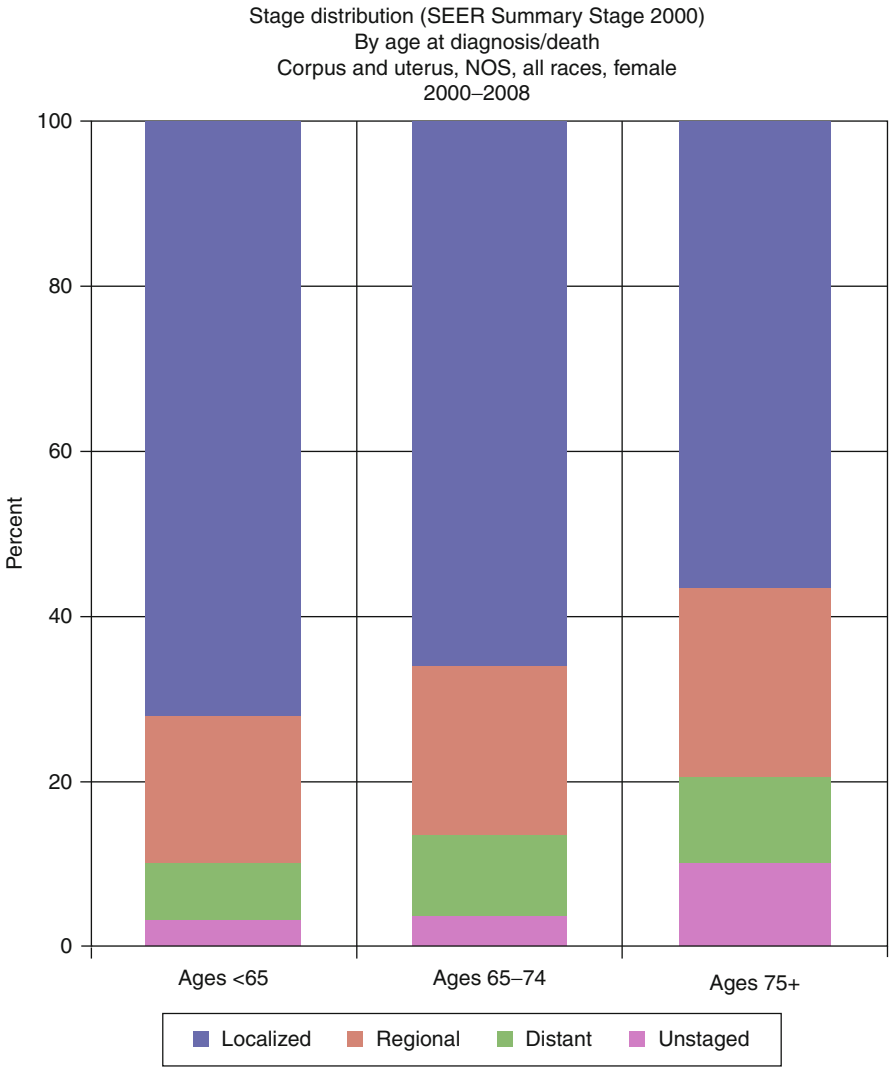

Fig. 16.1 Distribution of stage by age. Fast Stats: An interactive tool for access to SEER cancer statistics (Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/fast-stats. (Accessed on 4-2-2012))

women with early stage disease are more likely to have high-risk histology, deep myometrial invasion, and higher recurrence risk. They have been shown to have worse overall survival and disease-specific survival compared to younger cohorts of patients [2]. This is represented in Fig. 16.2a and b, which demonstrate relative survival rates over time in different age cohorts [1].

A review using SEER data from 1988 to 2001 showed that despite a relatively stable incidence, mortality due to uterine cancer has risen over time. This is attributable to an increased rate of presentation in advanced stage disease as well as a larger proportion of high-risk histology cases [3]. In the multivariate analysis of this data, older age, African-American race, lack of primary staging procedures, advanced stage, high-grade, and non-endometrioid histology were identified as independent

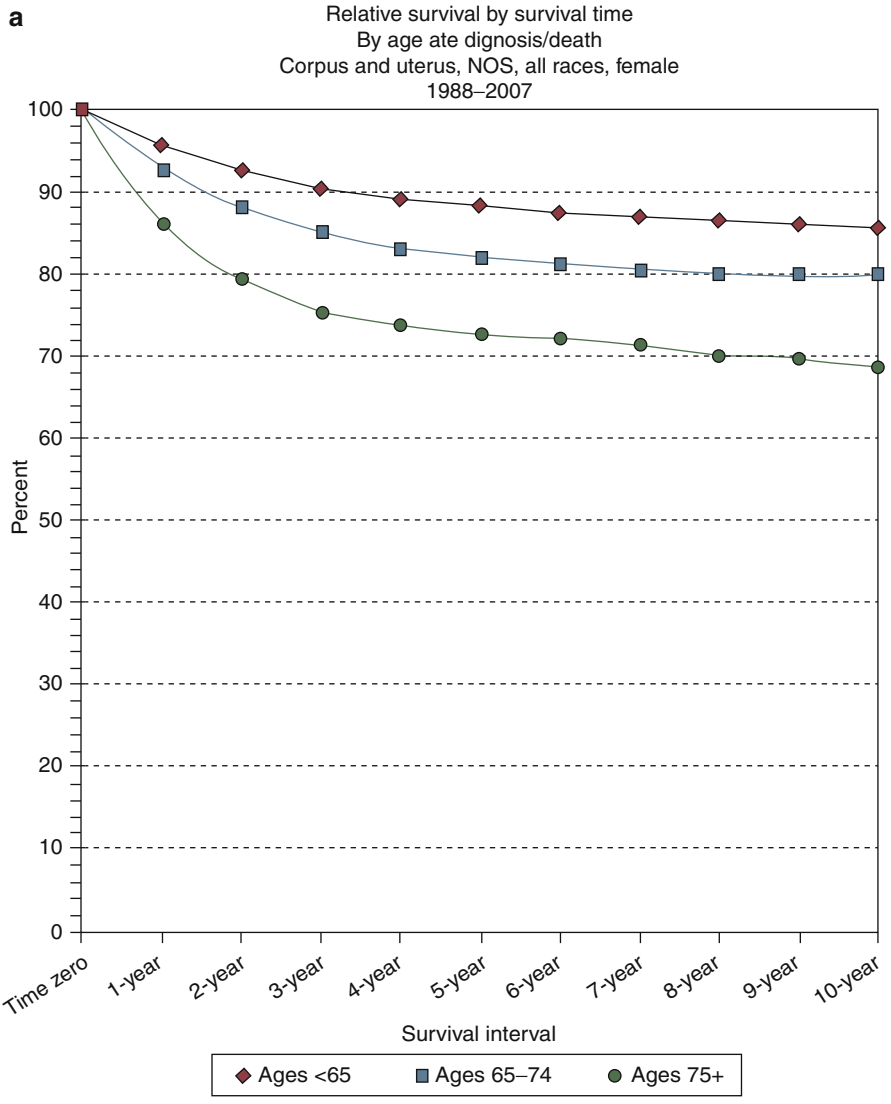

Fig. 16.2 (**a**) Relative survival time by age at diagnosis. (**b**) 5-year relative survival by age cohort

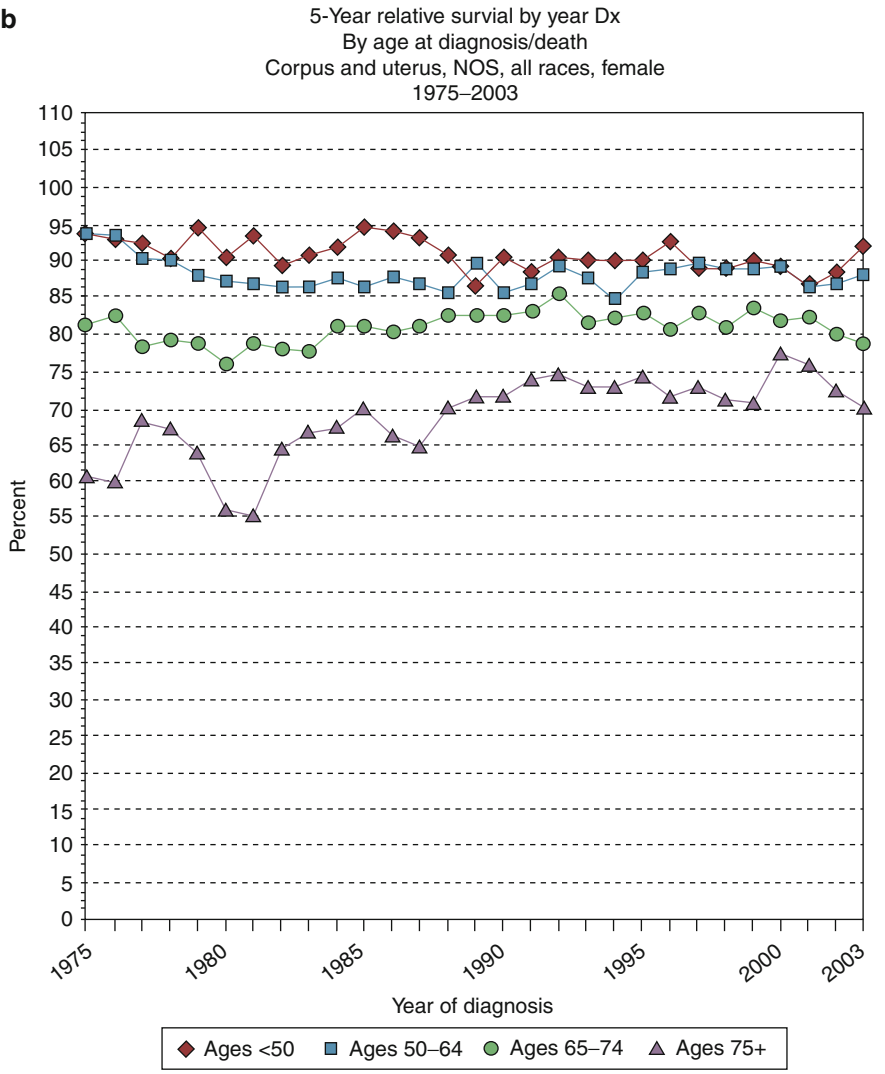

Fig. 16.2 (continued)

risk factors for poor survival. An increasing elderly population will clearly affect endometrial cancer incidence and treatment paradigms in the future.

While age is an established adverse prognostic factor for recurrence and survival in endometrial cancer, select large single-institution studies have suggested that it may not be as strong a prognostic factor when controlled for adverse pathologic factors and for treatment variables including surgery and postoperative therapy [4–6]. Older women are often treated differently from younger women, and there is documentation of

decreased rates of primary surgery and decreased use of adjuvant radiation in the elderly population [2, 7]. It is unclear how much of this is medically necessary caution, how much is related to logistics and preference of the older population, and how much might be inappropriate undertreatment, as there are no validated assessments for predicting which older patients will do well with treatment. The multimodal adjuvant therapy often used for advanced stage disease can cause serious toxicity. Limiting comorbidities such as obesity, hypertension, heart disease, stroke, and diabetes are more common in the elderly population and have unknown or unquantified effects on treatment options and medical decision making for both primary and recurrent disease. Rates of death due to intercurrent disease related to diabetes, obesity, or cardiovascular events remain high in endometrial cancer patients and are increased with age.

Women initially diagnosed with bulky stage III or stage IV disease and those who relapse have a poor prognosis in general. A few patients will have small volume disease that is controlled with resection or radiation, but in general median survival is in the range of only 1 year, and 5-year survival is below 15 % [8]. The advanced stage endometrial cancer population is very diverse and includes patients with lymph node-only disease, peritoneal disease with or without residual disease after surgery, and those with distant or inoperable metastasis. Studies of endometrial cancers generally include the most common endometrioid histology as well as less common unfavorable types such as clear cell carcinoma and serous carcinoma. Development and optimization of treatments that are both effective and well tolerated in this complex population in both first line and subsequent settings is challenging. Current treatment options include systemic chemotherapy, hormonal treatment, local radiation, or multimodal therapy including both chemotherapy and radiation. Biologic agents with novel molecular targets may also hold promise for future treatment. Unfortunately, very few prospective studies have analyzed age as a variable for differences in dosing, toxicity, or efficacy.

Radiation as Definitive Treatment in Non-operable Endometrial Cancer Patients

Standard recommended treatment for early stage endometrial cancer in the United States consists of total hysterectomy and bilateral salpingo-oopherectomy and possible lymph node dissection [9]. Hysterectomy may be performed via traditional laparotomy or minimally invasive techniques including laparoscopy or robotic-assisted surgery. Review of registry data suggests that only 30–40 % of patients with endometrial cancer undergo full staging with lymph node dissection in the United States [10]. Controversy has arisen regarding the benefit and need for systematic lymphadenectomy especially in lower risk patients. Older women, especially women over the age of 80, are less likely to have surgery including hysterectomy and less likely to undergo comprehensive staging including lymph node dissection [2, 7].

The combination of age and significant comorbidities can preclude surgery in patients with endometrial cancer. Physician choices as to who is deemed medically inoperable have not been well studied; however, age is an important clinical factor

often considered. Patient decisions to decline primary surgery are also not well studied or understood. Most studies of definitive radiation therapy for inoperable endometrial cancer are limited in size to 20–40 patients and often represent single-institution data. Primary radiation with external beam pelvic radiation and brachytherapy with either high-dose rate or low-dose rate techniques has been reported to be safe, well tolerated and effective in the elderly population. A representative recent retrospective study in medically inoperable elderly patients over the age of 75 identified 26 women with a median age of 83 who received external pelvic radiation and brachytherapy as primary treatment. Overall survival was 89 and 28 % at 1 and 2 years, while disease-specific survival was 93 % at 1 year and 73 % at 3 years [11]. In this small study, no patients required treatment breaks in the radiation, and only two patients (8 %) were reported to have late toxicity. Balancing the symptomatic benefit of palliation of bleeding and local disease control with the risks of comorbidities that may limit long-term survival makes primary radiation a viable option for select patients.

Postoperative Adjuvant Treatment Options for Advanced Stage Disease

Radiotherapy

Postoperative treatment for more advanced endometrial cancer (stage III-IV) has undergone a transition in the last 10 years from being primarily radiation-based to including consideration of chemotherapy, radiotherapy, or the combination. Chemotherapy, which previously was used primarily for palliation of metastatic or recurrent disease, is now more standard as adjuvant therapy for stage III disease and for earlier stage disease in select situations.

Traditionally, patients with stage III disease (nodal, vaginal, or pelvic extension) were treated postoperatively with pelvic radiation or extended field radiation to encompass the para-aortic nodal areas in patients with advanced disease limited to the pelvis or regional lymph nodes [8]. Whole abdominal irradiation (WAI) was also advocated due to the risk of primary peritoneal involvement or relapse within the abdominal cavity and acceptable progression-free survival and overall survival in published data [12]. WAI is not frequently used today as a result of the GOG 122 study which demonstrated superiority of the chemotherapy arm over WAI, described below.

Radiation tolerance in the elderly patient population has been evaluated in several studies. Pelvic-only radiotherapy in patients with early stage or completely resected stage III disease has been shown to have acceptable toxicity and has been suggested offer improved local control in retrospective studies [13, 14]. In early stage endometrial cancer, age is a prognostic factor and is used along with lymph vascular space invasion, and depth of myometrial invasion to risk stratify patients and define a “high-intermediate risk” group who may benefit in local disease control with either pelvic irradiation or vaginal brachytherapy [15, 16]. The PORTEC-2

trial randomized a high-intermediate risk group of patients to either pelvic radiation or vaginal brachytherapy [17]. Almost all patients were over the age of 60 with 48 % between 60 and 70 years of age and 47.5 % over the age of 70, making this a relevant trial for elderly patients. Overall survival and disease-specific survival were not statistically different between the two arms. Vaginal recurrences also occurred with similar frequency. Estimated 5-year recurrence in the pelvis was slightly higher in the vaginal brachytherapy arm (3.3 % vs. 0.6 %), but this was not statistically significant ($p = 0.06$). The vaginal brachytherapy arm had considerably less acute GI toxicity (12.6 % vs. 53.4 %) and less grade 3 late GI toxicity (<1 % vs. 2 %) but more vaginal atrophy than the external beam pelvic radiation arm.

The Role of Chemotherapy

A landmark GOG trial (GOG 122) randomly assigned 396 evaluable advanced stage patients to either whole abdominal irradiation (WAI) or combination chemotherapy with doxorubicin-cisplatin (AP) [18]. Stage III or IV patients were eligible if they had undergone total hysterectomy, bilateral salping-oopherectomy, surgical staging, and tumor resection and had no more than 2 cm of residual tumor. Nodal sampling was optional. Patients underwent WAI (30 Gy in 20 fractions) followed by additional radiation boosts to the nodal areas (15 Gy) if nodal disease had been found at surgery or if no sampling had been performed. Chemotherapy consisted of doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) (AP) on a 21-day schedule for a total of seven cycles with the eighth cycle consisting of cisplatin only. The study found statistically significant improvements in both progression-free survival and overall survival in the chemotherapy arm. Kaplan-Meier estimates of 5-year PFS were 42 % versus 38 %, and OS was 53 % versus 42 % when comparing AP to WAI. There was, however, greater acute toxicity including hematologic (although this trial was performed prior to the era of routine use of granulocyte colony stimulating factor), GI, cardiac, and neurologic in the AP arm. Chemotherapy appeared to reduce the number of distant relapses but offered slightly less local control than the radiotherapy arm. Of the 396 patients evaluable, approximately 20 % were over the age of 70. In the multivariate analysis, grade 3 tumor, older age (>age 70 years old), serous histology, and African-American race were associated with shorter PFS and OS, but the relative improvement in survival with chemotherapy was the same for older and younger women. Gross residual disease was also associated with shorter PFS but not OS. There were no prescribed chemotherapy dose reductions for older patients.

GOG 122 heralded the widespread use of chemotherapy in the advanced endometrial cancer setting following surgery instead of just in the palliative setting. In addition, the trial led to further investigations into treatment with both chemotherapy and directed pelvic or para-aortic radiation. Volume-directed radiation plus chemotherapy was studied in a subsequent GOG trial (GOG 184) [19]. This study randomized 552 patients who had all received surgical debulking and volume-directed radiation to the pelvic and/or para-aortic nodal areas to chemotherapy with doxorubicin (45 mg/m^2) and cisplatin (50 mg/m^2) (AP) with or without paclitaxel

(160 mg/m^2) (T). After radiation therapy, 80 % of patients were able to complete the planned six cycles of chemotherapy. The use of hematologic growth factor was required in both arms. The median age of patients in both arms was 58, significantly younger than the median age for endometrial cancer in the population at large. In the AP arm of the 270 eligible patients, 16 % were over the age of 69. In the TAP arm with 282 eligible patients, 12.4 % were over the age of 69. There was no difference in recurrence-free survival (RFS) in these two groups (PFS at 36 months, 62 % vs. 64 %) although in subgroup analysis, the TAP regimen was associated with a reduction of recurrence and death in patients with gross residual disease. In multiple variable hazard regression analysis controlling for stage, residual disease, and radiation, age along with histology and grade, positive para-aortic nodes, pelvic metastasis, and positive cytology were significantly negatively associated with RFS. However, treatment effect on PFS did not vary by age. Grade 3–4 acute hematologic toxicity, febrile neutropenia, pain, and neuropathy were all worse with the three drug regimen. There was a 4.7 % rate of late bowel toxicity (grade 3–5) reported. Toxicity data were not broken down by age, and therefore the tolerability of this regimen in the oldest population remains unclear.

Vaginal brachytherapy in combination with chemotherapy has been proposed as a less toxic approach that can still yield the benefit of vaginal disease control in stage III disease or completely resected stage IV disease. It is possible that there is no benefit to adding radiotherapy to chemotherapy in patients with stage III disease, and an ongoing trial, GOG 258, is testing this question. Patients with stage IIIA-IV disease with less than 2 cm of residual tumor or patients with Stage I-II clear cell or serous carcinoma are randomized to pelvic radiation with concurrent cisplatin followed by systemic chemotherapy or chemotherapy alone.

Combination Chemotherapy Regimens in Advanced and Recurrent Endometrial Cancer

Defining the most active regimens while minimizing toxicity remains challenging. A number of randomized phase III trials as seen in Table 16.1 have been performed in the advanced or recurrent endometrial cancer patient population. The patients in these studies had not received prior chemotherapy. Many trials specifically mandated a dose reduction for patients over the age of 65.

In the GOG 107 study, 281 women were randomized to doxorubicin (A) alone (60 mg/m^2) versus doxorubicin (60 mg/m^2) plus cisplatin (50 mg/m^2) (AP) [20]. There was a statistically significant advantage to combination therapy with regard to response rate (RR) (25 % vs. 42 %; $p=0.004$) and PFS (3.8 vs. 5.7 months; HR 0.74 [95 % CI 0.58, 0.94; $p=0.14$), although no difference in OS was observed (9 vs. 9.2 months). As a result the AP arm became a standard chemotherapy combination and the control arm of subsequent randomized trials. Approximately, 35 % of patients in the doxorubicin arm and 33 % in the combination chemotherapy arm were 70 years or older in age. Of note, this trial mandated an automatic initial dose

Table 16.1 Select randomized trials in advanced/metastatic endometrial cancer

Title	Total *N*	Chemotherapy arms	RR (%)	PFS (months)	OS (months)	% elderly in trial (>70)	Mandatory dose reduction for >65 years
GOG 107	281	Doxorubicin	25	3.8	9	35	Yes
		Doxo + Cisplatin	42	5.7	9.2	33	
EORTC 55872	177	Doxorubicin	17		7		No
		Doxo + Cisplatin	43		9		
GOG 163	317	Doxorubicin + Cisplatin	40	7.2	12.6	26	Yes
		Doxo + Paclitaxel	43	6	13.6	27	
GOG 177	273	Doxo + Cisplatin	34	5.3	12.1	21.7	Yes
		Doxo + Cisplatin + Paclitaxel	57	8.3	15.3	23	
GOG 209	1350	Doxo + Cisplatin + Paclitaxel	51.3	13.5	Not available	17.6	No
		Carboplatin + Paclitaxel	51.2	13.3		17.2	

= Statistically significant

reduction of doxorubicin (to 45 mg/m^2) in all patients who had received radiation or were over the age of 65. If no grade 2 or higher toxicities occurred, patients were then dose escalated during subsequent cycles. No subgroup analysis of PFS, OS, number of cycles received, or toxicity in relation to age was reported.

GOG 163 randomized 317 patients to paclitaxel and doxorubicin (TA) or the standard arm of AP for seven cycles [21]. Paclitaxel was given on day 2 at 150 mg/m^2 as a 24-h infusion. As in GOG 107, patients over the age of 65 or those having received pelvic radiation received initial dose reductions. In the AP arm, doxorubicin was given at 45 mg/m^2 (rather than 60 mg/m^2) and cisplatin was 40 mg/m^2 (rather than 50 mg/m^2). In the TA arm, the paclitaxel was reduced to 120 mg/m^2 and the doxorubicin to 40 mg/m^2 in these subgroups. Patients older than 70 accounted for approximately 26–27 % of patients in both arms. This trial did not demonstrate a significant difference in RR, PFS, or OS between the two arms, and thus AP remained the standard of care. Toxicity profiles in both arms were similar, but the paclitaxel-doxorubicin arm had the inconvenience of a 24-h infusion and required the use of granulocyte-colony stimulating factor (G-CSF). None of the above trials analyzed efficacy or toxicity by age; however, a separate pharmacokinetic analysis of data from GOG 163 (for cycle 1 in patients getting the 24-h paclitaxel) showed that paclitaxel clearance was related to patient age, SGOT, and weight, with a change in age from 30 to 80 years resulting in an approximately 39 % expected decrease in paclitaxel clearance [22]. Higher paclitaxel AUC was related to granulocytopenia; the association with neuropathy was not examined.

Until recently, the most effective chemotherapy regimen based on randomized clinical trial data was TAP-based GOG 177 [23]. This study randomized 263 patients to AP (doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2) versus TAP: doxorubicin (45 mg/m^2) and cisplatin (50 mg/m^2) on day 1, followed by paclitaxel (160 mg/m^2 IV over 3 h) on day 2 (with G-CSF support). The AP arm required a starting dose reduction in doxorubicin only (to 45 mg/m^2 in patients over 65 or having prior pelvic radiotherapy). Approximately, 70 % of the patients on the AP arm should have started with this dose reduction due to age or prior radiation, but only 61 % received the reduced dose. 21.7 % of patients on the standard AP arm and 23 % of patients on the TAP arm were over the age of 70. TAP was superior to AP in terms of overall response rate (57 % vs. 34 %; $p<0.01$), median progression-free survival (8.3 vs. 5.3 months; $p<0.01$), and overall survival with a median of 15.3 (TAP) versus 12.3 months (AP) ($p=0.03$). GOG 177 like other prior trials showed that age was associated with decreased PFS and OS.

Toxicity data in GOG 177 revealed 5 deaths attributable to chemotherapy in the TAP arm compared to none in the AP arm. Hematologic toxicity including neutropenia was high in both arms including 50 % in the AP arm and 36 % in the TAP (despite use of upfront G-CSF support). The TAP regimen also demonstrated significantly more peripheral neuropathy with 39 % of patients on this arm experiencing grade 2–3 neuropathy compared to 5 % in the control arm. On a prior phase I study of the TAP regimen using fixed doxorubicin and cisplatin doses and escalating paclitaxel (all with G-CSF support), the effects of age on hematologic toxicity were separately reported. A 10-year increase in age was associated with a 27 % reduction in cycle 1

ANC nadir and an 11 % decrease in platelet nadir. However, of the patients over age 70 treated with the drug doses eventually used in GOG 177, none had dose limiting hematologic toxicities [24]. In GOG 177, the frequency and severity of neutropenia did not differ when analyzed by age greater than or less than 65 years.

Barriers to use of the TAP regimen are its toxicity profile especially in older, fragile patients with other comorbidities or prior extensive radiation and the 3-day dosing schedule as the paclitaxel and the doxorubicin/cisplatin combination were administered on separate days in an attempt to minimize cardiac and neurologic toxicity. GOG 209 was designed to compare the TAP regimen to the potentially less toxic combination of carboplatin and paclitaxel (CT) which had demonstrated tolerability and efficacy in prior smaller studies in endometrial cancer [25, 26]. This was a non-inferiority design in which patients with both stage III and stage IV/advanced/metastatic disease were eligible. Patients were randomized to receive either the TAP regimen similar to GOG 177 or carboplatin and paclitaxel (CT) for a total of seven cycles [27]. Preliminary interim data analysis demonstrated no difference in overall response rate, PFS, or OS between the two arms, but the CT arm had a significantly better toxicity profile. The authors concluded that CT was not inferior to the prior standard of TAP. There are no data reported as yet on elderly specific outcomes, however, CT appears to be a reasonable choice for first line chemotherapy in elderly patients.

Ideally, future reports on chemotherapy trials will collect and separately describe the toxicity data and for older patients, as well as whether there is any apparent difference in efficacy in different age strata.

Chemotherapy Options in the Second-Line Setting

For the subset of patients who have an initial complete response to chemotherapy and relapse more than a few months later, retrial of platinum and/or taxane-containing regimens may produce a second response. There are limited choices in patients who have progressed on or recurred soon after initial first line therapy for advanced/metastatic disease. Performance status, prior pelvic radiotherapy, and extent of disease drive treatment choices in this setting. NCCN guidelines recommend consideration of best supportive care and palliation and/or clinical trials for patients failing first line chemotherapy [9]. There are currently no FDA-approved agents in second or subsequent line treatment for endometrial cancer. As recurrent metastatic endometrial cancer is generally not curable, patient and provider decisions must include frank discussion of goals of therapy, toxicity profile, and quality of life. This is true for patients of any age, but especially for older patients in whom the burden of toxicity and travel may be especially great.

Patients with prior chemotherapy for advanced disease have been studied in various phase 2 trials using single-agent cytotoxic chemotherapy. Most have shown minimal activity with overall response rates ranging from 0 to 9 % [8]. Paclitaxel at 175–200 mg/m^2 every 21 days (GOG129C) appeared effective with an overall response rate of 27 % [28]. However, all of these patients were taxane-naïve, and the

results do not necessarily apply in an era where most patients are treated upfront with paclitaxel. Oxaliplatin was studied and demonstrated a modest activity of overall response rates of 13.5 % even though 96 % of the 52 evaluable patients had received prior platinum [29]. Median duration of response was 10 months. Toxicities included neuropathy, anemia, and nausea/vomiting. Single-agent pegylated doxorubicin (50 mg/m^2) and docetaxel (36 mg/m^2 on D1, 8, 15 of a 28-day cycle) demonstrated more limited overall responses with only 9.5 and 7.7 % (PR only) reported [30, 31]. Ixabepilone, an epothilone, was studied in 50 patients on GOG 129P. 94 % had prior paclitaxel [32]. The overall response rate was 12 % with stable disease in 60 % of patients. Grade 3–4 hematologic toxicity occurred in 52 % of patients, but only 30 % of patients had limited grade 1–2 neurotoxicity making this an interesting agent for future study. There is an ongoing international open label randomized phase III trial (the IXAMPLE2 study) comparing ixabepilone to either doxorubicin or paclitaxel (depending on which agent patient might already have received) in the second-line setting [33]. This study will provide interesting data as well of single-agent doxorubicin in the second-line setting which will be more relevant as it is now less frequently used first line. Most of these single agents are tolerated in elderly patients, although prior neuropathy and hematologic toxicity may mandate dose reductions.

Hormonal Treatment Options

As the majority of endometrial cancers are believed to be hormonally driven tumors, the role of hormonal treatment in both the adjuvant and the advanced or metastatic setting has been widely studied. Progestin treatment can reverse and counteract the stimulatory effects of estrogen on proliferation and promote differentiation and apoptosis by inhibiting ER gene expression and promoting degradation of the estrogen receptor.

Progestin therapy has been studied in the adjuvant setting in both early and advanced stage disease after surgery in order to prevent recurrent disease. Six trials involving over 4,300 women were reviewed in a Cochrane database review and did not demonstrate a survival advantage in postoperative progestin therapy. Risks of venous thromboembolism were as high as 5 % with hormone treatment. In addition, noncancer-related deaths were increased in the progestin-treated groups [34].

Progestins have also been studied in the setting of advanced metastatic or recurrent endometrial cancers. NCCN guidelines include hormonal treatment in the recommendation for treatment in the recurrent metastatic setting [9]. Historically, the overall response rates to progestin therapy are approximately 25 % but range from 8 to 40 % depending on clinical features [8]. The likelihood of response is correlated to grade of the tumor, histology, estrogen and progesterone receptor status, and performance status. Grade 3 tumors, non-endometrioid histology, and receptor negative tumors demonstrate less response to progestins [35, 36]. Progression-free survival intervals of approximately 3 months have been reported. Overall survival in these

studies ranged between 7 and 13 months. The phase II trial of megestrol at 800 mg/day reported an overall response rate of 24 % with 11 % complete responses and 13 % partial responses [36]. Of the 63 patients enrolled, 55 % were over the age of 70. Endometrioid type grade 1–2 tumors generally demonstrated better response rates (37 %), whereas poorly differentiated tumors or serous and clear cell carcinomas had significantly lower response rates at approximately 8 %. There was no difference in response rates between age groups. For the entire evaluable group, median PFS was 2.5 months, and overall survival was 7.6 months. Three deaths due to cardiovascular events were possibly treatment related. Three patients had documented pulmonary embolism and one patient had an arterial thrombosis. Twenty-six percent of patients experienced weight gain. These results were similar to prior studies using more standard dose of 160 mg/day of megestrol and suggested that higher doses did not show advantage [37]. Similarly, no survival advantage or increased response to higher doses of progestins was noted in a separate randomized trial of medroxyprogesterone acetate at 200 mg/day versus 1,000 mg/day [38]. Although the data on thrombosis was not analyzed by age, elderly patients do have an increased risk of thrombosis in general, and the use of progestins warrants caution.

Biologically, the short duration of responses to progestin was hypothesized to be related to downregulation of progesterone receptors overtime with progestin exposure. Tamoxifen was thought to enhance or prolong response to progesterone by binding to estrogen receptors and promoting increased progesterone receptor expression. A number of small trials have evaluated the strategy of combining progestins with tamoxifen. A representative phase 2 trial used alternating megace (80-mg BID) and tamoxifen (20-mg BID) in 3-week intervals [39]. Sixty-one patients (56 evaluable) were enrolled, and the overall response rate was 27 % with 12/56 having complete response and 3/56 having a partial response. In more than half of the responders, the response duration was greater than 20 months. Improved response to treatment was associated with lower grade, younger age, and extra pelvic disease. The median PFS was 2.7 months, and the median OS was 14 months. The combination was generally well tolerated with only five patients with grade 3 or 4 thromboembolic events. Tamoxifen alone had more modest activity (10 %) in a phase 2 trial [40]. Other hormonal targets including aromatase inhibitors (anastrozole) and GnRH agonists (goserelin) showed only minimal activity [41, 42]. Studies using hormonal therapy in addition to chemotherapy have not shown added benefit when compared to chemotherapy alone [8]. The role of hormonal therapy in pretreated patients was recently explored in a randomized phase II trial comparing ridaforolimus to controls of either progestin or chemotherapy in women with 1–2 prior chemotherapy regimens for endometrial cancer. Interim analysis data presented in abstract form demonstrated that the median PFS for the progestin arm was only 1.9 months (vs. 3.6 months for ridaforolimus) [43].

A Cochrane database review of hormonal therapy in advanced and metastatic endometrial analyzed six trials (542 patients) and concluded no overall survival benefit for hormonal therapy in this setting though recognizing the small numbers of patients limited this data [44]. The potential clinical benefit in terms of disease stabilization and quality of life in avoiding cytotoxic regimens is still not well defined.

While hormonal therapy remains an important alternative, the lower responses seen in high-grade and non-endometrioid tumors may limit the overall use of progestins alone in elderly patients who have an increased frequency of these poor prognosis tumors. While hormonal therapy may be better tolerated, it does have a clinically significant risk of thrombosis, and chemotherapy remains the usual choice for first line therapy of advanced endometrial cancers in elderly patients.

Novel Pathways and Targeted Therapies

Over the past several years, multiple novel biologic and targeted agents have been investigated in many solid tumor types including endometrial cancer. Current investigations are promising but no agents are currently FDA approved for use in the advanced metastatic or recurrent endometrial cancer patients. The rationale for targeted agents also reflects further clinical and molecular chararacterization of endometrial cancers. Type I tumors of the endometrium which represent 80 % of all endometrial cancers have known clinical characteristics including younger patients, endometrioid adenocarcinoma histology, and lower grade. These tumors are more usually obesity-associated, have better defined precursor lesions, and are more likely to be hormone receptor positive. The distinct clinical phenotype also shows more distinct molecular changes. Type 1 tumors are more likely to have PTEN loss of function mutations (50–80 %), K-ras mutations (13–26 %), EGFR expression (46 %), and B-catenin gain of function mutations (25–38 %). In contrast, type 2 tumors have a different clinical and molecular profile. Patients with type 2 endometrial cancers are generally older, thin, more likely to have non-endometrioid cell types and high-grade tumors, and less likely to have hormone receptor positive tumors. Molecular mutations that are more common in type 2 tumors include p53 mutations (80–90 %), HER2/neu overexpression, EGFR mutations (36 %), p16 inactivation, and loss or reduced expression of Ecadherin (62–87 %) [45].

A significant majority of endometrioid (type I) endometrial cancers (40–80 %) demonstrate loss of PTEN tumor suppressor function [46]. In addition, approximately 36 % of endometrial cancers can demonstrate other mutations including PI3K mutations leading to constitutive activation of this pathway [47–50]. PIK3CA mutations are seen in type II as well as type I tumors. Because of this profile, inhibitors of the PIK/akt pathway have been studied in endometrial cancers. Temsirolimus, an mTOR inhibitor has been reported to produce a 14 % partial response rate when used in chemotherapy-naïve women with advanced or recurrent endometrial cancer but only had a partial response rate of 4 % in a more heavily pretreated cohort [51]. Interestingly, PTEN loss and molecular markers of this pathway were not associated with response. The most common adverse events on this trial were fatigue, rash, mucositis, and pneumonitis. The median age was 66 in chemo-naïve patients and 60 in patients previously treated. No specific analysis with respect to age was performed. A phase II study testing everolimus, another mTOR inhibitor, in more heavily pretreated endometrial cancer demonstrated a clinical benefit rate (partial response

and/or stable disease) at 8 weeks of 21 % [52]. The median age of patients was 58 and no specific age-related analysis was done. Grade 3–4 adverse effects included fatigue (23 %), nausea (11 %), and lymphopenia (29 %). Though less common and not as severe, lipid abnormalities due to the drug were approximately 15 and 26 % of patients developed mucositis (≤ grade 2). An efficacy and safety review in elderly patients who participated in a randomized placebo-controlled phase III trial of everolimus for metastatic renal cell carcinoma demonstrated similar PFS, OS, and overall response rate in patients over 65 and over 70 years of age [53]. Most toxicity was mild and similar to the general population including stomatitis. Older patients did have more edema, cough, rash, and diarrhea though mostly grade 1–2. Currently, there are no mTOR inhibitors approved for use in endometrial cancer patients; however, active clinical trials of the mTOR inhibitors and other inhibitors of the PI3K/akt/mTOR pathway continue.

Anti-angiogenic therapies represent another class of targeted agents with efficacy in endometrial cancer. Single-agent bevacizumab 15 mg/kg every 3 weeks was studied in a phase II trial (GOG229E) of 52 evaluable patients with 1–2 prior cytotoxic regimens [54]. Treatment consisted of bevacizumab 15 mg/kg IV q 3 weeks until disease progression or prohibitive toxicity. Results showed 13.5 % objective response rate, with 1 complete response and 7 partial responses, and 40.4 % of patients were progression-free at 6 months. Median PFS was 4.2 months. Median overall survival was 10.5 months. This is superior to results obtained in historical GOG trials testing standard cytotoxic agents in similarly pretreated populations. The median age of the patients on GOG 229E trial was 62 and ranged from 32 to 84. No separate age-related analysis was performed.

Extrapolation from other disease sites demonstrates that bevacizumab is tolerable and safe in select elderly patients. The ATHENA study treated locally recurrent/metastatic breast cancer with first line bev with standard chemotherapy. Subgroup analysis was performed for women ≥70 years of age. Only hypertension and proteinuria were found to be significantly higher in older women. Rates of grade 3 arterial or venous thromboembolism were similar [55]. A retrospective pooled analysis of four randomized trials reviewed effect of bevacizumab in metastatic colorectal cancer and demonstrated similar benefit in PFS and OS in both older and younger patients [56]. This review included a total of 3,007 patients and analyzed safety data in relation to age. Bleeding, hypertension, proteinuria, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), wound healing complications, fistulae, GI perforations, and CHF were more common in bevacizumab treatment. Patients less than 65 years had no increase in rates of ATEs or VTEs when comparing treatment with bevacizumab and control groups. In contrast, patients ≥65 years, the ATE rate was 5.7 % in those with bev treatment and 2.5 % in controls. In even older patients (≥70), the ATE rate was 6.7 % versus 3.2 % in controls. VTE rates were not related to age but showed a 1–2 % increase in incidence compared to controls who did not receive bevacizumab. Clinical trials using bevacizumab exclude patients with poorly controlled hypertension and prior CNS ischemic events, and this must be taken into account in the off protocol use of bevacizumab in the elderly patient population. Though not FDA approved for endometrial cancer, bevacizumab

is now listed as category 2B for consideration for patients who have progressed on prior cytotoxic therapy [9]. Combinations of targeted agents are also being developed, for example, bevacizumab and temsirolimus, and consideration for specific toxicities in the elderly will be critical.

A variety of anti-VEGF receptor tyrosine kinase inhibitors (TKIs) are being studied in advanced metastatic endometrial cancer and have demonstrated some activity. Initial data from phase II trials of multiple targeted tyrosine kinase inhibitors have varied. Sorafenib, a multitargeted tyrosine kinase inhibitor, showed only minimal partial response of 5 % with 42 % stable disease rate [57]. More preliminary data in sunitinib (preliminary response rate, 15 %) show a modest response rate of 15 % partial response and acceptable stable disease rates [58]. Several studies involving multitargeted tyrosine kinase inhibitors involved with angiogenesis including cediranib, brivanib are ongoing in endometrial cancers. A review of anti-angiogenic agents including the TKIs suggests specific clinical concerns in using these agents in the elderly population [59]. Review of sunitinib showed female gender and older age to be predictors for more severe toxicity. Drug-induced hypothyroidism remained high with 50–80 % of patients developing hypothyroidism. Patients with preexisting coronary artery disease were at increased risk of sunitinib-associated heart failure. Oral TKIs have also been shown to have a hypoglycemic effect which could be amplified in diabetic patients on oral hypoglycemic agents. Sorafenib demonstrated similar drug safety across age groups, but recommendations for additional cardiac monitoring in older patients is advised.

Several ongoing trials are attempting to integrate novel agents into the first line treatment of advanced endometrial cancer, including GOG 86P, a randomized phase II trial of carboplatin/paclitaxel/bevacizumab versus carboplatin/paclitaxel/temsirolimus versus carboplatin/ixabepilone/bevacizumab in women with chemotherapy-naïve disease. Hopefully, this and future trials will report efficacy and toxicity specifically in elderly patients to help best guide treatment in this complex challenging patient population.

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Chapter 17
Cervical Cancer in the Elderly: Staging and Surgical Management

Amanda L. Jackson and Linda Van Le

Abstract Cervical cancer is the third most common cancer in the world with 85 % of these cases occurring in developing countries [34, 35]. Cervical cancer is clinically staged with the assistance of a detailed physical exam and limited radiologic imaging. Cervical cancer that is limited to the cervix can be treated with surgery, while cervical cancer that has spread beyond the cervix is treated with a combination of radiation and sensitizing chemotherapy. Patients with a central, localized recurrence are also treated surgically with a pelvic exenteration. Elderly patients comprise a small portion of cervical cancer patients, and they are less likely to undergo surgical treatment.

Keywords Surgical management • Cervical cancer • Elderly

Abbreviations

ACRIN	American College of Radiology Imaging Network
CIN	Cervical intraepithelial neoplasia
CKC	Cold knife cone
CT	Computed tomography
FDG	F-fluorodeoxyglucose

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FIGO	International Federation of Gynecology and Obstetrics
GOG	Gynecologic Oncology Group
IVP	Intravenous pyelogram
LEEP	Loop electrosurgical excision procedure
LSIL	Low grade squamous intraepithelial lesion
MRI	Magnetic resonance imaging
N_2O	Nitrous oxide
PET	Positron emission tomography
SEER	Surveillance Epidemiology and End Results
SGO	Society of Gynecologic Oncology

Introduction

Cervical cancer is the third most common cancer in the world. However, 85 % of these cases occur in developing countries [34, 36]. In the United States, cervical cancer makes up less than 3 % of cancers in females with an estimated 12,200 new cases of cervical cancer and 4,210 deaths in 2010 [35]. In comparison there will be 230,000 cases of breast cancer, 106,000 cases of lung cancer, and 126,000 cases of gastrointestinal cancers in women in 2011. The predominance of cervical cancer in developing countries is attributed to the lack of screening in developing nations. The mean age of diagnosis is 51.4 years with a bimodal distribution between ages 30–39 and 60–69 [59]. In ages greater than 70, the risk of developing cervical cancer is approximately 1 in 552, which makes up less than 10 % of new cervical cancer cases [35, 65].

FIGO Staging

A uniform staging system is important to allow for better communication among health professionals and to provide an appropriate prognosis to the patients. The International Federation of Gynecology and Obstetrics (FIGO) clinical staging system for cervical cancer has undergone eight revisions since the development of the first staging system in 1958. An area of significant debate was the definition of microinvasive and early stage cervical cancer. In 1994, FIGO changed the definition of stage IA1 microinvasive cancer from “minimal” microscopic invasion to invasion less than or equal to 3 mm in depth and a width of less than or equal to 7 mm. By defining the limits of microinvasion, FIGO provided a uniform definition to allow improved clinical comparison among practitioners. Prior to 1994, no distinction was made between small and large or “bulky” stage IB cancers even though the difference in survival ranged from 90 to 50 %, respectively [12]. The 1994 revision further divided stage IB cancers into two groups based on tumor size of less than or greater than 4 cm. The FIGO guidelines were again updated in 2008. This current version deleted stage 0 or preinvasive tumors from the staging system. Tumor size was also applied to stage IIA in 2008. The 1994 system classified all patients with extension beyond the uterus to

Table 17.1 FIGO staging of carcinoma of the cervix: 1994 versus 2008

Stage 0	Carcinoma in situ Cervical intraepithelial neoplasia (CIN) 3	Deleted
Stage I	Carcinoma confined to the cervix	
Stage IA	Carcinoma can only be visualized with microscopy	
	Invasion is limited to maximal depth of 5 mm and maximal horizontal spread of 7 mm	
IA1	Depth of invasion is ≤3 mm	Same
	Horizontal spread is ≤7 mm	
IA2	Depth of invasion is >3 mm and ≤5 mm	Same
	Horizontal spread is ≤7 mm	
Stage IB	All macroscopically visible lesions confined to the cervix	
	Microscopic carcinoma greater than stage IA	
IB1	Carcinoma ≤ 4 cm	Same
IB2	Carcinoma > 4 cm	Same
Stage II	Carcinoma extends beyond the uterus	
	Carcinoma does not extend to pelvic wall or lower third of vagina	
IIA	No parametrial involvement	No parametrial involvement
		IIA1 carcinoma is ≤4 cm
		IIA2 carcinoma is >4 cm
IIB	Parametrial involvement	Same
Stage III	Carcinoma extends to pelvic sidewall or lower third of vagina	
	Hydronephrosis or nonfunctioning kidney is present	
IIIA	Lower third of vagina	Same
	No pelvic wall invasion	
IIIB	Carcinoma extends to pelvic wall	Same
	Hydronephrosis or nonfunctioning kidney	
Stage IV	Metastatic disease	
IVA	Carcinoma extends to adjacent organs	Same
IVB	Carcinoma has spread to distant organs	Same

the upper two-thirds of the vagina without parametrial invasion as stage IIA. The new guidelines divided this class into two subdivisions based on tumor size less than or greater than 4 cm [17]. The differentiation between small and bulky tumors is based on evidence that bulky tumors have a higher incidence of metastatic lymph nodes, recurrence, and lower 5-year survival rates [31]. Current FIGO staging, which was updated in 2008 [60], is summarized in Table 17.1.

Diagnostic Procedures

Cervical cancer uses clinical information to assign a stage of disease; surgery is not used to determine staging because not all patients with cervical cancer will undergo surgery. Clinical staging starts with a careful physical exam, which includes inspection

Table 17.2 Imaging and examinations approved to determine FIGO Clinical Stage of cervical cancer

Approved for use in determining clinical stage	Physical examination
	Colposcopy
	Conization (CKC)
	Endocervical curettage
	Hysteroscopy
	Cystoscopy
	Proctoscopy
	Plain film x rays
	Intravenous pyelogram (IVP)
	Barium enema
Not approved for use in determining clinical stage[a]	Computed tomography (CT)
	Magnetic resonance imaging (MRI)
	Positron emission tomography (PET)

[a]These modalities cannot change stage, but can assist in treatment planning

and palpation of the primary tumor through a pelvic and rectal exam. The supraclavicular and groin lymph nodes should also be examined for evidence of metastatic disease. If the patient is unable to tolerate an exam in the office, this exam can be performed with the assistance of anesthesia. In addition to the physical exam, the FIGO system sanctions additional examinations to determine the extent of disease, which are summarized in Table 17.2. These examinations include colposcopy, conization, endocervical curettage, hysteroscopy, cystoscopy, and proctoscopy. Because the burden of cervical cancer is largely in developing countries, FIGO approved additional examinations must be available at any institution, regardless of resources.

Colposcopy uses a microscope to magnify the cervical and vaginal tissues. Acetic acid or an iodine solution (Lugol's) is applied to the cervix to assist in identifying abnormal cells. When there is concern about obtaining an accurate diagnosis, a cold knife cone (CKC) may be performed. Performed under anesthesia, this procedure excises a portion of the cervix producing a specimen for pathologic evaluation; upon histologic review, the size and depth of tumors can be determined. An endocervical curettage is performed to determine if cancer cells are present in the cervical canal. Hysteroscopy and cystoscopy utilize a specialized camera to determine if the cervical cancer extends into the uterine cavity and bladder, respectively. Proctoscopy is undertaken if there is concern that cancer has extended into the rectum. Any areas that are suspicious for extension of the cancer should be biopsied.

Imaging is often used in treatment planning for cervical cancer; however, FIGO only sanctions the use of an intravenous pyelogram (IVP), barium studies of the lower colon and rectum, and radiographic examination of the lungs and skeleton to determine staging. An IVP is used to diagnose obstruction of the urinary tract by compression or extension from the primary tumor. A barium study can be ordered to determine if the cancer is compressing or involving the rectum. Plain film x rays can be used to identify metastatic disease in the lungs and bones.

Additional Radiologic Evaluation

Staging by clinical exam and simple imaging has its limitations. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are often used to improve treatment planning by further determining the extent of disease. These studies however cannot be used to change the clinical stage. When clinical exam and palpation was compared to CT and MRI in German patients, clinical exam was found to have superior accuracy, sensitivity, and specificity (75, 66, and 81 % versus CT 59, 43, and 71 % versus MRI 58, 52, and 63 %) [24].

CT scans are used to determine the extent of disease. A positive lymph node is considered to be greater than 1 cm. The sensitivity of the CT scan to detect nodal disease is reported from 18–71 %. While wide ranges of sensitivities are reported, the specificity is high and is reported as 91–100 % [68]. The use of CT scan to determine cancer extension is limited, and the tumor may appear only as cervical enlargement [58].

MRI has been used to assess paraaortic and pelvic lymph nodes in cervical cancer. The American College of Radiology Imaging Network (ACRIN) 6651/Gynecologic Oncology Group (GOG) 183 study compared MRI and CT for detecting nodal disease, tumor size, and parametrial involvement. MRI had higher correlation with tumor margins and size on final pathology than CT scan [53]. When MRI was compared to PET/CT, MRI was found to be superior to PET/CT for detection of lymph nodes with a sensitivity of 64 % versus 28.6 % [10]. However, in a multicenter study by ACRIN and GOG, CT and MRI were shown to perform similarly in patients with at least stage IB disease [32].

A PET scan utilizes an intravenous injection of radioactive glucose, F-fluorodeoxyglucose (FDG), and a dedicated camera with multiple rings of photon detectors. A complete evaluation for metastatic disease starts at the base of the skull through the top of the femur. Cervical cancer cells are metabolically active and rapidly consume the radioactive glucose. Areas of increased glucose uptake are identified on the PET scan. FDG however is not tumor specific, and inflammation and infection can lead to false positives. Because the scan is imaging metabolically active areas, it is important for the patient to fast for 4–6 h prior to the study. The scan is performed 60 min after injection of FDG.

PET imaging alone has a low sensitivity 53 % and a high specificity 90 % for detecting pelvic lymph node disease [72]. Positive lymph nodes on PET imaging correlate with clinical stage prognosis and outcome. Distant nodal disease is associated with increased risk of recurrence compared to positive pelvic nodes [40]. The standardized uptake value of pelvic lymph nodes on PET imaging has been found to be a prognostic biomarker of survival or treatment response. A higher standardized uptake value of the pelvic lymph nodes is associated with persistent disease after treatment, increased recurrence, and worse overall survival. The standardized uptake value of the cervix was not found to be an independent predictor [41]. The metabolic PET imaging can also be combined with the anatomical images of a CT or MRI to help delineate the area of cancer and metastatic disease.

The combined imaging increases the sensitivity and specificity for determining nodal metastases [33, 43].

With the additional information obtained with modern imaging, the utility of surgical staging has been evaluated for cervical cancer. Surgical staging included paraaortic lymph and pelvic lymph node dissection, pelvic cytology, and peritoneal biopsies. The experience at University of Southern California Medical Center showed that only 2.5 % of patients with advanced stage cervical cancer would benefit from the information obtained from surgical staging [47].

The 2008 FIGO guidelines did not include the use of CT, MRI, or PET in the staging guidelines; however, the FIGO committee encourages the use of these modalities to assist in evaluation of the extension and size of the tumor [17]. In 2009, the members of the Society of Gynecologic Oncology (SGO) were surveyed on their use of imaging in the evaluation of patients with a new diagnosis of cervical cancer. Eighty-three percent of members routinely order a CT scan while 28 % of members routinely order a PET/CT. Members reported that they were more likely to order a PET/CT if disease was advanced at presentation [44].

Clinical Staging

Cervical cancer confined to the cervix is defined as stage I. If the cancer can only be visualized with the assistance of a microscope, the cancer is classified as stage IA, which is further subdivided based on tumor size. Stage IA1 encompasses tumors that have an invasion that is less than 3 mm in depth and less than 7 mm in lateral spread, while stage IA2 included tumors with invasion greater than or equal to 3 mm but less than 5 mm and less than 7 mm of lateral spread. However, if the tumor is larger than the limits of stage IA2 even if the tumor is microscopic, the tumor is allotted to stage IB. Stage IB encompasses large microscopic tumors as well as clinical visible lesions confined to the cervix. The greatest dimension of the tumor is used to further divide stage IB; stage IB1 includes lesions that are equal or less than 4 cm, while stage IB2 includes all tumors greater than 4 cm.

When the tumor extends beyond the uterus and cervix into the upper two-thirds of the vagina, but not into the pelvic sidewall, the cancer is determined to be stage II. Stage IIA includes lesions without parametrial invasion and is subclassified into tumors less than 4 cm and greater than 4 cm in greatest dimension. If there is parametrial involvement regardless of tumor size, the lesion will classified as stage IIB. Stage III includes tumors that extend into the pelvic wall, the lower third of the vagina or result in hydronephrosis or a nonfunctioning kidney. Involvement of the lower third of the vagina without sidewall involvement or hydronephrosis is stage IIIA; if sidewall involvement or hydronephrosis is present, the lesion is stage IIIB. Pelvic wall involvement is determined if there is no cancer-free space between the tumor and the pelvic wall on palpation on rectal examination. Stage IV is when the carcinoma extends into the bladder or rectal mucosa (stage IVA) or extends beyond the true pelvis (stage IVB).

Surgical Treatment of Preinvasive Lesions

Preinvasive lesions of the cervix include cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ (AIS). CIN or cervical dysplasia is the precursor to squamous cell carcinoma of the cervix. AIS is the precursor for adenocarcinoma of the cervix. The treatment options for preinvasive lesions include close observation, cryotherapy, loop electrosurgical excision procedure (LEEP), CKC, and simple hysterectomy.

Cryotherapy is an appropriate treatment for persistent CIN 1, but not for CIN 2–3. Following cryosurgery, 90 % of patients will have a primary complete response. The technique utilizes compressed nitrous oxide (N_2O), which crystallizes the water inside a cell causing the cell to die. The compressed nitrous oxide is applied through a probe that covers the cervical lesion and the transformation zone. Improved results have been achieved with a freeze-thaw-freeze technique, where a second application is applied after the tissue has thawed from the first application. After the procedure, patients should be counseled that a malodorous watery discharge could be present for several weeks.

A LEEP is another treatment. A LEEP is performed by passing an electrocautery loop through the surface of the cervix and obtaining a specimen that can be evaluated histologically. This procedure is somewhat similar to a CKC. Postoperative bleeding can occur in approximately 5 % of patients, and patients should be counseled to avoid intercourse and tampons for several weeks, which could increase the chance of bleeding. Response rates approach 95 % following a LEEP.

An excisional cervical conization or a CKC is excision of a cervical lesion using a scalpel in an operating room setting. The benefits of an excisional cervical cone allow for interpretation of margins because there is no cautery effect. This is also the indicated procedure for adenocarcinoma in situ to rule out malignancy given the skip lesion nature of this cancer and the high incidence of underlying malignancy.

All of the above procedures are considered minor surgical procedures performed predominantly for the treatment of preinvasive disease. In some cases, the CKC can be therapeutic as well. The majority of cases of preinvasive disease occur in younger women where maintenance of fertility is a major goal. Preinvasive disease occurs most commonly in premenopausal women and less frequently in postmenopausal women and the elderly; thus, these procedures are offered less frequently to this group of patients.

Major Surgical Procedures

Definitive surgery is more often considered in women who are no longer considering childbearing, postmenopausal women, and elderly women. In this population, a hysterectomy can be offered for the treatment of preinvasive lesions such as CIN

and AIS after a diagnostic excisional procedure has been performed to rule out an underlying malignancy. A hysterectomy can be considered if the patient has completed childbearing and has persistent dysplasia or if the patient has a coexistent gynecologic condition such as dysfunctional uterine bleeding, ovarian mass, prolapse, or symptomatic fibroids. However, because AIS is found in skip lesions, a woman who has completed childbearing should undergo a hysterectomy since persistent AIS can be found in the cervix at the time of hysterectomy.

Simple hysterectomy is curative for microinvasive disease. However, women with more advanced disease such as stage IB1–IIA carcinoma of the cervix can be treated with a radical hysterectomy or with chemoradiation. Studies have shown similar survival results for both forms of treatment [37, 55, 56]. Surgical treatment allows ovarian conservation that is a benefit to younger patients. In contrast when radiation is chosen as primary therapy, the ovaries are often caught in the radiated field. A surgical approach also has the advantage of obtaining definitive histologic evaluation of the pelvic lymph nodes, which is a significant prognostic risk factor. Radiotherapy is often chosen for ease of administration in obese patients, in the elderly, and in patients with significant comorbidities that contraindicate surgery. In patients with IB2 cervical cancer, surgery with tailored adjuvant therapy was more cost-effective than chemoradiation in patients with no evidence of metastatic disease on PET scan [37]. Review of the Surveillance Epidemiology and End Results (SEER) database [2] found that radical hysterectomy was superior to radiation with a 49 % decrease in mortality if the tumor was less than 6 cm. Tumors which were greater than 6 cm in diameter had similar outcomes with either treatment modalities.

In stage IB1-IIA cervical cancer where there is invasive disease, a radical hysterectomy can be offered. Compared to a simple hysterectomy, this is a longer procedure that has traditionally been associated with more blood loss, longer operating time, and risk of injury to more organs (see section Surgical Complications).

A radical hysterectomy is classified into five categories, which are listed in Table 17.3. A type 1 "radical hysterectomy" is actually a simple hysterectomy, which can be offered for stage IA1 disease where there is minimal invasive disease. Stage IA2 disease is treated with a modified radical hysterectomy or a type 2 hysterectomy. The uterine artery in a modified hysterectomy is ligated where it crosses the ureters, which allows resection of the medial portion of the cardinal ligament and the proximal portion of the uterosacral ligament. The top third of the vagina is sacrificed to obtain adequate margins. Stage IB to IIA cervical cancer is treated with a type 3 radical hysterectomy where the uterine artery is taken from its origin from the superior vesical artery, which allows resection of the entire cardinal ligament and the uterosacral ligament. Up to the upper half of the vagina is resected. Type 4 and 5 radical hysterectomies are used for local recurrences or when the disease is found to be more extensive at the time of surgery. In a type 4 or an extended radical hysterectomy, the superior vesical artery is ligated. The ureter is completely dissected from the vesicouterine ligament, and the upper three-fourths of the vagina is resected. A partial exenteration or a type 5 radical hysterectomy is when a portion of the bladder and or ureters is resected to obtain disease-free margins. If the ureters are resected, they are reimplanted into the bladder at the time of surgery.

Table 17.3 Types of radical hysterectomy

Type	Description	Uses
1	Extrafascial hysterectomy: simple hysterectomy.	CIN3 Stage IA1 carcinoma
2	Modified radical hysterectomy: the uterine artery is ligated as it crosses the ureter. Resection of the proximal uterosacral ligaments and the medial cardinal ligaments. Top third of the vagina can be resected to ensure clear margins.	Stage IA2 carcinoma
3	Radical hysterectomy: the uterine artery is ligated at its origin. The entire cardinal ligament is resected as well as the uterosacral ligaments and the upper half of the vagina.	Stage IB-IIA carcinoma
4	Extended radical hysterectomy: a type 3 radical hysterectomy is performed. In addition, the ureters are completely dissected away from the vesicouterine ligament and the superior vesicle artery is transected. Three-fourths of the vagina is resected.	Small central recurrences after radiation
5	Partial exenteration: radical hysterectomy is performed in addition to excision of the involved ureters and/or bladder. The ureters are reimplanted into the bladder.	Central recurrence involving a portion of the bladder. Unexpected extension of carcinoma into ureters or bladder at time of primary surgery

The initial approach of the radical hysterectomy was through a laparotomy where either a low transverse incision with transection of the rectus muscles or a midline vertical incision can be utilized. The paravesical and pararectal spaces are developed with sharp and blunt dissection to skeletonize the cardinal ligaments. The paravesical space is bordered by the cardinal ligament posteriorly, the superior vesicle artery medially, the pubic bone anteriorly, and the obturator internus muscle laterally. The pararectal space utilizes the cardinal ligament as its anterior border while the rectum forms the medial border, the sacrum the posterior border, and the hypogastric artery is the lateral border. Great care is then taken to skeletonize the uterine artery to its origin from the superior vesicle and to dissect the ureters away from the cervix, uterine artery, and bladder. A pelvic lymph node dissection is performed with a radical hysterectomy.

In a survey of the SGO, 91 % of reporting members offered a laparoscopic approach to cancer surgery. While 87 % of endometrial cancers cases are performed laparoscopically, only 37 % of cervical cancer surgeries are undertaken using a laparoscopic approach [49]. The smaller portion of cervical cancer cases being performed laparoscopically may be due to the limitations of 2 dimensional images and straight stick instruments. While no survival data has been published, the robotic-assisted radical hysterectomy is a feasible approach [42]. The robotic radical hysterectomy is associated with longer operative times, but the approach offers less blood loss and shorter hospital stays. When comparing complication rates, there is no statistical difference between the two approaches [45, 50, 51].

Surgical Complications

Given the close proximity to the rectum, bladder, ureters, and pelvic vessels and nerves, these structures are most commonly injured during a radical hysterectomy. With a laparotomy approach, blood loss is reported to be between 222 and 665 mL [45, 50]. The blood loss is reported to be lower with a laparoscopic or robotic approach with an average of 78–335 mL [42, 50]. Thromboembolic events are also a common after radical hysterectomy.

Intraoperative urologic injuries can include cystotomy to the bladder and injury of the ureters. Given the extensive dissection around the bladder, a urinary catheter is usually placed postoperatively for at least a week to decrease the amount of bladder dysfunction. The prolonged placement of the urinary catheter is associated with urinary tract infection. Postoperatively vesicovaginal or ureterovaginal fistulas have been reported to occur in 1 % of cases.

Surgery for Recurrence

Early stage cervical cancer has 5-year survival of 75.7–97.5 % while advanced stage cervical cancer has a survival from 22–73.4 %. Survival by stage is reported in Table 17.4. Recurrence of cervix cancer either locally or manifested as distant metastases is an ominous occurrence. Salvage rates are low. Chemotherapy and radiation therapy are viable options; however in certain cases a total pelvic exenteration is a surgical option for women with a localized central recurrence with no evidence of metastatic disease. Alexander Brunschwig first introduced the exenteration for treatment of cervical cancer [6]. Historically, some stage IVA cervical cancers were treated with a pelvic exenteration; however, given advances in chemotherapy and radiation, this approach is rarely utilized. While not common practice, case reports show the possible utility of a pelvic exenteration as a first line treatment in women with locally advanced cervical cancer [20].

The surgery encompasses removal of the pelvic viscera, including the uterus, bladder, rectum, and vagina together, or in en bloc fashion. An anterior exenteration is limited to the removal of the anterior organs including the bladder, uterus, and various amounts of the vagina while a posterior exenteration involves removing only the posterior pelvic organs including the rectum, sigmoid, anus, uterus, and portion of the vagina. The approach of an exenteration has traditionally been through a laparotomy. The robotic approach is being utilized for anterior exenteration for bladder cancer [39, 61]. Case reports indicate that a robotic approach may be feasible for an exenteration for recurrent cervical cancer [13, 71]. Because of the extensive surgery and reconstruction required, this procedure is often performed in conjunction with plastic surgery and urology.

A pelvic exenteration requires the appropriate patient. Patients need to have appropriate social support and understanding of the procedure prior to undertaking an exenteration given the prolonged convalescence period, the high risk of

Table 17.4 Survival based on FIGO clinical stage

		Overall survival		
FIGO stage	Number of patients	1 year	2 years	5 years
IA1	829	99.8	99.5	97.5
IA2	275	98.5	96.9	94.8
IB1	3,020	98.2	95.0	89.1
IB2	1,090	95.8	88.3	75.7
IIA	1,007	96.1	88.3	73.4
IIB	2,510	91.7	79.8	65.8
IIIA	211	76.7	59.8	39.7
IIIB	2,028	77.9	59.5	41.5
IVA	326	51.9	35.1	22.0
IVB	343	42.2	22.7	9.3

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complications, and permanent long-term sequelae. The morbidity of this procedure can be as high as 60 %, and complications include development of bowel or urinary fistulas, bowel obstructions, extensive blood loss, and prolonged hospital stay [51]. The average blood loss reported from large retrospective evaluations is 1.2–3.5 L [4, 51, 69]. The average length of stay in the hospital following an exenteration is 21.6–26 days [4, 69]. The mortality of this procedure is 0–9.2 %. The rate is declining and is below 5 % in most major institutions with refinements in intraoperative technique such as the routine use of surgical staplers and reconstruction techniques and advancements in postoperative care including in the intensive care unit [4, 48, 69]. Given the high morbidity and mortality of the surgery, the appropriate candidate for an exenteration should only have a localized recurrence without hydronephrosis, sidewall extension, or metastatic disease.

When considering an exenteration, a complete physical exam should be performed including a rectovaginal exam and palpation of the groin and supraclavicular lymph nodes. The classic triad of unilateral leg swelling, ureteral obstruction, and sciatic pain is highly predictive of sidewall extension [54]. An area concerning for metastatic disease should be biopsied prior to attempting surgery. Metastatic disease should be thoroughly excluded with the use of additional imaging techniques such as a PET/CT scan. PET/CT can diagnose distant metastasis at the time of recurrence with 100 % specificity and 94 % positive predictive value. A high sensitivity of the PET/CT is associated with diagnosis of spinal, liver, and extrapelvic lymph node metastasis, but a low sensitivity is associated with detection of small lung metastasis [38]. The presence of extensive disease would increase the risk of future recurrence, and therefore, would limit the utility of this morbid procedure. Positive margins highlight this risk. The 5-year survival decreased from 50 % in patients with negative margins to 10 % in patients with positive margins [18].

At the time of surgery, the entire abdomen should be explored for metastatic disease. If extensive disease or metastatic disease is found at the time of surgery, the exenteration should be aborted. If lymph nodes are enlarged on palpation, they should

be sampled and sent for frozen section. If pathology is consistent with positive lymph nodes, the procedure should also be aborted. Positive lymph nodes have been correlated with a decreased survival. Patients with negative lymph nodes have 60 % 5-year survival rate while survival is decreased to 30 % in patients with positive lymph nodes [50, 51]. However, other studies show no association with nodal status and survival and question the exclusion of these patients [3]. Approximately 30 % of patients are found to be unsuitable candidates intraoperatively due to intraoperative findings of nodal involvement, distant disease (bowel/liver), or parametrial fixation [52]. Other poor prognostic indicators are tumor size > 3 cm, recurrence within 1 year from initial treatment, lymph node involvement, and sidewall involvement [48, 67]. In a the 20-year experience at Barnes-Jewish Hospital younger age at time of surgery and negative margins were associated with longer disease-free survival [3].

Patients also need to have a complete health screening to ensure that comorbid conditions are not present that would put the patient at higher risk for intraoperative complications such as myocardial infarction, pulmonary embolism, heart failure, stroke, or organ failure. An appropriate patient should be able to tolerate a prolonged procedure, large fluid shifts, and blood loss. The average operative time is 7–8 h [4, 51, 69]. In the postoperative period, infection is a common complication. Studies report 58–86 % of patients will experience wound infections, urinary tract infections, development of an abscess, or sepsis [4, 48]. In the late postoperative period, bowel obstructions occur in 9–22 % while fistulas occur in 23 % (8 % urinary 15 % bowel) [4, 22]. The average 5-year survival rates are 40–54 % [4, 22, 69].

While a total pelvic exenteration includes a cystectomy, the bladder can be reconstructed using a portion of the ileum, ascending colon, or transverse colon. Bricker first described this procedure in 1950 where he utilized a loop of ileum [5]. His novel procedure replaced the previously used wet colostomy where the ureters were reimplanted into the colon and the terminal end was brought up as a colostomy. The ileal neobladder offered benefits over the wet colostomy, which had high rates of pyelonephritis, renal failure, and hyperchloremic acidosis [16]. However, because the ileum is in the radiation field, the reanastamosis site of the ileum can have a high rate of small bowel fistula formation and the risk for a small bowel obstruction [15]. Portions of the ascending and transverse colon have also been utilized. The colon especially the transverse colon is less likely to have fibrosis from radiation, and the transverse colon, therefore, may have an increased rate of healing. Because the colon absorbs water, sodium, and chloride, hyponatremia, hyperkalemia, and hypochloremic acidosis can occur if drainage is blocked from a stomal stricture. The complications of urinary conduits include pyelonephritis, neobladder anastomotic leakage, urinary fistulas, ureteral strictures, urinary incontinence, and stone formation [1, 19, 26, 27]. Over time, 60 % of patients will experience a complication from their urinary conduit.

Avoiding a colostomy may also improve a patient's perceived quality of life. If the rectum is excised approximately 2–3 cm from the anal canal, the rectum retains the urge to defecate, the rectal anal reflex, and the support of the levator muscle, which improves fecal continence and storage [25]. A colonic J-pouch rectal anastomosis can increase rectal compliance when compared with direct reanastomosis. The colonic J pouch has been shown to improve continence of stool and flatus,

improved control of urge to defecate, and decrease anastomotic leaks [30]. The success of a reanastomosis is related to the blood supply of the rectum, the tension of the anastomosis and the remaining amount of rectum [63]. Some patients have difficulty completely emptying the J pouch. A smaller J pouch has been shown to have better evacuation rates than larger pouches [29].

The vagina can be recreated using the assistance of flaps. The neovagina is beneficial because by filling the pelvis with tissue with adequate blood supply it can decrease abscess and fistula formation. Over a 17 year experience, investigators have demonstrated a decreased in complication rate when a gracilis myocutaneous flap was used to reconstruct the vagina and fill the pelvic floor [69]. Placement of a flap allows a patient to regain some sexual function and could improve overall quality of life. Patients with vaginal capacity have improved scores in all areas of quality of life based on a prospective study of patients undergoing an exenteration [28]. In the elderly patient, maintaining vaginal function needs to be discussed individually with each patient. The benefits of vaginal reconstruction should be weighed against the longer operating time and risk of infection and complications.

Pelvic exenterations are long procedures that are associated with many complications. Given the number of medical comorbidities associated with aging, many elderly patients are usually not considered for this procedure when recurrence in the pelvis occurs.

Novel Surgery

Radical trachelectomy has been considered an option to radical hysterectomy for early invasive cervical cancers [57]. The radical trachelectomy is composed of a wide dissection of the complete cervix and pelvic lymphadenectomy. The objective of this approach is to spare the uterus so that childbearing options are preserved. Viable pregnancies have been recorded after patients have undergone this procedure. However, for the elderly patient uterine preservation for this purpose is not relevant.

A robotic minimally invasive procedure is rapidly gaining acceptance as the optimal approach to performing a radical hysterectomy. The robotic system offers three-dimensional view, ergonomic surgeon positioning, and articulated wrist maneuvers, all which lend to improved operative precision and dexterity. Patients undergoing a robotic approach to surgery experience reduced blood loss, lower operative morbidity, and improved postoperative recovery [64].

Surgery and the Elderly

The incidence of cancer increases with age with the greatest portion of cancer occurring in the population greater than 65 [73, 74]. With the second peak of cervical cancer occurring in the seventh decade of life and with the rapidly aging

population, which will reach 72 million in 2030 [70], the treatment of cancer in the elderly population is a significant issue. Elderly patients present at a more advanced stage, often receive inadequate treatment, and have a lower survival rate [23]. The morbidity and mortality of a radical hysterectomy in patients greater than 65 years has not been demonstrated to be different from a younger cohort [21].

Age at the time of diagnosis appears to be an important factor in treatment choice by patients and their providers. In a population-based study of cervical cancer in the Netherlands [14], elderly patients made up a small portion of the cases with 5 % of patients aged greater than 70 years old. In patients with stage IB–IIA disease, 50 % of patients aged 70 years or older underwent primary radiotherapy while only 8 % of patients younger than 50 years old underwent radiotherapy as primary treatment. Of the patients with advanced disease older than 70 years old, 12 % of patients opted to undergo no treatment. In this study, survival was influenced by stage and treatment choice, but not by age at diagnosis. A review of the SEER database [66] demonstrated that women older than 70 were less likely to undergo surgery or adjuvant treatment. Similarly, in a study of women who were at least 85 years old with a new diagnosis of cervical cancer, 100 % of patients were treated with radiation [8]. A study from China showed that in stage I–II disease, women greater than 70 years old had similar survival rates when treated with external beam and high-dose brachytherapy as surgical treatment [9]. However, Sharma and associates [66] showed that the rate of brachytherapy declined with age in patients with stage IIB–IV4.

The effect of patient age on outcome appears to be variable. Studies [7, 11] show that age at diagnosis significantly decreases survival even when comorbidities are controlled and that older age is associated with a more advanced stage at diagnosis. Another study [46] showed that patients between the ages of 60 and 69 had improved survival rates when compared to younger patients. Since all patients greater than age 65 have access to the Medicare system, no significant differences in survival were found based on race or socioeconomic status [11].

Conclusion

Cervical cancer constitutes a minority of the cancer burden in this country. Early stage disease can be treated by surgery or radiation therapy. Surgical treatment can be tailored to preserve special needs of the reproductive age women such as vaginal length and integrity and ovarian preservation. These needs may be not be important to the elderly patient who additionally, due to medical comorbidities associated with aging, may not be suited to primary surgical therapy. Select cases of recurrent disease can be treated with pelvic exenteration. While outcomes and complications associated with this long multipart procedure have improved with better surgical technique and postoperative innovative care, the patient for whom exenteration is offered needs to be selected with care.

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Chapter 18
Cervical Cancer: Advanced Stage and Relapse Treatment – Standard and Experimental Therapy

Kimberly L. Levinson and Peter G. Rose

Abstract Cervical cancer is a common gynecologic cancer in women greater than age 65. The standard treatment for advanced disease in the general population is chemoradiation, and evidence suggests that elderly patients tolerate radiation therapy well. More prospective trials are needed in the elderly population to determine the superiority of chemoradiation over radiation alone or neoadjuvant chemotherapy followed by surgery. The standard treatment of metastatic or recurrent cervical cancer is chemotherapy. While studies suggest that age alone should not influence the use of chemotherapy in the elderly population, physiologic changes, medical comorbidities, and performance status of each individual must be considered. Dose reductions or altered regimens may therefore be appropriate. Several new therapeutic drugs and strategies are currently under investigation for advanced disease as well as metastatic and recurrent disease, and prospective evidence specific to this population will be needed to evaluate the efficacy of these strategies for elderly women with cervical cancer.

Keywords Cervical cancer • Elderly • Chemoradiation • Chemotherapy

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Introduction

Cervical cancer has a bimodal distribution of incidence, with peaks at ages 30–39 and 60–69 [1]. As a consequence, a significant number of elderly women are affected by cervical cancer, with approximately 27 % of cervical cancers occurring in patients over 65 years of age [2]. The risk of developing cervical cancer for a woman who is over the age of 65 is approximately 10 % higher than that of a woman between the ages of 40–65, and the risk of cancer-related death in this age group is also significantly higher with women who develop the disease after the age of 65 having a 50 % greater risk of dying from it than women age 40–64 [3]. This may be partially due to the fact that approximately 16 % of elderly women (≥65) with stage IIB/IV cervical cancer never receive treatment for their disease [4].

Locally Advanced Disease

Locally advanced cervical cancer is defined as stage IIB–IVA. While approximately 32 % of all cervical cancers present between stages IIB–IVA [5], older women tend to present with less localized tumors and more advanced stage of disease at the time of diagnosis. This may be partially due to the facts that older women are less likely to have had recent screening for cervical cancer, and they are also more likely to tolerate symptoms for a longer time before presenting to a physician [3]. Current screening recommendations from both the American Cancer Society and the American College of Obstetricians and Gynecologists advise that women over the age of 65–70 may stop routine screening for cervical cancer if they have had three negative pap smears in a row and no abnormal pap smears within the past 10 years [6, 7]. Therefore, many women older women are told to stop screening, and for those high-risk women who might be advised to continue screening, many elect not to present for a pap smear. Additionally, there are age-related social and anatomic factors that can also contribute to increased incidence of locally advanced disease in the elderly population. False-negative rates for pap smears may be higher due to the location of the squamocolumnar junction, and colposcopy may also be less sensitive [3].

Radiation Therapy in the Elderly Population

From 1950 through 1999, the standard therapy for locally advanced disease in the general population was radiation therapy [5]. Radiation therapy in the elderly population has been studied extensively, and although some biological and molecular data indicate an increase in radiation toxicity with advanced age, there is no convincing evidence from either animal studies or clinical studies to indicate that

radiation therapy is generally less well tolerated by the elderly [8]. Alternatively, most studies do suggest that elderly patients tolerate radiation therapy well [9, 10] and have comparable tumor response rates and survival rates when compared to younger patients [11]. In a large retrospective study (727 patients), Ikushima et al. showed that there were no differences in disease-specific survival rates or morbidity from radiation therapy between "young patients" (<65), "young-old patients" (65–74), and "old patients" (≥75, with a range up to 92) [12]. Lindegaard et al. did a prospective analysis of 114 patients between the ages of 70–85.9 who were referred for curative radiotherapy; 81 of these patients had stage IIB disease or greater. Results suggested that elderly patients tolerate radiotherapy (including both brachytherapy and external beam radiotherapy) well, with good completion rates, reasonable toxicity profile, and excellent 5-year survival rates [13].

While radiation therapy appears to be efficacious and tolerated reasonably well in the elderly population, there may be important dose-limiting factors or toxicities, which differ from those in a younger population. Some age-specific considerations may include an increase in incidence of uterine or vaginal perforation with difficulty with insertion of the tandem in older patients [13] and a higher prevalence of sexual dysfunction. On the other hand, younger patients tend to suffer more from acute toxicity during pelvic radiation, including skin damage, nausea, and deterioration of performance status [8]. Despite some qualitative differences in the toxicities experienced from radiation therapy, studies suggest that acute and late radiation morbidity affect young and old patients in the same proportions [14].

While studies have shown that age itself should not influence the dose or dose intensity of therapy, there is an increased incidence of concurrent disease in the elderly population, and this may affect patients' reactions to radiation therapy. For example, extensive concomitant atherosclerotic vessel damage is more common in the elderly population, and, when present, should be considered in the decision for dose intensity of radiation therapy. Additionally, older patients may require close monitoring during radiation therapy, since the loss of electrolytes or fluid may not be well tolerated [8].

Chemoradiation in the Elderly Population

Since 1999, concurrent chemoradiation, rather than radiation therapy alone, has been considered the standard treatment for locally advanced cervical cancer. This therapeutic change was based on five randomized controlled trials (RCTs) that established an increase in overall survival with chemoradiation as compared to radiation therapy alone [5]. However, although RCTs have established chemoradiation as the standard of care for advanced disease for the female population in general, few elderly patients were included in these trials. Specifically, in one of these trials, the median age of enrolled women was only 47 [15], and in another of the studies, the median age of the women was 41 and 38 in each of the two

Table 18.1 Age distribution of RCT chemoradiation studies

Author	Study arms	Survival (%)	*p* value	Ages included
Whitney et al.	Arm 1: CDDP 50 mg/m^2 + 5-FU 4 g/m^2 + RT	67	0.018	<61:147, 61–70:26, ≥71:4
	Arm 2: Hy 80 mg/kg + RT	57		<61:158, 61–70:26, ≥71:7
Rose et al.	Arm 1 : CDDP 40 mg/m^2/week + RT	65	<0.001	<61:140, 61–70:32, ≥71:4
	Arm 2: CDDP 50 mg/m^2 + 5-FU 4 g/m^2 + Hy 2 g/m^2 + RT	65		<61:141, 61–70:24, ≥71:8
	Arm 3: Hy 3 g/m^2 + RT	47		<61:151, 61–70:21, ≥71:5
Morris et al.	Arm 1: CDDP 75 mg/m^2 + 5-FU 4 g/m^2 + RT	75	<0.001	Median age 47
	Arm 2: RT	63		Median age 47
Peters et al.	Arm 1 : CDDP 70 mg/m^2 + 5-FU 1 g/m^2 + RT	81	<0.007	Median age 41 (20–74)
	Arm 2: RT	71		Median age 38 (20–77)
Keys et al.	Arm 1 : CDDP 40 mg/m^2/week + RT	83	<0.008	<61:167, 61–70:10, 71–80:5, 81–90: 1
	Arm 2: RT + hysterectomy	74		<61:174, 61–70:8, 71–80:4

arms [16]. In the other three studies, the total number of patients over the age of 71 was extremely low, including 11, 17, and 10 elderly patients, respectively [17–19] (see Table 18.1). Therefore, these studies appear to have insufficient data to verify whether chemoradiation is superior to radiation alone for the elderly population.

Although the literature lacks supportable data for the elderly from RCTs, several retrospective analyses have been performed specifically to examine radiation therapy versus chemoradiation in the elderly population. The results from these studies suggest that there may be no significant difference in survival for the two treatment approaches in this population and therefore no additional benefit to employing chemoradiation. In a large retrospective study performed by Cheng et al., including 215 elderly patients, the analysis showed no difference in 5-year survival between those who received radiation and those who received chemoradiation [20]. Park et al. also performed a retrospective analysis comparing radiation with chemoradiation for 105 elderly patients; it demonstrated no difference in either disease-specific or overall survival. This study also found that acute grade 2 hematologic and gastrointestinal toxicities were more common with chemoradiation ($p < 0.001$); however, there were no differences in acute grade 3 or 4 toxicities or late toxicities [1]. Although a much smaller retrospective analysis performed by Goodheart et al. (with only 27 elderly patients) showed a trend toward an advantage for chemoradiation, the difference in disease-specific survival was not statistically significant [21].

Experimental Therapies

While there are not presently RCTs addressing the two primary treatment options in the elderly, research continues on potential alternative therapies that might increase therapeutic success and/or ameliorate side effects in this population. Cisplatin has been shown to be the most active chemotherapeutic agent in cervical cancer [22]. However, due to the higher toxicity of this drug, some investigators have explored the use of alternate platinum chemotherapeutic agents, such as carboplatin, for chemoradiation in the elderly. Although this drug appears to be inferior to cisplatin with respect to survival, it appears to be better tolerated. Cetina et al. performed a retrospective review of 59 patients who received carboplatin combined with radiation. Patients receiving this regimen were >70 years old or had a diagnosis of diabetes or hypertension. While 5-year survival for cisplatin or cisplatin + 5-FU ranges from 65 to 83 %, 30-month survival in this study was only 63 %. However, leucopenia and neutropenia rates were <15 %, which is significantly lower than rates for these adverse reactions with cisplatin. The authors therefore concluded that combining carboplatin with radiation may be considered in populations with significant comorbid conditions [23].

Other therapeutic strategies currently under investigation for the treatment of advanced cervical cancer include varying schedules and doses of cisplatin and the use of neoadjuvant chemotherapy followed by surgery. While specific studies of these therapeutic strategies have not yet been undertaken in the elderly population, those that have been done for women in the general population suggest decreased toxicity profiles and improved outcomes that may also be promising for the elderly. For example, in a recent randomized clinical trial by Ryu et al., cisplatin given triweekly rather than weekly showed less grade 3/4 neutropenia (9.2 % vs. 22.6 %) and a higher 5-year survival rate (88.7 % vs. 66.5 %) [24]. In a 2003 study, neoadjuvant chemotherapy combined with surgery was found to result in improved survival when compared with radiation therapy alone [25]. While neoadjuvant chemotherapy became a less utilized approach to locally advanced disease when chemoradiation was adopted as the standard of care, this approach has not been directly compared to chemoradiation in a RCT. There is therefore an ongoing study (55994, EORTC) that is currently comparing these two strategies [26]. This study may help to further clarify the advantage of each of these treatment strategies for the general population, but once again, specific studies for the elderly population will also be needed.

Metastatic and Recurrent Cervical Cancer

As previously mentioned, elderly women are more likely to present with advanced stage disease, and studies suggest that elderly women may be more likely to present with metastases as well. In a study by Fox et al., 65.2 % of

patients over age 60 were found to have positive lymph nodes, increased from 52 % of patients with nodal metastases in the general population at the same institution [27]. Furthermore, elderly patients more often present with recurrent disease. Systemic therapy is therefore critical in the treatment of elderly patients with cervical cancer.

Chemotherapy in the Elderly Population

The treatment of choice in the general population for both recurrent cervical cancer and metastatic cervical cancer is systemic palliative chemotherapy. Age-related physiologic changes include reduced kidney and liver function, both of which may affect the toxicity and the clinical response to chemotherapeutic agents in the elderly population. Renal function changes include a decrease in glomerular filtration rate (GFR) of 1 mL/min for every year after 40 years of age. Therefore, careful calculation of GFR is necessary in the elderly patient to avoid increased risk of receiving either excessive or suboptimal doses of chemotherapeutic agents [28]. This, for example, may lead to increased severity of cis-platinum-induced nephrotoxicity [23]. In conjunction with this effect, Moore et al. showed that creatinine clearance <65 mL/min and albumin level <2 g/dL are predictors of inability to complete chemotherapy among the elderly population [29]. Physiologic effects on liver function include decreases in hepatic blood flow and cytochrome P450 activity [30]. Studies have shown that drugs with hepatic excretion, such as paclitaxel, have decreased clearance in the elderly, and doses for patients taking these drugs may therefore need to be adjusted accordingly [31]. Other than such changes in pharmacokinetics that lead to an increased risk of therapeutic complications of chemotherapy, there is no evidence showing that chronologic age itself is a predictor of toxicity [32]. Therefore, the changes in renal and hepatic function must be considered objectively for each individual patient along with all the other factors that affect treatment course and outcomes for chemotherapy.

Performance status and medical comorbidities are known independent predictors of chemotherapy-related toxicity, therefore, playing a critical role in chemotherapy tolerance among the elderly [33]. Chen and colleagues have shown that performance status may have a greater decline from baseline in the elderly after receiving chemotherapy, and survival may be shorter in elderly patients with lower performance status [34]. Therefore, these elements must also be considered when deciding upon chemotherapeutic regimens.

While age alone does not predict a given patient's ability to tolerate chemotherapy, studies suggest that age-related physiologic changes, performance status, and comorbidities, all seem to affect both the risk of toxicity and the ability of elderly women to tolerate aggressive regimens [35]. While it is difficult to determine the role that selection bias may have played in the above studies due to increased frequency of reduced-dose regimens for the elderly women, the participation of elderly patients in randomized clinical trials continues to be limited. Additionally, much of the above data is from

ovarian cancer patients who, in contrast to cervical cancer patients, have not received pelvic radiation therapy. The toxicity profile of chemotherapeutic agents for elderly patients who have already received prior radiation may therefore be worse than these studies suggest. This makes objective conclusions of treatment tolerance in this population extremely difficult. Therefore, there remains a need for validated measures of predictors for therapy. While some proponents have suggested that reduced doses and alternative chemotherapy regimens may improve treatment tolerance among the elderly, it remains unclear which patients should receive which specific regimens.

Chemotherapy Protocols for Recurrent or Metastatic Disease in the Elderly Population

Based on several phase III studies comparing different chemotherapeutic protocols, the regimen most often utilized to treat recurrent or metastatic cervical cancer is the combination of a platinum-based chemotherapeutic agent with either paclitaxel or topotecan [36]. The most recently completed study, GOG 204, showed a trend in progression free survival and overall survival which favored cisplatin and paclitaxel as the superior regimen. Toxicity profiles were found to be comparable between all four regimens in this study. The median age of participants in each arm of the study, however, was 50 for the Paclitaxel arm, 49 for the vinorelbine arm, 45 for the Gemcitabine arm, and 48 for the topotecan arm. Therefore, it is difficult to draw conclusions specific to the elderly population from GOG 204 [37].

While there is prospective evidence for the efficacy of each of these regimens in the general population, there is limited data in the elderly. In a recently conducted pooled analysis of three studies (GOG 110, GOG 169, and GOG 179), Moore et al. identified a trend towards poorer response with increasing age. However, the model that these authors proposed has not yet been studied in a prospective manner [38]. One strategy commonly employed in elderly patients is to reduce the dose of chemotherapy administered in the elderly. This is sometimes done prophylactically in elderly patients with poor performance status or may be based on renal function or on the absolute neutrophil count to prevent febrile neutropenia. This strategy, however, also has not been studied in a prospective or randomized approach in this population [39].

The toxicity profile for the treatment combination of carboplatin and paclitaxel is significantly improved when compared to cisplatin and paclitaxel, and this finding may have important implications in the elderly population [40]. In retrospective analyses, carboplatin/paclitaxel appears to have more favorable response rates and toxicity profiles when compared to cisplatin/paclitaxel. In the study by Moore et al., however, the mean age was only 46.7 in the cisplatin arm and 51.1 in the carboplatin arm [41]. The Japanese Clinical Oncology Group is currently conducting a study to compare these regiments; however, the published manuscript of this study is not yet available [42]. Furthermore, it is unclear how many elderly patients will be included in their analysis, and therefore additional studies are warranted to answer questions

regarding effectiveness and toxicity of carboplatin/paclitaxel versus cisplatin/paclitaxel specific to this population.

Experimental Treatments for Recurrence and Metastasis

One of the most promising advances in the treatment of all cancers is molecular-based targeted therapies. Bevacizumab and pazopanib are antiangiogenesis agents that have shown preliminary promise for the treatment of cervical cancer. Phase II studies of bevacizumab have been conducted in the general population, showing promising activity and toxicity profiles, but few elderly patients have been included. Phase III studies are currently underway in the general population but have not yet been planned in the elderly [43]. Pazopanib is an oral agent that has been shown to have minimal toxicity, and it therefore may prove to be a promising therapeutic drug for treatment for cervical cancer; however, once again, further studies are needed to examine the potential benefits of this drug in the elderly population [44].

Other experimental treatments currently being investigated for the treatment of metastatic or recurrent cervical cancer include hyperthermic chemotherapy and vaccination strategies. In a Phase II study examining carboplatin and whole body hyperthermia, the response rate was found to be 33 % which is similar to other palliative regimens. The oldest patient included in this study, however, was 57 years old, and grade 3–4 myelosuppression was not uncommon (leucopenia 35 %, thrombocytopenia 61 %, anemia 22 %) [45]. While immunotherapy has been studied extensively for HPV disease and prevention of cervical cancer [46], some investigators have also started to examine immunotherapy and vaccination strategies for recurrent and metastatic disease as well. A case report of a 52-year old woman with metastatic cervical cancer who was treated with HPV-18 E7-pulsed dendritic cells showed no evidence of progression for 13 months [47]. Although there is minimal evidence for this strategy as of yet, future developments are promising. As the immune system does undergo changes with age, however, specific studies in the elderly will be needed to determine the effectiveness in this population.

Conclusion

As cervical cancer incidence is increased in elderly women, it is critical to evaluate specific treatment strategies for this population. While there is a significant body of evidence that supports the tolerance and effectiveness of aggressive therapy in this population, several factors must be considered in treatment decisions. These should include patient's desires for treatment, comorbid conditions, performance status, and prior therapy; however, evidence suggests that treatment should not be based on age alone [27]. Prospective data further informing optimal treatment strategies for this population are also needed to further inform optimal treatment strategies.

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Chapter 19
Vulval and Vaginal Cancer

Niyati Nadkarni and Amina Ahmed

Abstract Vulvar and vaginal carcinomas are primarily cancers of the elderly. Vulvar carcinomas are treated and staged surgically with adjuvant therapy consisting of radiation therapy in the majority of cases. Conversely, vaginal carcinomas are typically treated with radiation therapy, with surgery being utilized in select cases. This chapter will review epidemiology, diagnosis, and treatment of vulvar and vaginal carcinomas, with a focus on the effect of treatment on elderly women affected by these cancers.

Keywords Vulvar cancer • Vaginal cancer • Chemotherapy • Radiation • Treatment toxicity

Vulvar Cancer

Epidemiology

Vulvar cancer is a rare malignancy whose clinical manifestations are found in the younger patient population though it predominantly occurs among the elderly. According to the SEER database, the median age of diagnosis from 2004 to 2008 was 68 years of age, with 24.3 % of cases occurring between the ages of 75 and 84. Of the remaining cases, 14.6 % were women aged 85 and older, and 17.5 % were between the ages of 65–74. Women under the age of 44 comprised 7.3 % of those diagnosed with vulvar cancer, with 0.1 % of those cases diagnosed under age 20 [34]. These data show that the predominance of vulvar cancers is diagnosed in the

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postmenopausal female. In reference to the distribution of vulvar cancer across race, the incidence between 2004 and 2008 was 2.3 cases per 100,000 women for all races, with 2.4 cases per 100,000 white women. The lowest incidence of vulvar cancer cases are in Asian/Pacific Islanders with an incidence of 0.9 per 100,000 women [34].

Mortality data in the United States between 2004 and 2008 indicate that the median age of death was 79 years of age. The age range accounting for the most deaths is 85 years and older, (29.5 %) accounting for 0.5 deaths per 100,000 white women. Based on the SEER database, the lifetime risk of developing cancer of the vulva is 1 in 372 women [34]. A study of cancer incidence in 2010 estimated 3,900 new cases of vulvar cancer with 920 deaths [20]. Although vulvar cancer appears to be a disease that predominantly affects postmenopausal women, its rarity poses a challenge to this field of study, particularly the optimal management of the elderly patient.

A number of factors have been associated with increased risk in development of vulvar cancer, including human papillomavirus (HPV) infection, tobacco use, history of immunodeficiency, prior history of vulvar or cervical dysplasia, as well as a prior history of cervical cancer [9].

The pathophysiology of the development of vulvar cancer has been attributed to a number of factors, which include infection with HPV, specifically types 16 and 33, and vulvar dystrophy. The overall classification of vulvar dystrophy pertains to a history of chronic inflammation with resultant mucosal injury, thereby predisposing the vulvar mucosa to carcinogenesis. HPV infection appears to be more common among women who are younger and who have a history of tobacco use [9]. Interestingly, younger women tend to have multifocal disease while elderly women tend to present with unifocal lesions. Vulvar pruritus appears to be one of the most common presenting symptoms along with a vulvar mass. Lesions may be raised or flat and may be ulcerated or resemble condyloma. Other symptoms include urinary discomfort or bleeding [16].

Histology

There are various histological types associated with vulvar cancer, with squamous cell carcinoma accounting for 90 % of vulvar cancers [9]. Within the squamous histological type, there are different subtypes including a warty type, which is associated with HPV infection, and a simplex type found more often in the elderly population. The simplex type tends to be associated with precursor vulvar dystrophies such as lichen sclerosus, which is characterized by thinning of the vulvar epithelium and inflammatory changes. Previous studies have shown that approximately 60 % of squamous cell carcinomas of the vulva appear to arise in a background of lichen sclerosis. There is less than a 5 % chance of progression to invasive cancer from lichen sclerosis as a precursor lesion.

Other less common types of vulvar cancers, which occur predominantly in postmenopausal women, include melanoma, basal cell carcinoma, and extra mammary

Paget disease. Melanoma of the vulva tends to occur at a median age of 68 years, accounting for 5–10 % of vulvar cancers, making vulvar melanoma the second most common vulvar histology [9]. Generally, a pigmented lesion is seen with vulvar melanoma, but there are instances when there are hypopigmented lesions associated with vulvar melanoma. Basal cell carcinomas of the vulva have the characteristic central ulceration with ragged edges and account for 2 % of vulvar cancers. They are often associated with malignancies in extra-vulvar sites. Less than 1 % of vulvar cancers are associated with extra-mammary Paget disease with lesions resembling eczematous changes, similar to Paget disease of the breast. There is an approximately 20 % chance of developing another adenocarcinoma at an extra-vulvar site as well as an approximately 15 % chance for the development of an underlying adenocarcinoma of the vulva. An enlarged Bartholin gland should always be biopsied in any patient older than age 40 to evaluate for adenocarcinoma. Bartholin gland adenocarcinoma tends to be highly vascular, giving them the propensity to metastasize [9].

Diagnosis

Biopsy of a suspicious-appearing vulvar lesion is the mainstay of diagnosis of vulvar cancer. Oftentimes, particularly in elderly patients, diagnosis is delayed secondary to inadequate access to examination by a health care professional. Additionally, some patients may receive topical treatments without a biopsy-proven diagnosis to alleviate symptoms, which can also delay the actual diagnosis. Given that this disease is more common in the postmenopausal female, the patient may suffer from other comorbidities or have a poor performance status, which precludes her from seeking medical attention for the vulvar lesion [12, 24]. Sometimes, the patient is immobile and is not routinely examined which can often cause delay in diagnosis as well [12].

Many vulvar cancers in the elderly present at more advanced stages than younger patients secondary to the lack of consistent gynecologic care for the elderly patient. One study by Vlastos et al. studied 230 women with vulvar cancer ranging from ages 21 to 93. Younger patients (less than age 50) were found to be diagnosed with vulvar cancers at earlier stages than elderly patients simply because younger patients underwent more screening gynecologic examinations. Sixty-nine percent of women over the age of 80 ($n=49$) were found to present at more advanced stages. Elderly patients were more likely to have a delay in diagnosis, attributed to both their reluctance to seek medical attention for their symptoms and also due to inadequate experience of the health care professional to recognize a potential precursor or invasive lesion [39]. Another study by Kumar et al. showed that the overall survival of elderly women might actually be improved by having the awareness of the manifestations of precursor and cancerous lesions of the vulva [24]. Educating health care professionals on the pathology of vulvar cancers in order to allow for earlier diagnosis is imperative.

Prognostic Factors

There are a number of prognostic factors associated with vulvar cancer, particularly in the elderly. A retrospective review was performed by Ghebre et al. which included 146 women with vulvar cancer with a median age of 79 years old. According to this study, disease-specific mortality was noted to be most evident within 3 years from diagnosis, specifically related to advancing age, particularly among patients that were 85 years of age and older. Other prognostic factors affecting mortality in the elderly patient population included involvement of lymph nodes, other comorbidities, and type of surgery that had been performed. As discussed in this study, elderly women were more likely to undergo nonstandard surgical therapies, which were likely based on their performance status and comorbidities [4, 12].

According to another study by Hyde et al., performance status appears to be a more important prognostic factor for overall survival in the elderly patient compared to increasing age. This retrospective study included 75 patients aged 80 years and older of which 57 patients received standard treatment, and 18 patients received nonstandard treatment. Radical local excision with unilateral or bilateral inguinal-femoral lymphadenectomy was considered standard treatment for squamous vulvar lesions with a depth of greater than 1 mm. If there was extracapsular involvement of the lymph nodes and/or evidence of metastatic disease to at least one inguinal-femoral lymph node, the standard of treatment also included radiation therapy to the groin and pelvis. The median age of patients in this study was 84.6 years. It was noted that patients who were older were not as likely to receive standard treatment regardless of their performance status. Therefore, treatment of the elderly patient must be individualized and age should not bias treatment, particularly with an acceptable performance status [19].

Surgical Management

Various management strategies for women with vulvar cancer are utilized, but the standard of care generally involves a form of surgical excision. For lesions that are have a depth of stromal invasion on Keyes punch biopsy of ≤1 mm, a simple vulvectomy can be performed to assess the actual depth of stromal invasion. For lesions with greater than 1-mm invasion, a radical excision should be performed. In general, management of early-stage disease involves surgical excision of the lesion with at least a 1-cm lateral margin and removal of deep tissue to the level of the urogenital diaphragm. Lesions that are in close proximity to the urethra can be managed with distal urethrectomy with removal of the distal 1 cm of the urethra, which still enables retention of urinary continence. There is less than a 1 % chance of having metastatic disease to the lymph nodes with T1 tumors with stromal invasion of ≤1 mm. However, depending on the location of the lesion, patients should undergo ipsilateral inguinal-femoral lymph node dissection with T2 lesion and all patients with T1 lesions with greater than 1-mm stromal invasion. Patients with midline

tumors or lateral lesions within 2 cm of the midline should undergo bilateral inguinal-femoral lymph node dissection [14].

Inguinal lymph node involvement has been found to have prognostic significance [3, 18]. In fact, the Gynecologic Oncology Group had previously performed a study that showed that patients would benefit from postoperative bilateral pelvic and groin radiation therapy with any of the following: one macro metastasis, defined as >1 cm in diameter, extracapsular spread, and/or ≥2 micrometastases in the inguinal lymph nodes [17].

For patients with clinically suspicious nodes in the groin, a CT scan performed preoperatively can be useful. Debulking of grossly positive inguinal lymph nodes can be performed, but a complete inguinal-femoral lymph node dissection performed in the setting of grossly positive nodes may actually be associated with more comorbidity, particularly if postoperative radiation therapy is recommended [14].

Morbidities associated with vulvar and groin excision involve changes along the operative sites. In elderly patients, particularly atrophy of the involved skin can cause significant difficulty with wound healing. The limited use of topical estrogen preoperatively may actually improve wound healing postoperatively by way of improving the quality of the atrophic tissue that is planned on being excised and potentially reapproximated [1]. Urethral stenosis can be encountered, particularly in the elderly patient, which can be managed with excision of any granulation tissue that may have developed postoperatively as well as cystoscopy with progressive urethral dilation if necessary. Additionally, fecal incontinence or constipation may also result from surgery which can be attributed to anatomic manipulation of the anal sphincter during surgery and medications postoperatively including narcotics and antibiotics [1].

Follow-up evaluation for women who have undergone surgical excision is imperative. Wound infection and wound breakdown appear to be major complications encountered postoperatively. Utilization of sitz baths and cleansing of the wound following urination and defecation are recommended [14].

Chemotherapy and Radiation Therapy

Chemoradiation therapy has become part of a multimodality approach for the management of advanced vulvar carcinoma [36, 37]. The efficacy of preoperative chemoradiation therapy in patients with N2/N3 inguinal lymph nodes was addressed in a study conducted by the Gynecologic Oncology Group. The goal of using preoperative chemoradiation was to determine if the extent of surgery could be decreased, thereby possibly improving overall morbidity associated with vulvar and inguinal lymph node resections. This particular study by Montana et al. included 46 patients with N2/N3 lymph nodes who were given 4,760 cGy in split-course fraction with concurrent chemotherapy including cisplatin and 5-fluorouracil. These patients were noted to have favorable resectability rates with acceptable rate of control of local disease of inguinal lymph nodes. The median age of diagnosis in this study was 69 with an age range of 35–88. Forty-two patients completed chemoradiation.

Of these 42 patients, 4 patients did not undergo surgery. Interestingly, of the remaining 38 patients who had undergone surgery after receiving preoperative chemoradiation therapy, 12 patients showed no evidence of disease. Nine patients showed evidence of recurrent disease along the primary site, and eight patients had evidence of distant metastases. The resectability rate was noted to 95 %. According to the study, the majority of patients actually tolerated chemoradiation therapy relatively well with the most frequent toxicity related to grade 3 and 4 cutaneous toxicity. Other toxicities included grade 2 hematologic toxicity and grade 2 nausea and vomiting. The median age of this study was 69 years [26, 28, 29].

Another study by Gerszten et al. also addressed the utility of chemoradiation therapy in patients with locally advanced carcinoma of the vulva. This study included 17 patients, with a median age of 72, who were treated with preoperative chemoradiation therapy which also included T2, T3, and T4 lesions. The results from this study showed that preoperative chemoradiation therapy is an acceptable treatment regimen with patients with bulky and locally advanced disease with good tolerability of toxicities from therapy even in the elderly. There was a 78 % complete clinical response rate in this study. The most common toxicity was noted to be cutaneous skin reaction with otherwise other acceptable toxicities. In review of the demographics, patients with an age range from 77 to 85 were able to tolerate chemotherapy with cisplatin and 5-fluorouracil [11].

Another study by Mak et al. involved a retrospective review of 44 patients with a median age of 63 with Stage II–IVA squamous cell carcinoma of the vulva. The primary goal of the study was to examine the outcomes in patients treated with radiation therapy with concurrent cisplatin versus every 3- to 4-week chemotherapy containing 5-fluorouracil. There was no significant difference in survival and recurrence between the two regimens. The complete pathologic response rate was 53.8 %. There was more grade 3 or skin toxicity in those patients who received weekly platinum as part of the chemoradiation arm and more non-cutaneous toxicities associated with patients receiving 5-fluorouracil [25].

Consideration for chemotherapy in the elderly patient must take into account baseline renal and liver function as well as overall performance status for tolerance of chemotherapy [38]. The toxicities associated with various chemotherapeutic regimens must be addressed. Cisplatin, for instance, is associated with hypomagnesemia, renal insufficiency, ototoxicity, peripheral neuropathy, nausea and vomiting, and bone marrow suppression [38, 40]. Toxicities associated with 5-fluorouracil include diarrhea, bone marrow suppression, hepatotoxicity, and cerebellar syndrome which are characterized by confusion, headache, and ataxia [7]. Elderly patients benefit from serotonin-receptor antagonists as well as steroids for prevention and treatment of severe nausea and vomiting [7]. According to Wasil et al., the glomerular filtration rate decreases “by approximately 1 ml/min for every year over the age of 40” [40]. Additionally, elderly patients tend to have lower baseline albumin and hemoglobin levels. Therefore, it is important to be aware that bone marrow reserve and baseline metabolic parameters vary between the elderly and the younger patient [38, 40].

There are a number of comorbidities associated with radiation therapy. There are two phases associated with radiation toxicity including an acute phase and a delayed phase.

The acute phase is characterized by development of inflammatory changes, generally within 3 months of completion of radiation therapy. Delayed effects include paresthesias, fibrosis, and scarring [1]. Chronic lymphedema is a prevalent problem which can be located along the inguinal lymph node dissection bed and/or lower extremities. Once limb edema occurs, there are no specific measures to reverse this process; there are only various ways to palliate symptoms, such as the use of external compression stockings, in order to prevent further progression of the edema. Patients who suffer from lower extremity edema should avoid trauma to the skin as women with lower extremity edema may be at increased risk for worsening edema and/or development of superimposed cellulitis [1]. Additionally, women who suffer from lower extremity edema benefit from elevation of the involved limb in an attempt to increase venous return to the heart and to decrease undue pressure from gravity on the involved limb [1, 32].

In terms of late radiation effects of the bladder, some women may suffer from radiation cystitis or proctitis. Late radiation proctitis can be managed symptomatically with steroids, but some patients may require coagulation of any ulcerated or actively bleeding areas which may be noted on colonoscopy. Radiation cystitis can also be managed with cystoscopy to rule out recurrent disease followed by bladder irrigation as well as possible hyperbaric oxygen. Bladder infection should be considered as a possible cause for the patient's symptoms [1].

Follow-Up Evaluation

Once a diagnosis of vulvar cancer has been established and the patient has undergone primary treatment, recommendations are for pelvic examinations every 3 months for 2 years and then every 6 months for the subsequent 3 years with annual examinations thereafter [16]. Other studies recommend examination every 3 months for 1 year, then every 4 months for the second year, followed by every 6 months for the subsequent years [8]. Any new symptoms and/or lesions that develop should be thoroughly inspected and biopsied as needed. Some women may require repeat surgical excision of lesions. However, once there is a diagnosis of recurrent disease to the groin, cure of disease is unable to be achieved, and palliative control of symptoms may need to be instituted [16].

Vaginal Cancer

Epidemiology

Primary vaginal cancer is one of the rarest of all malignancies. These tumors represent approximately 2 % of all female genital malignancies or between 0.1 and 0.2 % of all cancers [6]. The prognosis for patients with vaginal carcinoma depends on several

factors including age of the patient, histology, and stage of the cancer. The 5-year relative survival rates are approximately 95 % for stage 0, 75 % for stage I, 60 % for stage II, 35 % for stage III, 20 % for stage IVA, and 0 % for stage IVB. A multivariate analysis of prognostic factors performed on the FIGO database revealed that age older than 60 years was the only significant prognostic factor [15]. Primary vaginal cancer is a disease of the elderly; 70 % of patients with vaginal carcinoma are older than age 60 years, and 20 % are older than age 80 years [15]. In a SEER analysis, survival declines from 67.9 % in the youngest age group, ages 40 years and younger, to 33.3 % for women in the oldest age group, ages 70 years and older [23].

Histology

The distribution of vaginal carcinoma by histology: squamous cell carcinoma 78 %, adenocarcinoma 4 %, endometrioid carcinoma 1 %, clear cell carcinoma in 3 %, melanoma in 4 %, and other tumor types in about 10 % [2]. The majority of women with squamous lesions were elderly; younger women had a higher incidence of adenocarcinoma of the vagina [6]. Metastatic lesions to the vagina are common. Mazur and associates found in a study of 269 patients with metastatic disease involving the vagina, 16 % were from extragenital sites and 84 % from genital sites. Among the most common genital site, metastasis to the vagina, endometrial carcinoma was the most common, 78 %, followed by ovarian carcinoma, 17 % [10].

Diagnosis and Treatment

After confirming primary vaginal cancer with a diagnostic biopsy, an evaluation for metastatic disease should be undertaken, primarily to assess the status of the lymph nodes. Lymph node metastases are similar to patients with cervical carcinoma, except that distal vaginal carcinomas will potentially involve the inguinal lymph nodes. Positron emission tomography (PET) may be more sensitive than computed tomography (CT) in evaluation for lymph node metastases. Studies in cervical cancer have shown PET scanning to be more sensitive than CT in detecting lymph node metastases; a review of 14 patients with primary vaginal carcinoma demonstrated lymph node metastases were detected in 43 % of patients with PET scanning compared to 14 % detected by CT [10].

The choice of treatment for primary carcinoma of the vagina is often based on individual and institutional policy. It is difficult to derive strict treatment recommendations from the literature as there are no prospective studies of patients with primary vaginal carcinoma and the data guiding therapy is retrospective in nature. Radiation therapy is the most common form of treatment for patients with carcinoma of the vagina. Both external beam and brachytherapy play important roles in management of vaginal carcinoma involving stages I–IVA of disease. In situ lesions,

if treated with radiation, can be dealt with by intracavitary radiation to a vaginal surface dose of approximately 70 Gy. For early-stage disease, a combination of external bean radiotherapy with brachytherapy is given to total dose 75 Gy. For more advance disease, the boost may be increased for a total dose of 80 Gy [5, 15]. Surgical therapy for patients with vaginal carcinoma is usually confined to patients with early-stage disease. Small lesions in the upper vagina may be treated with an upper vaginectomy with a pelvic lymphadenectomy with 5-year survival rates from 75 to 100 %. Radiation therapy is considered standard therapy for vaginal carcinoma; however, with appropriate case selection, surgery can be equally effective [33]. Chemotherapy is used as primary therapy very infrequently; approximately 5 % is the frequency of using chemotherapy alone in management of vaginal carcinoma [6].

The role of chemoradiation in the treatment of primary vaginal cancers has been supported by multiple retrospective studies, yet to be defined in a prospective fashion [13]. In 1999, the NCI issued a clinical alert defining concurrent chemotherapy with radiation as the standard treatment of cervical carcinoma [21, 27, 30, 41]. Given the similarities between cervical and vaginal cancers, many clinicians have extrapolated the data from the cervical cancer trials to vaginal cancer as justification for combined therapy. In a recent SEER-Medicare analysis of patient with vaginal carcinoma, with all patients over the age of 65 years, there was no difference in overall survival or disease-specific survival between those receiving radiation alone compared to those receiving chemoradiation. As age increased, the rates of chemoradiation decreased; chemoradiation was less likely utilized in patients 80 years or older (10.1 %) relative to younger age groups [13].

Cisplatin has been the chemotherapy agent of choice to be used as a radiation sensitizer. This choice was extrapolated from the cervical cancer literature, primarily when five articles published almost simultaneously supported the use of Cisplatin with radiation therapy [21, 27, 30, 41]. Cisplatin has been found to be tolerable when given weekly as a radiation sensitizer, with a treatment completion rate of 92 % with no grade 3 or 4 toxicities in studies of patients being treated for vaginal carcinoma [31].

Treatment Effect

Serious complications from primary treatment of vaginal carcinoma, complications that were fatal, require prolong hospitalization or surgical intervention, approximate 13 %. In a large series of patients who were followed after primary treatment for vaginal carcinoma, long-term follow-up identified a complication rate of 19 % at 20 years [5]. The majority of treatment side effects were secondary to radiation therapy including fistula formation, rectal ulceration and/or proctitis, and small-bowel obstruction. Those treated with surgical intervention, the most frequent severe side effect was pulmonary embolism. Patients who underwent pelvic lymphadenectomy had a 10-year complication rate of 35 % compared to 11 % who did not undergo this procedure [5].

Recurrence

The recurrence rate after treatment of primary vaginal carcinoma is approximately 31 % [5]. Survival after relapse is very poor and few patients can be salvaged after primary therapy. Patients with recurrence locally have a better 5-year survival, 20 % than patients whose tumor has recurred beyond the primary site [5]. Patients with local recurrence may be salvaged with pelvic exenteration. Those whose tumor has spread beyond the primary site may be served by palliative chemotherapy. There are only a few reports of the use of chemotherapy for recurrent vaginal carcinoma. The Gynecologic Oncology Group (GOG) conducted a phase II study in patients with advanced or recurrent vaginal carcinoma receiving Cisplatin 50 mg/m^2 every 3 weeks. Amongst 16 patients with squamous cell carcinoma, there was 1 responder, 5 with stable disease. The researcher concluded that there was insignificant activity of Cisplatin in advanced or recurrent vaginal carcinoma [35]. Other agents which have been reported as active in advanced disease include 5-FU, mitomycin and epirubicin [22, 42]. None of these studies were randomized.

In conclusion, the majority of vaginal carcinoma has squamous histology and occurs in elderly women. Overall, approximately 60 % of patients can be cured of their disease with radiotherapy. Given the cervical cancer literature and the tolerability of Cisplatin, this chemotherapeutic agent should be used a radiation sensitizer.

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Chapter 20
Uterine Sarcomas in the Elderly

Robert G. Maki and Afsheen Iqbal

Abstract Uterine tumors other than carcinoma represent a minority of tumors of this anatomic site. They demonstrate significant variety in terms of molecular pathogenesis and options used for their therapy. Tumors vary from those with specific translocations such as endometrial stromal sarcoma to those with aneuploid karyotypes such as leiomyosarcoma and carcinosarcoma (and other mixed Müllerian tumors). The treatment choices for uterine sarcomas and related tumors are further tempered by their development in an older population, limiting the ability to give some systemic therapeutics that can be safely given to younger patients. We review herein several of these diagnoses and their management, with emphasis on systemic approaches used in younger and older patients alike.

Keywords Leiomyosarcoma • Endometrial stromal sarcoma • Undifferentiated endometrial sarcoma • Carcinosarcoma • Rhabdomyosarcoma • Perivascular epithelioid cell tumor • PEComa

Introduction

Uterine sarcomas are a rare group of neoplasms, arising from uterine mesenchymal elements. They comprise less than 1 % of all gynecologic malignancies and 3–7 % of all cancers of the uterus [61]. They often behave in a more aggressive fashion compared to endometrial carcinomas and carry a worse prognosis. We hope to review carcinosarcomas

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as well as the major sarcoma subtypes as they affect the uterus, with a focus on elderly patients while at the same time trying to include diagnoses also found in younger patients so that the arc of age and sarcomas diagnoses can be appreciated as well.

Classification

Histologically, uterine sarcomas are classified into carcinosarcomas and other members of the malignant mixed Müllerian tumor (MMMT) family, accounting for 40 % of cases, leiomyosarcomas (40 %), endometrial stromal sarcomas (10–15 %), and undifferentiated sarcomas (5–10 %). Carcinosarcoma is perhaps now best reclassified as a metaplastic form of endometrial carcinoma due to its composition of both epithelial and mesenchymal element, defining it as a biphasic neoplasm [93]. Carcinosarcoma, one of the forms of MMMT, is included in the 2003 World Health Organization (WHO) classification of uterine sarcomas [19], but this may change as the WHO definitions are updated.

The issue of classification is further complicated by the finding of distinct translocations in a subset of high-grade undifferentiated uterine sarcomas, formerly called high-grade endometrial stromal sarcoma. For example, it is not clear if translocation-negative high-grade undifferentiated uterine sarcomas should be considered a separate class from those that have the translocation. Finally, different organizations use different classification for parsing this family of tumors.

The International Society of Gynecologic Pathologists and the WHO devised classifications of uterine sarcomas depending on whether the tumor is purely nonepithelial or has mixed epithelial and nonepithelial features. Table 20.1 indicates one potential classification of uterine tumors with mesenchymal components during this period of flux.

Table 20.1 A classification of uterine tumors with mesenchymal components

Pure mesenchymal tumors unique to the uterus
Endometrial stromal tumors
Low-grade endometrial stromal sarcoma t(7;17)(p15;q21) *JAZF1-SUZ12(JJAZ1)*
Undifferentiated endometrial sarcoma
17p13 (*YWHAE*) translocation positive
Translocation negative
Mixed endometrial stromal and smooth muscle tumors
Adenomatoid tumor
Other sarcomas in common with other anatomic sites
Smooth muscle tumors
Leiomyoma
Smooth muscle tumor of uncertain malignant potential (STUMP)
Leiomyosarcoma
Variants
Myxoid
Epithelioid

Table 20.1 (continued)

PEComa family of tumors, including lymphangioleiomyomatosis
Rhabdomyosarcoma
Alveolar
Embryonal
Botryoid
Spindle cell
Angiosarcoma
Undifferentiated pleomorphic sarcoma (UPS), formerly malignant fibrous histiocytoma (MFH)
Others
Mixed epithelial-mesenchymal tumors (Mixed Müllerian Tumors)
Benign
Adenofibroma
Adenomyoma
Malignant
Adenosarcoma
Carcinosarcoma

Sarcomas of the uterus are either homologous or heterologous as a function of histology. Homologous uterine sarcomas, which are the majority, arise from native uterine tissues including the endometrium, smooth muscle, connective tissue, or blood or lymphatic vessels. Heterologous tumors include elements of nonnative uterine tissue including skeletal muscle, cartilage, and bone.

Risk Factors

Due to the rarity of these neoplasms, few large epidemiologic studies have emphasized risk factors for sarcoma development. One significant risk factor that has been identified is race. African-Americans have a twofold increased incidence of uterine leiomyosarcoma compared to Caucasians. Carcinosarcomas have a 2.5-fold greater incidence in the African-American population compared to Caucasians [9]. Increasing age is also a risk factor for uterine sarcomas, with most tumors developing after menopause. A history of exposure to pelvic irradiation has been noted to be a risk factor as well, particularly in the development of uterine carcinosarcomas [81]. Long-term use of tamoxifen may also modestly increase the risk of uterine sarcomas, most commonly presenting 2–5 years posttreatment [110].

Uterine Leiomyosarcomas

Leiomyosarcoma (LMS) accounts for 30–40 % of all uterine sarcomas and has an annual incidence of 0.64 per 100,000 women in one study [19, 41]. These tumors have high malignant potential and tend to either spread locally or metastasize, mainly

to the lungs [78]. Diagnosis of LMS is often incidental, mostly during routine hysterectomies for benign leiomyomas. Women over age 40 present with abnormal vaginal bleeding (56 %), a palpable pelvic mass (54 %), and pelvic pain (22 %). Bleeding can range from spotting to menorrhagia. Upon pelvic examination, an enlarged uterus can often be appreciated, and tumor can prolapse into the vaginal canal. Preoperatively, they can be difficult to distinguish from benign leiomyomas due to the similarities in signs and symptoms. Other presenting manifestations include hemoperitoneum from tumor rupture and symptoms related to extrauterine extension [19].

Pathological Features

Uterine tumors exhibiting smooth muscle differentiation are diagnosed as LMS based on the Stanford criteria, which include the presence of at least two of the following three: (1) high mitotic rate > 10 mitotic figures per 10 high-power fields, (2) moderate to severe cellular atypia, and (3) areas of coagulative tumor cell necrosis [6, 101]. Others often present supportive clinicopathologic features include peri- or postmenopausal age, extrauterine extension, large size (over 10 cm), infiltrative borders, and atypical mitotic figures [19].

While a spindle cell histology most common describes LMS (Fig. 20.1), there are two uncommon forms of LMS: epithelioid and myxoid. Epithelioid LMS have round to polygonal cells with abundant eosinophilic or clear cytoplasm with the absence of coagulative necrosis. Myxoid LMS (Fig. 20.2) are not classified into the Stanford criteria and have a dense myxoid appearance, making it difficult to visualize the extent of nuclear pleomorphism and number of mitotic figures [53]. Both variants are diagnosed as sarcomas based on their histology and infiltrative borders [19].

Immunohistochemistry and Molecular Biology

Leiomyosarcomas typically express smooth muscle markers including desmin, smooth muscle actin (SMA), h-caldesmon, and histone deacetylase 8 (HDAC8). They also express epithelial markers such as keratin and epithelial membrane antigen (EMA). LMS are occasionally immunoreactive for CD10, although this marker is more commonly found in endometrial stromal sarcoma [1]. In 30–40 % of LMS patients, estrogen receptors (ER), progesterone receptors (PR), and androgen receptors (AR) are expressed [19]. LMS contain an aneuploid karyotype, and polysomy is not uncommon.

Immunohistochemical analysis has shown that uterine LMS has statistically higher levels of Ki67 compared to benign smooth muscle tumors [15]. Overexpression of p53 and p16 has also been described in uterine LMS, compared to its benign counterparts, as well as MIB1 overexpression [76]. These findings seem to suggest that these markers could be implicated in the pathogenesis of uterine LMS. Subtypes with specific gene expression profiles are recognized as well [5].

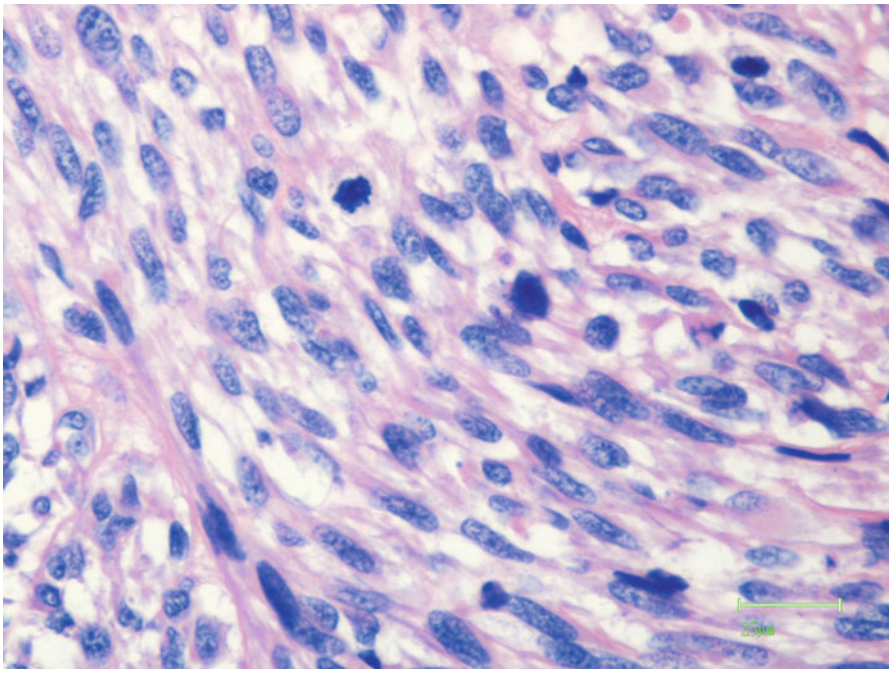

Fig. 20.1 High-power (400×) view of leiomyosarcoma, with hematoxylin/eosin staining showing bundles of cells with cigar-shaped nuclei

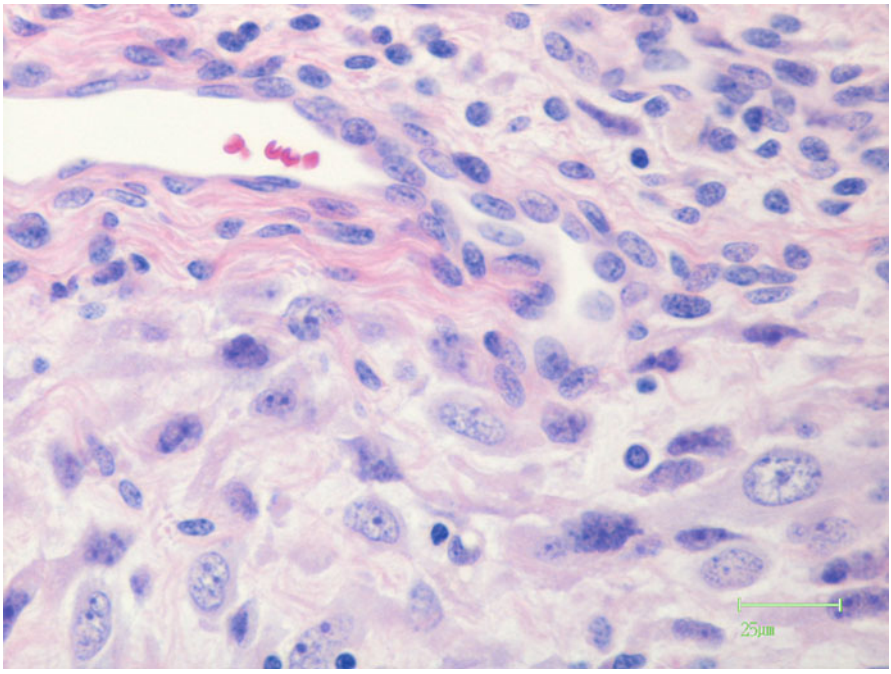

Fig. 20.2 High-power (400×) view of myxoid leiomyosarcoma, with hematoxylin/eosin staining demonstrating abundant myxoid matrix and more irregular pattern of cellularity

Table 20.2 FIGO staging system for uterine leiomyosarcomas and endometrial stromal sarcomas 2009

Stage		Definition
Leiomyosarcomas		
I		Tumor limited to uterus
	IA	<5 cm
	IB	>5 cm
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	> one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis
Endometrial stromal sarcomas (ESS) and adenosarcomas		
I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	> one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

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Staging and Primary Surgical Treatment

Prior to 2009, all uterine sarcomas were staged according to the criteria for uterine carcinoma. In 2009, the International Federation of Gynecology and Obstetrics (FIGO) devised a staging system for uterine leiomyosarcomas and endometrial stromal sarcomas [26] that differs from that for carcinosarcoma and uterine carcinoma (see Table 20.2). The American Joint Commission on Cancer (AJCC) have also published staging systems regarding uterine tumors, without specific reference to sarcomas.

Uterine sarcomas are staged surgically, and not clinically. The standard staging procedure and primary management of localized uterine sarcomas is a total abdominal hysterectomy with bilateral salpingo-oophorectomy (BSO) [30]. Staging should be complete with peritoneal washings for cytology, and biopsies should be taken of any suspicious metastatic lesions.

Lymphadenectomy in uterine LMS is usually unnecessary due to the low frequency of metastases of LMS to lymph nodes in general and without evidence of

its utility. Metastases to the lymph nodes are rare unless there is visible extrauterine disease. In the largest retrospective review of uterine LMS with 1,396 patients, 6.6 % of patients who underwent lymph node dissection had evidence of metastatic disease to lymph nodes. Of those that did metastasize, 70 % had extrauterine spread [52]. There was no improvement in disease-free survival with lymphadenectomy; as a result routine para-aortic or pelvic lymphadenectomy is not recommended.

Ovarian Conservation

Data are limited for ovarian conservation and vary by tumor type. In early-stage LMS, for those premenopausal women who wish to retain their fertility, ovarian conservation may be considered [40]. In one series, 341 women under 50 years of age with stage I or II LMS were found to have no difference in 5-year disease-free survival in those who did or did not undergo BSO [52]. There was no documentation however of ovaries being removed prior to the study. While not an issue in the elderly population, younger women who wish to retain their ovaries should follow up closely with serial physical examinations and imaging of the abdomen, pelvis, and thorax.

Prognosis

Unfortunately, due to their aggressive nature, uterine LMS carry a poor prognosis. Recurrence rates range from 50 to 75 % [61]. The two major prognostic factors include tumor size and spread outside the pelvis [36]. The overall 5-year survival for uterine LMS is under 50 % in stages I and II and less than 15 % in patients with advanced disease [61].

In order to help better predict 5-year overall survival in patients with uterine LMS post-resection, a nomogram was created to help prognostic individual patients (see Fig. 20.3) [114]. The nomogram includes the following prognostic variables: age at diagnosis, tumor size, histologic grade, uterine cervix involvement, extrauterine spread, distant metastases, and mitotic index. These predictors allow for more accurate prediction of outcome compared to the traditionally used FIGO and AJCC staging systems. Since mitotic rate is often high even in leiomyomas, better markers of tumor aggressiveness than mitotic rate are needed to improve the prognostication of leiomyosarcoma outcome.

Adjuvant Radiotherapy

Adjuvant radiation therapy (RT) for uterine LMS is generally not recommended unless there is overt sidewall involvement/adhesion by tumor. Some retrospective studies of uterine sarcomas of all histologies have suggested adjuvant pelvic RT to improve local control. In 2008, a randomized phase III trial by the European Organization for Research and Treatment (EORTC) assigned 219 women with uterine sarcoma stage I and II, of

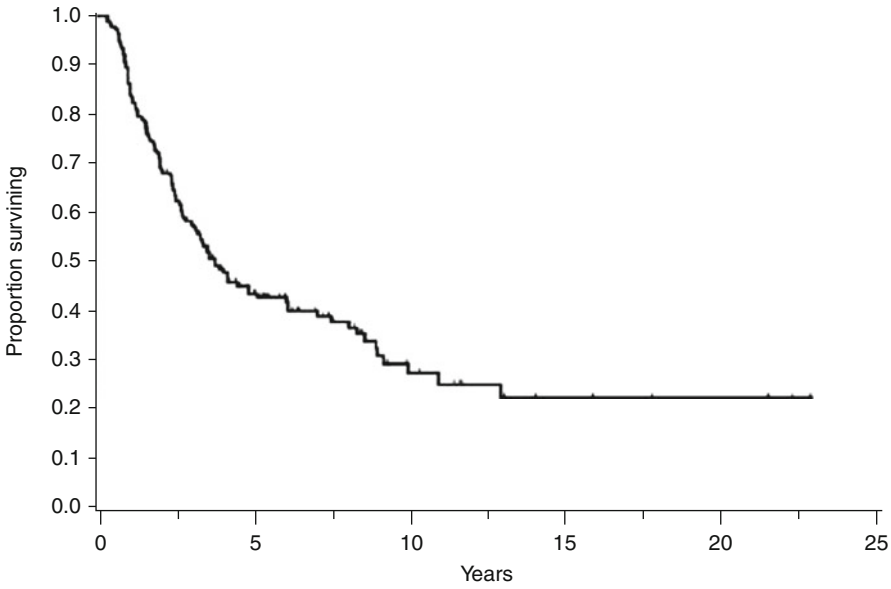

Fig. 20.3 Median overall survival of patients with uterine leiomyosarcoma who were included in a nomogram analysis ($n = 185$). *CI* indicates confidence interval (Zivanovic et al. [114]. Reproduced with permission from John Wiley & Sons, Inc.)

which 99 had LMS, 92 carcinosarcomas, and 30 ESS. Patients underwent pelvic external beam RT of 51 Gy in 28 fractions over 5 weeks or observation. The local relapse rate was 22 % in the adjuvant RT arm and 40 % in the control arm after a median follow-up of 7 years. There was no difference in overall survival though (8.5 vs. 6.8 years) and no difference in median progression-free survival (6.2 vs. 4.9 years) [85].

Adjuvant Chemotherapy

To date, there are no prospective randomized trials showing survival benefit with adjuvant chemotherapy.

In 1985, 156 patients with stage 1 and II uterine sarcomas of all histologies were assigned to either adjuvant doxorubicin for 6 months versus no further treatment. There was no statistical significance between the two arms with no difference in progression-free survival (PFS) or overall survival (OS) [75].

In 2009, a prospective trial of 25 women with uterine LMS with completely resected stage I–IV disease was given gemcitabine (900 mg/m^2 over 90 min d1, d8) and docetaxel (75 mg/m^2 d8) every 3 weeks for 4 cycles [47]. Forty-five percent of patients remained progression-free at 2 years, and the median PFS was 13 months. Patient with early-stage I and II disease had a 59 % PFS at 2 and 3 years, respectively,

with a median PFS of 39 months. Adjuvant gemcitabine plus docetaxel for stage I–IV uterine leiomyosarcoma compares favorably to 2-year PFS rates without adjuvant therapy (19–30 %).

In 2010, a phase II multicenter trial was reported for patients ($n=47$) with primary uterine LMS FIGO stage I, II, or serosa-positive-only IIIA disease. The adjuvant regimen consisted of gemcitabine (900 mg/m^2 over 90 min d1, d8) plus docetaxel (75 mg/m^2 d8) every 21 days for four cycles, followed by doxorubicin (60 mg/m^2) every 3 weeks for four cycles. Seventy-eight percent of women remained progression-free after a median follow-up of 23 months with a median PFS of 39 months. While early results compared favorably with historical estimates of PFS [42] with longer follow-up there is no apparent improvement in overall survival compared to historical patient series [44].

We conclude that adjuvant chemotherapy in patients younger or older is not recommended for resected stage I–IVA uterine LMS, given the lack of evidence of clinical benefit. Patients should be enrolled in clinical trials when feasible.

Treatment of Recurrent or Metastatic Disease

Common sites of metastasis for uterine sarcoma are the lungs, liver, and peritoneum more than other sites such as skin/subcutaneous tissues, bone, and pelvic and paraaortic lymph nodes. Management of recurrent or metastatic uterine LMS is similar to the management of metastatic STS arising from other sites.

Doxorubicin has been the standard first-line treatment in soft-tissue sarcomas, and this is often the case for recurrent/metastatic uterine LMS as well [22]. In addition, trabectedin is approved in Europe for treatment of patients with metastatic sarcomas, after evidence of benefit from a randomized phase II clinical trial of patients with metastatic leiomyosarcoma or various forms of liposarcoma [20]. Dacarbazine also has a long history of use and perhaps greatest activity in leiomyosarcoma, at least compared to other sarcomas [11, 39]. By extension, it is not surprising that temozolomide has activity in leiomyosarcoma as well [32].

Gemcitabine-based therapy is frequently used in the United States for metastatic leiomyosarcoma. The data are now over 10 years old regarding the clinical benefit of gemcitabine-based therapy in leiomyosarcoma. After demonstration of minor activity of leiomyosarcoma in phase II studies of gemcitabine, in 2002, a phase II trial with gemcitabine 900 mg/m^2 d1, d8 plus docetaxel 100 mg/m^2 d8 every 3 weeks in patients ($n=34$) with unresectable leiomyosarcoma who did not respond to zero to two prior chemotherapy regimens resulted in an overall radiological response rate of 53 %. It was active in both previously treated and untreated patients with LMS and was tolerable [48].

Gemcitabine alone was also compared to gemcitabine and docetaxel in a randomized phase trial of metastatic soft-tissue sarcomas. This study, SARC002 from the Sarcoma Alliance for Research through Collaboration consortium, was conducted as a phase III

clinical trial, but in biostatistical review, the study was retitled a randomized phase II clinical trial as a condition for its publication. Median PFS was 6.2 months versus 3 months for gemcitabine alone, and overall survival was 17.9 months versus 11.5 months. The gemcitabine-docetaxel combination was superior in terms of PFS and OS to gemcitabine alone but was associated with an increase in toxicity, such that half of patients were off treatment due to toxicity at 6 months [62]. Accordingly, off trial, the authors suggest a lower dose of docetaxel when this combination is used or use an alternative schedule, such as lower doses weekly of docetaxel with gemcitabine.

Follow-up studies have confirmed that gemcitabine-docetaxel combinations have demonstrated significant radiological benefit in both first-line and second-line settings for metastatic LMS [45, 46].

A retrospective analysis was performed in France of 133 unresectable or metastatic STS patients treated with gemcitabine-docetaxel, of which 76 were LMS, using the Hensley schedule of gemcitabine-docetaxel. Overall response was 18 %, with no difference between LMS and other histologic subtypes. Median OS was 12.1 months with a better OS correlated with leiomyosarcoma ($p = 0.01$) [4]. Notably, a follow-up French study examining gemcitabine versus gemcitabine-docetaxel showed no benefit for the addition of docetaxel to gemcitabine specifically in uterine or non-uterine leiomyosarcoma [77]. Based on our experience as well as the SARC002 clinical trial data, docetaxel may be more beneficial in combination in other sarcoma subtypes, such as UPS (undifferentiated pleomorphic sarcoma, formerly MFH (malignant fibrous histiocytoma)), rather than in leiomyosarcoma.

Most recently, gemcitabine with dacarbazine (DTIC) was compared to gemcitabine alone in a phase II multicenter randomized trial of 113 previously treated patients with advanced STS [33]. Patients received either fixed-dose-rate gemcitabine (10 mg/m^2/min) at 1,800 mg/m^2, followed by DTIC 500 mg/m^2 every 2 weeks or single-agent DTIC 1,200 mg/m^2 every 3 weeks. At 3 months, the arm with gemcitabine and DTIC had a progression-free rate (PFR) of 56 % versus 37 % for DTIC alone ($p = 0.001$). Median PFS was 4.2 months versus 2 months, and the median OS was 16.8 months versus 8.2 months, favoring the gemcitabine plus DTIC arm. These data are similar to the data collected from the SARC002 gemcitabine ± docetaxel study, suggesting synergy of different agents with gemcitabine. As a result, the gemcitabine-DTIC combination is as reasonable as gemcitabine-docetaxel in patients with metastatic leiomyosarcoma, and given the negative data from France, it is plausible that the gemcitabine-DTIC combination is superior to gemcitabine-docetaxel for leiomyosarcoma, although this has not been examined prospectively.

Hormonal Therapy

Like many gynecologic neoplasms, estrogen and progesterone receptors (ER and PR) are expressed in uterine LMS, in 57 % and 43 % of patients in one study [7], although there is variability from study to study. Expression of hormonal receptors does not seem to correlate with clinical stage, age, or recurrence of the disease. ER and PR status does not appear to influence overall or disease-free survival [7].

A retrospective analysis was performed on 34 patients with advanced or recurrent LMS of which majority had positive hormonal receptor status. Patients received an aromatase inhibitor with majority being given letrozole (74 %), anastrozole (21 %), and exemestane (6 %). PFS at 1 year was 28 % for ER- and/or PR-positive uterine LMS with best objective response being a partial response in 9 % of all ER-positive patients [72]. Aromatase inhibitors and other hormonal manipulation appear to have limited benefit in uterine LMS, although consideration to their use can be considered in the elderly or otherwise asymptomatic patient with small volume metastatic disease, in which the use of cytotoxic chemotherapy is associated with greater side effects than the metastatic tumor itself. We consider this option most useful in asymptomatic patients with small volume disease.

Summary: Leiomyosarcoma

For elderly patients with uterine leiomyosarcoma, there is no obvious clinical benefit for the use of adjuvant chemotherapy, at least as of early 2012. For metastatic disease, anthracyclines, dacarbazine, and gemcitabine, alone or in combination, are useful options for patients with rapidly progressive disease. In our experience, ifosfamide has less activity and is relatively contraindicated in elderly patients given the central nervous system toxicity of the agent. Gemcitabine and DTIC is another option for combination therapy that is associated with a survival advantage in a phase III clinical trial. Data from France indicate that gemcitabine alone may be as useful as gemcitabine-docetaxel for patients with metastatic leiomyosarcoma. Temozolomide has activity in uterine leiomyosarcoma and is a good option for systemic therapy. Hormonal therapy can be considered for asymptomatic patients with low-volume disease, but response rates are low. Trabectedin is approved in Europe for sarcomas and another option for patients with metastatic leiomyosarcoma, although the RECIST response rates are very low.

Uterine Carcinosarcoma (Malignant Mixed MüllerianTumors)

Introduction

Uterine carcinosarcoma, also known as malignant mixed Müllerian tumor (MMMT) or mixed mesodermal sarcoma, is an aggressive malignancy associated with a poor prognosis. It accounts for 1.2 % of all uterine malignancies with an incidence of 1–4 per 100,000 women older than 35 years of age [9] and a median age at diagnosis of 62–67 years [30]. Incidence in African-American women is twice as high as in Caucasian women [92]. This tumor typically occurs in postmenopausal women with clinical symptoms of vaginal bleeding and an enlarged bulky uterus and tends to present in an advanced stage up to one-third of the time [19].

Risk Factors

Risk factors implicated with uterine carcinosarcomas are similar to those of endometrial carcinomas. A study by Zelmanowicz et al. found that marked obesity increased the risk of uterine carcinosarcoma by 3.2-fold [113]. Nulliparity also was associated with a 1.7-fold increase in carcinosarcomas compared with women who bore children [113]. Tamoxifen has also been implicated as a risk factor. In NSABP studies, tamoxifen was associated with an increased risk of both endometrial adenocarcinoma and uterine sarcoma, predominately uterine carcinosarcoma [27, 108].

Recent and long-term users of non-contraceptive estrogens have also been directly associated with an increased risk of uterine carcinosarcomas [90]. Pelvic irradiation is also a risk factor for uterine carcinosarcoma. In a comparison study between radiation-associated endometrial cancers (RAEC) and sporadic endometrial cancers, it was noted that patients who developed either endometrial carcinoma or carcinosarcoma had higher stage and grade tumors than their sporadic counterparts [80, 81]. A history of pelvic irradiation can be elicited in as many as 37 % of patients with carcinosarcomas in one study [19].

Pathological Features

The inclusion of MMMT/carcinosarcomas in this chapter is made for completeness, given the term "sarcoma" in the term carcinosarcoma. Carcinosarcomas have been largely reclassified as metaplastic carcinomas due to their frequent recurrence as pure adenocarcinomas, their frequency of endometrial adenocarcinoma being found within same hysterectomy specimen, and their similar metastatic pattern [19]. Specifically, while both epithelial and mesenchymal elements are found in uterine carcinosarcomas, the metastases from this diagnosis are usually carcinoma. We note here that of all the neoplasms in which the somewhat clumsily used term "epithelial-mesenchymal transition" is used, carcinosarcomas (be it of the uterus or other sites such as lung or breast) are perhaps the best example of tumors that demonstrate divergent differentiation from the primary tumor.

Microscopically, the carcinomatous portion of carcinosarcoma is either papillary serous (66 %) or endometrioid (33 %). The sarcomatous portion is purely high grade and heterogeneous; homologous elements usually include spindle cell sarcoma (sarcoma not otherwise specified), and heterologous portions can include malignant skeletal muscle or cartilage neoplasms [19, 25]. In two separate GOG studies, patients with tumors composed of heterologous sarcomatous elements have a significantly increased rate of recurrence and decreased rate of survival compared to those with purely homologous elements [25, 61].

High-grade-, serous-, or clear-cell carcinomatous components as well deep myometrial invasion and lymphatic or vascular space invasion are also associated with increased incidence of metastases [25, 93]. Surgical stage, in particular the depth of myometrial invasion, is the most important prognostic indicator [19].

Immunohistochemistry

Not surprisingly, carcinomatous and sarcomatous elements of this family of tumors express markers appropriate for both histologies. Expression of cytokeratins, epithelial membrane antigen (EMA), and p53 is often observed from the serous components [19]. Desmin, myogenin, and MyoD1 are found in rhabdomyosarcomatous elements [19]. Vimentin and CD10 are also frequently observed [19]. Carcinosarcomas overexpress Trop-2 and are sensitive to hRS7, a monoclonal anti-Trop-2 antibody, suggesting a novel therapeutic approach [84].

Staging

The most important prognostic factor for carcinosarcomas is surgical stage, which is assessed surgically and not clinically. The 2009 FIGO staging system for carcinoma of the endometrium is presently used for staging carcinosarcoma, although AJCC staging for uterine carcinoma can also be used in this setting. With the new FIGO staging system for uterine carcinoma, the 5-year disease-specific rates have changed [38].

Surgical Treatment

Standard of care for uterine carcinosarcoma includes a total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, peritoneal cytology and biopsy of suspected metastasis, and pelvic and para-aortic lymphadenectomy [19, 30], as is appropriate for uterine carcinomas as well. The incidence of regional lymph node metastases is 20% [30, 102]. A study by Temkin et al. demonstrated higher disease-free and overall survival in patients with higher lymph node count [102]. The only risk factor that correlated with survival and recurrence in early-stage carcinosarcoma was the number of lymph nodes removed [102]. A Surveillance and Epidemiology and End Results (SEER) study demonstrated that women who had lymphadenectomy had an overall survival of 54 months compared to 25 months in those who did not [70].

Omentectomy is recommended in uterine carcinosarcoma because of the high risk of upper abdominal spread. Uterine carcinosarcoma is the only uterine sarcoma in which lymphadenectomy and omentectomy are the standard of care, unless there are visibly large nodes upon surgical resection in other histologic subtypes [68].

Optimal surgical cytoreduction is the present standard of care performed in women with advanced carcinosarcoma, although there are no randomized data to support its use. Given the nondurable responses to chemotherapy in the metastatic setting of carcinosarcoma, surgical debulking represents the fastest way to obtain meaningful cytoreduction and as a result is not likely to be challenged as a standard of care for advanced disease.

Adjuvant Therapy

Chemotherapy

A phase III trial by Wolfson et al. compared three cycles of ifosfamide, mesna, and cisplatin with whole abdominal irradiation (WAI) therapy for all stages of uterine carcinosarcoma that had undergone optimal debulking surgery [43, 109]. The ifosfamide, mesna, and cisplatin arm had a 29 % lower risk of death with benefit seen in all stages of disease [43, 109]. However, no statistically significant advantage in recurrence rate or survival was seen in the adjuvant chemotherapy group over WAI. In fit patients, chemotherapy remains a reasonable standard of care, although we have trepidation for any ifosfamide-based regimen in elderly patients.

Carboplatin and paclitaxel were also studied in the adjuvant setting, demonstrating chemotherapy alone or with radiation therapy was associated with a longer PFS and OS in all stages of carcinosarcoma, compared to radiation therapy alone. In the radiation-only arm, recurrences in the lung and abdomen were much higher [43, 63]. The superior tolerance of this combination in elderly patients makes it a better standard of care for older patients than ifosfamide-based therapy, and if adjuvant chemotherapy is to be entertained, this appears to be an appropriate combination of agents to consider.

In an earlier trial by Omura et al., single-agent doxorubicin did not show improvement in PFS or OS in early stage sarcoma, with carcinosarcoma making up 52 % of the sarcomas represented [75]. As a result, doxorubicin is not employed in the adjuvant therapy of carcinosarcoma, although anthracyclines can be considered for advanced disease.

Radiation Therapy

The role of adjuvant pelvic irradiation in early-stage carcinosarcoma remains controversial. Retrospective analyses from single-institution studies have demonstrated a decrease in local recurrence with adjuvant pelvic radiation therapy, but no increase in overall survival [17, 35, 89]. A European Organization for Research and Treatment of Cancer (EORTC) trial also studied adjuvant radiation therapy for stage I–II disease [85]. The study found a significant benefit for local control in carcinosarcoma patients, but no increase in disease-free survival or overall survival [85]. Per National Comprehensive Cancer Network guidelines, vaginal brachytherapy is also an acceptable alternative to external beam pelvic radiation therapy for adjuvant treatment of uterine sarcomas [69]. Brachytherapy has demonstrated to decrease vaginal recurrences in high-risk endometrial carcinoma patients. Whole abdominal irradiation is also an option.

Given the toxicity of radiation therapy, we suggest radiation therapy, if it to be considered, in patients with disease that involves the pelvic sidewall, in which microscopic disease is anticipated to be an even greater problem than with uterus-confined disease alone.

Recurrent and Metastatic Treatment

Recurrent and metastatic disease is predominately carcinomatous; however, metastases are observed that are carcinomatous, sarcomatous, or both [25]. Cisplatin is an active agent in uterine carcinosarcomas with an overall response rate of 19 % in first-line treatment and 18 % in second-line treatment [103, 104].

Another active agent is ifosfamide, with response rates of 32 % in previously untreated groups and 18 % in treated groups [98, 99]. In a phase III trial, ifosfamide and cisplatin were compared to ifosfamide alone showing higher response rates but no change in overall survival [97]. Another phase III trial comparing ifosfamide and paclitaxel with ifosfamide alone showed higher response rates, longer PFS, and longer overall survival [49]. In a very fit patient, ifosfamide-paclitaxel can be considered, but these data also underscore the activity of taxanes in this diagnosis.

Due to the toxicity of ifosfamide and regimen schedule of ifosfamide and paclitaxel, paclitaxel was then combined to carboplatin. The combination of carboplatin and paclitaxel has been shown to have a 54 % total overall response rate in advanced carcinosarcoma in previously untreated patients, making it a logical first-line treatment for advanced carcinosarcoma [82], especially in the elderly.

Second-line agents including topotecan, gemcitabine, and etoposide have been studied in phase II trials and have been demonstrated relatively poor radiological response rates [66, 67, 94].

Biomolecular agents including imatinib, and thalidomide have each been studied in phase II trials and have demonstrated minimal activity [50, 112]. As a result, fit patients with disease no longer responding to carboplatin, taxanes, and/or ifosfamide are candidates for phase I–II clinical trials of novel agents.

Summary: Malignant Mixed Müllerian Tumors/Carcinosarcoma

Carcinosarcomas are now better defined as uterine carcinomas with divergent differentiation. Surgery remains the standard of care, and adjuvant chemotherapy may be associated with slightly better prognosis than using whole abdominal radiation. Carboplatin and paclitaxel are a good standard of care for adjuvant chemotherapy. Anthracyclines, platinum agents, and ifosfamide have modest activity in recurrent/metastatic disease. In elderly patients, ifosfamide is given with caution owing to substantial risk of CNS side effects over the age of 60. Systemic therapy overall for carcinosarcoma leaves much to be desired, and as with uterine carcinoma, newer approaches and agents are needed.

Endometrial Stromal Tumors

Traditionally, ESS has been categorized into low-grade and high-grade tumors based on their maximal mitotic count. However, ESS now refers to only low-grade tumors as long as the tumor cells resemble proliferative endometrial stromal cells [30].

Per WHO (2003), the endometrial stromal tumor group is divided into endometrial stromal nodules (ESN), low-grade endometrial stromal sarcomas (ESS), and undifferentiated endometrial sarcomas (UES). UES will be discussed in the next section.

Endometrial Stromal Nodule

ESNs are typically solitary round unencapsulated benign tumors, ranging from 1 to 22 cm [19]. They occur during the reproductive or postmenopausal years and are often present as vaginal bleeding or are found on incidental hysterectomy specimen. Endometrial stromal nodules have expansile, non-infiltrating smooth margins compared to the infiltrating irregular margins of stromal sarcomas [3]. Another distinguishing feature between the two is that ESSs permeate the myometrium and invade vasculature. For ESN, surgical resection with hysterectomy is the standard treatment choice. ESNs do not relapse and carry an excellent prognosis.

Endometrial Stromal Sarcoma

Endometrial stromal sarcomas (ESSs) account for 0.2 % of all uterine malignancies [54] and 10–15 % of all uterine sarcomas. ESS arise from the mesenchymal stroma of the endometrium. ESS are well-differentiated tumors lacking significant cellular atypia with mitotic activity typically <5 MF/10 HPF and rare necrosis [19] (Fig. 20.4). They usually invade the endometrium, myometrium, or both and may even invade serosa. At presentation, up to one-third have extrauterine pelvic spread, most commonly involving the ovaries. The FIGO staging system for uterine leiomyosarcomas and ESS is the same (see Table 20.2). These tumors are relatively uncommon in the elderly population, while undifferentiated endometrial sarcomas are more common in a somewhat older population than typically seen for ESS.

Immunohistochemistry and Molecular Biology

Both ESN and low-grade ESS are immunoreactive for vimentin, muscle-specific actin, alpha-smooth muscle actin, and very often keratin [19, 74]. Desmin and h-caldesmon are generally negative in low-grade ESS [74]. Estrogen and progesterone receptors are frequently expressed in low-grade ESS. A retrospective series of 21 low-grade ESS found ER and PR in 71 and 95 %, respectively [30, 88]. The leading chromosomal aberrations are translocations, most commonly the *JAZF1-SUZ12* fusion gene found in 64 % of endometrial stromal tumors, followed by rarer *JAZF1-PHF1* and

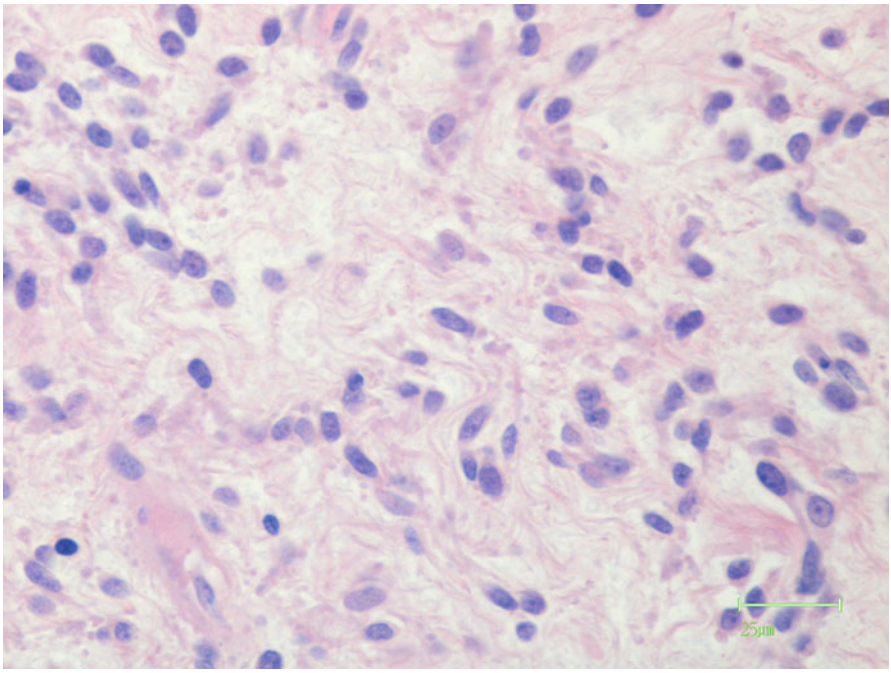

Fig. 20.4 High-power (400×) view of endometrial stromal sarcoma, with hematoxylin/eosin staining demonstrating little cellular atypia and a low mitotic rate

EPC1-PHF1 [18, 71]. A novel translocation-induced genetic rearrangement of *YWHAE* was described in 2008 in a fibrous variant of ESS, raising questions about its relationship to undifferentiated endometrial sarcoma, which has a much higher frequency of *YWHAE* translocations (see the section on undifferentiated endometrial sarcomas below [86]. In the subset of ESS patients in which it was identified, ESS with *JAZF1* rearrangement exhibited more aggressive histologic features than the usual low-grade ESS [57].

ABL was detected in all 13 paraffin-embedded ESS specimens in a retrospective analysis, but the utility of receptor tyrosine kinase-based therapy is unknown [16]. The presence of a marker does not foreordain activity of an inhibitor of that protein, as is demonstrated by the lack of response of KIT-positive small-cell lung cancer to imatinib.

Treatment

ESS tend to have an indolent clinical course and carry a relative good prognosis. Five- and 10-year survival for stage-1 tumors are 98 and 89 %, respectively [14]. Furthermore, low-grade ESS is characterized by long-term survival despite late recurrences and

metastasis [83]. Recurrences develop in about one-third of patients, mostly in the abdominal and pelvic regions and less commonly in the lung and vagina [14]. Distant metastatic disease is found in 15–30 % of patients [43, 56]. It is not surprising that clinical outcomes are dependent upon the extent of the tumor at diagnosis.

Surgical Treatment

The mainstay of therapy for ESS is surgery. Surgical treatment mandates a hysterectomy and bilateral salpingo-oophorectomy for early-stage disease. As these tumors frequently express estrogen and progesterone receptors and are hormone sensitive, patients whose ovaries are not removed have a higher risk of recurrence [95]. Lymphadenectomy remains controversial, and the role is unclear. In a recent large study, 100 of 384 women with ESS underwent lymphadenectomy; at 16-year median follow-up, no difference in overall survival was detected between women who did or did not have lymph node spread [91]. In this study, only 7 % of 100 women had lymph node metastasis [91]. Lymph node involvement does increase the stage; however, it has not been proven to decrease survival rates.

Adjuvant Radiation Treatment

Adjuvant radiation therapy is not generally recommended. Some argue radiation therapy is not beneficial because of the indolent natural history of ESS and long remissions [16]. However, NCCN guidelines suggest radiation therapy for ESS greater than stage I disease for reducing local recurrences [69]. As a practical matter if there is pelvic sidewall involvement, radiation therapy would be expected to help minimize local-regional recurrence, but data in this regard are lacking.

Adjuvant Systemic Treatment

There are no data to support the use of adjuvant systemic therapy. The low-grade nature of this malignancy may in part explain why cytotoxic chemotherapy has not been proved to affect prognosis.

Adjuvant Hormonal Treatment

Hormonal therapy is often employed in the adjuvant treatment for ESS, without randomized data to support its use [64]. We are skeptical that the already favorable outcomes enjoyed by patients with low-grade ESS are affected significantly by the use of

hormonal therapy in the adjuvant setting. Any claims of the utility could be chalked up to the good outcomes seen as part of the natural history of this disease, rather than the effect of hormonal therapy. Perhaps poor outcomes seen in patients with undifferentiated endometrial sarcoma (formerly called high-grade endometrial sarcoma) have been the driving force in the use of antiestrogens in patients with resected ESS.

ESS frequently express both estrogen and progesterone receptors [88]. Active agents used in the metastatic setting that are often seen to be used in the adjuvant setting include megestrol, aromatase inhibitors including anastrozole, letrozole, and exemestane, and gonadotropin-releasing hormone (GnRH) analogs such as leuprolide, goserelin and triptorelin, which can also suppress ovarian estrogen production and are a good option for premenopausal women who wish to retain ovarian function [12]. Without even phase II data to support its use, the authors find it difficult to recommend hormonal therapy in the setting to patients with low-grade ESS.

Recurrent and Metastatic Treatment

The activity of hormonal therapy in the metastatic setting is the likely reason physicians have used adjuvant hormonal therapy. First-line therapy in the setting of recurrent or metastatic disease is hormonal therapy. For example, in a retrospective analysis of 47 women with advanced ESS treated with antiestrogen therapy, 17 % had a complete response and 10 % had a partial response with a median time to tumor progression being 24 months [16]. First-line agents for estrogen-receptor-positive tumors are aromatase inhibitors with or without GnRH analogs [87]. For those tumors that do not express estrogen receptors but are progesterone receptor positive, GnRH analogs alone are appropriate. Another option for progesterone-receptor-positive-only tumors is progestin therapy [87]. Since aromatase inhibitors can cause osteoporosis, bone scans and prophylactic osteoporosis care appears warranted, in particular in the unusual older patients who present with ESS, typically a diagnosis of younger women.

There are limited data on chemotherapy in the setting of advanced ESS. Extracting data from small case reports and from other soft-tissue uterine sarcomas, doxorubicin is a common agent of choice. Ifosfamide alone, ifosfamide with doxorubicin and cisplatin, and the combination of carboplatin and paclitaxel have all been given with evidence of radiological responses [96, 100, 111].

Prognostic Factors

Age, race, primary surgery, stage, and grade are prognostic factors for outcome in ESS [13]. In a large study of 800 patients with ESS, age < 52 was associated with a 20 % higher 5-year disease-specific survival (DSS) compared with older patients. African-Americans had poorer survival as well [13]. Patients with stage I and II disease had a 5-year DSS of 89 % compared to 50 % in stage III and IV disease [13]. Patients with grades 1 and 2 ESS had a 5-year DSS over 90 % compared to only

42 % in those with grade 3 tumors, supporting that high-grade ESS, now called undifferentiated stromal sarcomas, have distinct biologic behavior [13].

Summary: Endometrial Stromal Sarcomas

Patients with ESS tend to be younger than those with undifferentiated endometrial sarcoma. Nonetheless, if ESS is seen in this population, surgery alone appears to be a good standard of care for primary therapy, with radiation withheld unless there is overt sidewall involvement. Estrogen antagonism is a useful treatment strategy in the metastatic setting, but it is entirely unclear if it affects survival in the adjuvant setting. Chemotherapy can be useful in metastatic disease as well.

Undifferentiated Endometrial Sarcoma

Pathological Features

Previously termed, or at least overlapping with what has been called high-grade endometrial stromal sarcoma, undifferentiated endometrial sarcomas (UESs) are highly aggressive tumors with a poor prognosis. These tumors tend to have early recurrences and recur frequently, and occur in an older population than those patients with endometrial stromal sarcoma (ESS). Unfortunately, most die from UES within 2 years of diagnosis [19].

The diagnosis of UES is made by the following characteristics: myometrial invasion, severe nuclear pleomorphism, high mitotic activity and/or tumor cell necrosis, and lack of smooth muscle or endometrial stromal differentiation [19, 101]. Mitotic activity almost always exceeds 10 MF/10 HPF and can approach 50 MF/10 HPF [19]. Histologically, the mesenchymal cells resemble a carcinosarcoma more than an endometrial stromal tumor [101]. In a Norwegian study, the only significant prognostic factor found was vascular invasion, with a 5-year overall survival of 83 and 17 % when vascular invasion was absent or present, respectively [2].

Immunohistochemistry

Unlike endometrial stromal sarcomas, UES do not express estrogen and progesterone receptors. UES does not stain for actin or desmin, helping differentiate it from LMS. Cyclin D1 can serve as a marker for UES with at least a subset of YWHAE translocations, however (see below) [58].

Molecular Biology

A series of translocations involving *YWHAE* are found in patients with UES, which also distinguishes this unique tumor from ESS [57]. Some ESS are also positive for *YWHAE* translocations, and as a result, the relationship between these forms of endometrial sarcoma remains a topic of discussion. One of the downstream targets of the 14-3-3 kinase-scaffolding protein YWHAE is IRS1, suggesting possible utility of (insulin-like growth factor 1 receptor) IGF1R inhibitors in the treatment of this disease. The negative study of an IGF1R inhibitor in non-small cell lung cancer has unfortunately all but shut down research on IGF1R inhibitors in cancer, save for small studies, making it difficult to test this hypothesis in this diagnosis.

Treatment

Primary treatment for UES is surgical. Total abdominal hysterectomy with bilateral salpingo-oophorectomy with radical cytoreduction of extrauterine disease remains the standard of care in early disease [31]. There are no data to support use of nodal resection improving survival, and it is difficult to routinely recommend. There is also no consensus regarding adjuvant radiation therapy and chemotherapy. Despite this, adjuvant radiation therapy is recommended to those patients with a high risk of recurrence, given the high local recurrence risk without radiation therapy. Unfortunately, like other uterine sarcoma, patients usually die more often of metastatic disease than local-regional recurrence, and as a result, it is not clear that radiation improves overall survival. There are also no data that chemotherapy improves overall survival.

A reason some physicians suggest adjuvant chemotherapy is that distant metastasis and local recurrences lead to a high mortality rate [19]. In metastatic or recurrent disease, the combination of ifosfamide and doxorubicin is often used [96]. In elderly patients, a baseline evaluation and constant clinical observation during the infusion should be performed to reduce the risk of encephalopathy from ifosfamide, if it is to be used at all [10]. Case reports of ifosfamide, doxorubicin, and cisplatin have also demonstrated clinical response [111]. To date, no prospective clinical trials have been carried out for UES due to the rarity of the disease.

Summary: Undifferentiated Endometrial Sarcoma

UES is a newly defined diagnosis given translocations involving *YWHAE* 14-3-3 kinase interacting proteins that define the diagnosis, and can occur in women over 60 years of age. Beyond surgery, adjuvant chemotherapy and radiation are not proved helpful, although local-regional involvement of primary tumor is a reasonable rationale for adjuvant radiation. We look forward to the investigation of IGF1R inhibitors and other kinase inhibitors in this diagnosis based on our anecdotal experience with these agents.

Rhabdomyosarcoma

Rhabdomyosarcoma is mostly seen in children and is very uncommon in the elderly but is mentioned in this review for completeness [79]. The three principal subtypes of rhabdomyosarcoma are embryonal, alveolar, and pleomorphic, of which the pleomorphic subtype gives rise to most rhabdomyosarcomas of the uterine corpus in the elderly [24]. This tumor is exceedingly rare. Of the pure heterologous sarcomas of the uterine corpus and cervix, rhabdomyosarcoma is the most common [24]. Since the description of this tumor in 1869 by Anderson and Odmansson, there have been fewer than 100 case reports on pleomorphic uterine rhabdomyosarcoma [21, 24, 55]. The average age at diagnosis is 68 years, but it has been reported anywhere from 35 to 87 years [24]. In one review of 27 patients with this disease, upon surgical staging, 59 % of patients were found to have extrauterine disease [24]. Local metastasis is more common, with lymph nodes in the pelvis involved. The most common site for distant metastasis is the lung parenchyma [37]. Staging follows FIGO or AJCC systems, or in younger patients, an entire staging system has been developed for rhabdomyosarcoma, which is beyond the scope of this manuscript.

Pleomorphic uterine rhabdomyosarcoma is a highly aggressive tumor with a high case-fatality rate [24]. At the time the review concluded, 73 % of patients died from their disease, 19 % had no evidence of disease, one patient died from other causes, one was alive with disease, and one was lost to follow up [24]. More than half of the patients who died did so within 6.5 months from diagnosis [24].

The etiology and risk factors for uterine rhabdomyosarcoma are unknown. Pelvic irradiation has been reported in a few case reports [60, 65]. Tamoxifen has also been implicated in a few case reports [37, 73].

Pathology and Immunohistochemistry

Features suggestive of rhabdomyosarcoma are a significant population of cells with abundant eosinophilic cytoplasm and eccentrically placed nuclei. Histologically, they are round, polygonal, or spindle-shaped cells that grow among rhabdomyoblasts in a diffuse random pattern [37]. Morphologic features can also include tumor giant cells, osteoclast-like giant cells, and a patchy myxoid stroma [24].

Uterine rhabdomyosarcomas stain positive for myogenin, myoD1, smooth muscle actin, desmin, muscle-specific acting (HHF-35), and occasionally stain for calponin [24]. They do not stain for cytokeratin 7, synaptophysin, epithelial membrane antigen, placental-like antigen, chromogranin, and a pan-keratin. These tumors frequently express CD10 and CD56 [24].

Treatment

The wide variety of therapies that have been tried in the past have no significant impact on outcomes. Most women receive a total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic dissection; rhabdomyosarcomas are one form of sarcoma with a higher lymph node metastatic rate than other sarcomas. Given the poor prognosis, an adjuvant regimen based on vincristine-dactinomycin-cyclophosphamide can be considered in fit patients. The weekly schedule of vinca alkaloids of pediatric studies cannot be delivered to adults, and thus, every 3-week cycle of therapy appears appropriate in an off study setting. Gemcitabine-docetaxel may have at least minor activity in pleomorphic rhabdomyosarcoma in the metastatic setting [62], activity greater than that of gemcitabine-based therapy in pediatric subtypes of rhabdomyosarcoma [34, 107], further substantiating pleomorphic rhabdomyosarcoma as a unique sarcoma subtype.

Perivascular Epithelioid Cell Tumor (PEComa)

Perivascular epithelioid cell tumors (PEComas) of the uterus are rare mesenchymal neoplasms with uncertain malignant potential that have been recognized by the WHO as a distinct entity [23, 28]. They are again mentioned in this review for completeness and may be more common than pleomorphic rhabdomyosarcoma of the uterus in patients over 60 years of age.

The perivascular epithelioid cell was first described in 1992 and was found to share features with melanocytes, neuroendocrine cells, and muscle cells [8]. The most frequent site of origin for PEComas is in the uterus and retroperitoneum [23]). Occasionally, PEComas are associated with tuberous sclerosis. PEComas are linked histologically to angiomyolipoma, clear-cell sugar tumor of the lung, and lymphangioleiomyomatosis. As implied by the relationship to tuberous sclerosis, PEComas frequently lack *TSC2* expression and as a result have activation of the TOR kinase pathway [29].

In a series of eight patients with uterus PEComa, age range at presentation was between 40 and 75 years with a mean age of 54 [105]. Women presented with abnormal vaginal bleeding and were found to have a mass in the uterine corpus [105].

The clinical behavior of PEComas ranges from indolent aggressive tumors with distant metastases [51]. There are no data to suggest why some tumors may be more aggressive than others. In another series of 31 patients with uterine PEComa, the 13 patients in the “malignant” group and 18 patients in the “non-malignant” group did not differ significantly in regards to duration of follow-up or patient age [23]. The malignant group had tumors significantly larger than the

nonmalignant group [23]. Both coagulative necrosis and a mitotic count >1/10 HPF were highly associated with the malignant group [23]). Other criteria associated with aggressive clinical behavior include tumor size >5 cm, high nuclear grade, and an infiltrative growth pattern [29].

Pathology and Immunohistochemistry

Perivascular epithelioid cells are round to polygonal epithelioid and spindle-shaped cells with clear to eosinophilic granular cytoplasm. They are located next to vessel walls [23]. They express melanocytic markers HMB45 and MART-1, and they positively stain for smooth muscle actin, confirming the myoid lineage as well [23]. This tumor can also express MIB-1 in both primary tumor and recurrence in about 5 % of cases [40]. In order to avoid a misdiagnosis, Vang et al. have recommended for all epithelioid mesenchymal uterine tumors to stain immunohistochemically for HMB45 [105].

Treatment

The majority of PEComas are benign, and after complete surgical resection, they do not recur [106]. For those PEComa tumors that exhibit malignant behavior, either local recurrences or distant metastasis, they need further treatment. The most commonplace to metastasize is the lung [106]. Given their usually indolent behavior, neither postoperative radiation nor chemotherapy is given.

A possible etiology for PEComas could be linked through activation of the TOR-signaling pathway [106]. In 2010, TOR inhibitor sirolimus was found to have clinical activity in malignant perivascular epithelioid cell tumors by targeting TORC1 [106]. Activity of temsirolimus in PEComa is also reported [51]. Unfortunately, the responses to TOR inhibitors are generally less durable than that of imatinib in gastrointestinal stromal tumors, so strategies using combinations of agents based on TOR inhibition are warranted. Cytotoxic chemotherapy is largely inactive in this diagnosis, in our experience, and patients with this diagnosis are good candidates to participate in clinical trials of new agents.

Conclusion

In keeping with the anatomy of the uterus, it is not surprising that several different forms of sarcoma can develop. Each has a distinct and unique clinical behavior and is as different from one another as uterine carcinoma is from ovarian carcinoma, if not more so. There are different age distributions of each sarcoma subtype with

leiomyosarcoma, MMMT and UES as the most common varieties all of which can occur in an older population. As more clinical trial data are accumulated and molecular methods brought to bear on this interesting group of tumors, we expect improvements in diagnosis and treatment options in both the metastatic and hopefully in the adjuvant setting as well. In the meantime, careful attention to side effects in an older population is necessary to find the balance between toxicity and clinical efficacy with available agents. We lack specific data on many clinical scenarios in the 8th and 9th decade, a topic worthy of further research in our aging population.

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Chapter 21
Sexual Medicine in the Management of Older Gynecologic Cancer Patients

Cara Stabile, Rebecca Steed, and Jeanne Carter

Abstract Although rates of sexual activity and function have been noted to decline over time in gynecologic cancer populations, it is important not to presume that sexuality is an insignificant aspect of life for older adults. The sexual and vaginal health impact of cancer treatment can be devastating for women of all ages. Disease type, stage of disease, and type of treatment can contribute to vaginal atrophy and sexual difficulties in female cancer patients, and particular gynecologic cancer diagnoses may present their own unique challenges. Regardless of the type or extent of surgery, surgical scars are constant reminders of a woman's cancer experience and can influence her view of herself. Unfortunately, the epidemiology of sexual dysfunction in female cancer populations has not been extensively studied, and future clinical trials focusing on age, race, ethnicity, and treatment factors are needed. Vaginal health issues are especially problematic for all women with advancing age; however, there are many simple strategies to alleviate vaginal estrogen deprivation symptoms, but this information needs to be delivered to our patients. Maintaining overall vaginal health is crucial for comfort, especially since gynecological and pelvic examinations are a necessary part of routine care and cancer surveillance.

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Despite positive changes in the oncology and sexual medicine fields over the past several decades, past several decades, there is still a paucity of targeted and a paucity of targeted interventions addressing sexual and vaginal health issues. Prospective research with uniform measures and methods are needed to fully comprehend the impact of gynecologic cancer on the sexual function and vaginal health of women of all ages coping with cancer.

Keywords Gynecologic cancer • Older adults • Sexuality • Vaginal health

Gynecologic cancers account for approximately 11 % of the newly diagnosed cancers in women in the United States and 18 % in the world [1]. As the cancer population continues to grow, survivorship issues, which are centrally linked to quality of life (QOL), are becoming increasingly important. The impact of cancer treatment on sexual and vaginal health can be devastating for women of all ages. Although rates of sexual activity and function decline over time in both the general population [2] and gynecologic cancer populations [3], it is important to avoid the assumption that sexuality is not important to older adults. In fact, studies suggest that older adults engage in nonintercourse sexual activities [4]. The normal aging process produces many physical changes that influence vaginal health and sexual activity. Intercourse may be avoided if a woman struggles with vaginal health issues such as dryness, itching, or pain/dyspareunia. Approximately 40 % of women will experience some type of sexual difficulty [5], and unfortunately, cancer and its treatment can compound these difficulties both physically and emotionally. Female sexual dysfunction can include loss of sexual desire and arousal, orgasm difficulties, and dyspareunia, stemming from vaginal dryness, discomfort, atrophy, and stenosis, which can also impede gynecologic examinations [6]. These issues will not abate over time without appropriate intervention [7]. Therefore, early identification and treatment strategies are essential in improving the QOL of women whether they are cancer free or managing chronic disease.

Older patients may mistakenly believe that sexual changes are an inevitable result of aging rather than as a result of cancer treatment [8]. Stereotypes and stigma may lead healthcare providers to erroneously assume that older adults are not sexually active. However, healthcare providers should not presume that these needs are insignificant, and instead, assess the sexual health needs of their patients. Research does support the claim that sexual activity among older adults decreases as age advances [4] but it still is meaningful and important to many. In one study, respondents were grouped according to age: 57–64, 65–74, and 75–85 years, and prevalence of sexual activity was reported to be 73, 53, and 26 %, respectively [4]. Whether or not an older woman had a partner contributed to her participation in sexual activity. Older adults were also found to participate in nonintercourse sexual activities, including oral sex and masturbation, which may also contradict societal beliefs or expectations.

The epidemiology of sexual dysfunction in female cancer populations has not been extensively studied. Factors such as age, race and ethnicity, as well as disease

type, stage and treatment regimens need to be considered in the design of future trials. Only then can we fully comprehend the risk and impact of sexual dysfunction and vaginal toxicities on a woman's sexuality throughout the continuum of care and into long-term survivorship. In particular, research is needed within the gynecologic oncology setting to determine the true prevalence of sexual activity and function, as well as difficulties unique to each disease site.

Of the existing research, gynecologic cancer patients scored well below the diagnostic cutoff score indicating sexual dysfunction on the Female Sexual Function Index (FSFI). Two recent cohort studies showed that 89 % of early-stage endometrial cancer survivors and 69 % of menopausal gynecologic cancer survivors scored in the range of sexual dysfunction [9, 10]. Quality of life, histologic grade, and diabetes were highly correlated with sexual dysfunction in the endometrial study [9], while bothersome menopausal symptoms were associated with increased distress and depression in the gynecologic cancer survivors' study [10]. Despite a high prevalence of sexual morbidity, female cancer survivors value their sexuality yet are often dissatisfied with their physician's level of care for their sexual function [11]. Busy clinics, inadequate knowledge, limited training and resources, as well as embarrassment are the major obstacles that preclude gynecologists and oncologists from discussing sexual health issues with their patients [12, 13]. Some clinicians prefer to focus their time and effort on "combating the disease" rather than discussing topics of intimacy, sexuality, or other QOL issues following cancer [14, 15]. In one survey of cancer survivors, approximately two-thirds of patients claimed they never spoke with a physician about how gynecologic cancer or treatment would influence their psychological well-being and sexual health [11]. However, patients indicate a need for basic advice on the prevention and treatment of vaginal and sexual difficulties and would like to discuss these topics with their doctors [6]. One way to assist the physician-patient communication process may be to utilize brief surveys or checklists to evaluate vaginal dryness, dyspareunia, and other survivorship concerns (i.e., lymphedema) [16–18].

Many issues, such as disease type, stage of disease, and treatment modality (surgery, chemotherapy, and/or radiation therapy), can contribute to a decrease in sexual activity of female cancer patients, although particular cancer diagnoses may present unique challenges for women. Body image concerns, medical comorbidities, and the natural physical changes of aging can all impact intimacy, sexual relations, and vaginal health. Pelvic floor weakness (incontinence and prolapse) can influence sexual health and functioning in older cancer patients by reducing desire and arousal [19]. Disorders of the pelvic floor, particularly urinary and fecal incontinence, are common in gynecologic cancer patients and survivors but under-assessed by their treatment teams [19]. Pelvic floor issues are not usually transient conditions but lifelong concerns for women as they attempt to build their lives and relationships after cancer. Lack of a partner, being widowed, or erectile dysfunction in male partners can also deter sexual activity. However, even if a woman chooses not be sexually active, maintaining vaginal health is still imperative. If problems exist, issues can negatively impact compliance with gynecologic surveillance.

Ovarian Cancer

Rates of ovarian cancer tend to increase with age [20]. Ninety percent of women are diagnosed over the age of 40, but the majority are diagnosed during their postmenopausal years (>60 years old) [21]. The standard of care for ovarian cancer consists of a surgical staging procedure involving hysterectomy, bilateral salpingo-oophorectomy (BSO), omentectomy, lymph node sampling, and tumor debulking [20]. Cancer treatments that involve removal of the ovaries (or impairment) can result in hormonal deprivation, leading to serious adverse effects of sexual and vaginal health (i.e., vaginal atrophy) [22]. Removal of the ovaries in postmenopausal women can also potentially hinder QOL because the ovaries produce androgens that aromatize to estrogen even in a menopausal state [23, 24]. As ovarian cancer patients are generally diagnosed in advanced stages (III–IV), surgery can be extensive and require a lengthy recovery. This in itself can negatively influence interest in or energy for sexual activity. Fatigue is a common problem in cancer patients, with estimates as high as 100 % [25, 26]. Disease status, cancer treatment, medications, nutrition, sleep, pain, depression, and anxiety all may contribute to fatigue. Fatigue may persist after cancer treatments are complete and can have a significant impact on QOL [8, 25]. One possible coping strategy may be to allocate time for closeness or intimacy, focusing on times when energy may be at higher levels (e.g., a specific time of day or ideal times during treatment cycles when blood counts are rebounding).

In the geriatric population, other medical issues (i.e., diabetes), which are further compounded in cancer patients, can lengthen the healing process. Approximately 26.9% of adults over the age of 65 have diabetes [27], which is projected to increase due to the rapidly aging population and the exponential growth of obesity in the United States [28]. SEER project data show that approximately 10–15 % of ovarian cancer patients who are older than 55 years of age have diabetes [29]. Women with type 2 diabetes [30] or metabolic syndrome [31] are at increased risk for sexual dysfunction [30]. Diabetes can severely impact sexual functioning in various ways. Imbalanced blood sugar levels can decrease vaginal mucosal hydration, limit blood movement to the genitals, and reduce sexual desire [30]. Older age [32–34] and menopause [35, 36] have been associated as possible risk factors for sexual dysfunction in female cancer patients with diabetes, although there is conflicting evidence [37, 38]. Diabetic cancer patients also show lower survival rates; however, more research is needed to understand this finding [28].

For most ovarian cancer patients, the disease will become a chronic condition requiring long-term chemotherapy treatment. Many women will experience side effects and neurotoxicities from chemotherapy (i.e., neuropathy). This chemotherapy-induced condition may be more commonly associated with sensory changes in hands and feet; however, nerve changes may also occur in the pelvic and clitoral area, which may diminish pleasurable sensations [39]. Multimodal treatment also enhances the frequency and severity of toxicity [40, 41].

Multiple recent randomized trials have shown that IP (intraperitoneal) therapy can reduce mortality in ovarian cancer patients [42]; however, toxicity and QOL

issues should not be overlooked [42]. In 2006, Wenzel and colleagues [43] found patients receiving IP therapy experienced poor health-related QOL (HRQoL) and significant neurotoxicity 3–6 weeks post-chemotherapy ($p = 0.0004$) and 1 year later ($p = 0.0018$) [43]. Although IP therapy is still debatable as an acceptable standard of care due to these adverse outcomes, it has propelled further research efforts to discover less toxic therapeutic combinations. Menopause may be induced or previously resolved menopausal symptoms may recur as a result of chemotherapy; hot flashes, changes in mood, and difficulty sleeping may negatively impact a woman's desire for sexual activity as well as ability to achieve arousal and pleasure [44]. Negative QOL can translate into poor sexual functioning in a variety of ways. Fatigue, nausea, vomiting, diarrhea, and mucositis from treatment may decrease interest in intimacy, and loss of hair, eyebrows, eyelashes, and pubic hair can challenge a woman's view of herself [44].

Endometrial Cancer

Endometrial cancer is the most prevalent gynecologic cancer, with 43,470 estimated cases in the United States in 2010 [1]. Cancer treatment generally includes surgical staging with the removal of the uterus, fallopian tubes, and ovaries. Lymph node sampling in these patients is debatable due to lack of data supporting its overall and recurrence-free survival benefits [45, 46] and concerns about possible negative effects (i.e., lymphedema) in a cancer population that is largely elderly, obese, and with multiple comorbidities. Minimally invasive surgery may be used in place of open procedures, resulting in a decreased number of complications and hospital length of stay [47]. Recently, nerve-sparing surgical techniques have been applied during hysterectomy procedures to decrease rates of sexual dysfunction and bladder and bowel difficulties that may arise from damage to the autonomic nerves in the pelvis [48]. Regardless of surgical technique, removal of the ovaries will cause estrogen deprivation, leading to hot flashes, vaginal dryness, dyspareunia, and an overall decrease in QOL [22, 49–52].

Radiation therapy is recommended for patients with high-risk features or advanced disease and is commonly utilized to prevent recurrence [53]; however, it can cause various symptoms that can impact a woman's sexual and vaginal health. Radiation to the vagina can create agglutination, ulceration, stenosis, and/or scar tissue [54, 55], degrading vaginal depth and elasticity [56, 57] and diminishing sexual function [54, 58]. These treatment effects are worrisome for all women, even those who are not sexually active, since it can cause difficulties tolerating follow-up pelvic examinations. Patients who receive external beam radiation therapy (EBRT) can experience bowel side effects (e.g., diarrhea and fecal leakage) that can negatively affect QOL [59, 60] and can decrease a willingness for intimacy due to fear of incontinence. High-dose intravaginal radiation therapy (HDIVRT) has been gaining favor as a treatment modality, with research demonstrating less morbidity [53, 61–63] and excellent recurrence-free and overall survival rates [64] compared

to EBRT [60, 65]. The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) study found better QOL in patients who received HDIVRT versus EBRT [60, 65]. Vaginal toxicities were noted with HDIVRT (dyspareunia, vaginal dryness, tightness, and shortening of the vagina); however, further research is warranted to understand how these vaginal issues translate directly to sexual function for these women.

Vulvar Cancer

Vaginal and vulvar cancers are less common female cancers but seem to occur to a greater extent in older women. Treatment of vulvar cancer or vulvar intraepithelial neoplasia (VIN) may require local vulvar excision or radical vulvectomy, and in some cases, resection of the clitoral area [66]. Radical vulvar excision has been significantly associated with lower sexual function and QOL, especially in older women [66]. Excision of the clitoris, for example, could inhibit a woman from experiencing pleasurable sensations and clitoral orgasms [8].

Surgical staging includes groin nodal evaluation. Lymph node dissection plays a major role in the surgical treatment of vulvar cancer to evaluate regional metastasis. Wound breakdown and other postoperative surgical complications may be quite high in these cases [67–69]. Vulvar cancer set the groundwork for sentinel lymph node mapping and revealed that lymphedema is a major issue among these patients. Little is known about the incidence of lymphedema in the gynecologic cancer population, and there is a major gap in the research regarding its impact on sexual health and QOL. Nodal sampling seems to be a major contributory factor in lower extremity lymphedema [70]. Sentinel lymph node biopsy is a more recent surgical technique that can assess the lymph nodes without exposing patients to an entire lymphadenectomy. This procedure has been associated with lower acute and chronic complications, including lower extremity lymphedema. There is a great need to prospectively study lower extremity lymphedema and develop an assessment tool to evaluate the incidence and impact of lymphedema in gynecologic cancer patients of all ages. It would be extremely beneficial to focus research on the geriatric population, as this issue can follow women into the later years of survivorship, severely impacting their sexual health, body image, and psychosocial well-being.

Cervical Cancer

Although cervical cancer is more prevalent in premenopausal women in their childbearing years, as the general population over the age of 65 continues to increase, older women are more likely to be diagnosed with the disease [71]. In fact, approximately 20 % of new cervical cancer cases and more than 36 % of all cervical cancer deaths involve women over the age of 65 [71–73].

Human papillomavirus (HPV) is the most common sexually transmitted disease in the United States and is a major cause of cervical cancer [71]. Although much of the literature supports a high incidence of HPV in younger women in their 20s, recent evidence demonstrates that many cases are also identified in women between the ages of 40 and 50 years [73, 74], with 4 out of 5 women acquiring HPV over 50 years of age [71, 73]. The sexually active geriatric population is at increased risk for cervical cancer, but unfortunately, the majority of older women have limited knowledge about the dangers of HPV and its relationship to cervical cancer, and believe they are not at risk [73]. The American Cancer Society (ACS) recommends women age 70 years and older who have tested positive for HPV to continue screening, but at the discretion of their clinician [75]. Programs targeting those 40 years of age and older need to be developed to improve awareness and continue screenings of cervical cancer risk [73, 74].

In older adults, surgical treatment for early-stage cervical cancer usually consists of radical hysterectomy. This surgery has been associated with bladder, intestinal, vaginal and sexual dysfunction such as decreased lubrication, shortened vaginal length, lack of sensation, and dyspareunia [54, 76, 77]. However, nerve-sparing techniques have produced similar surgical outcomes while enhancing QOL and minimizing these issues [78].

For cervical cancer patients with disease beyond stage IB1, chemotherapy and radiation is usually recommended [20]. This combination treatment can result in significant vaginal toxicity and sexual dysfunction (i.e., vaginal stenosis, dryness, atrophy, and dyspareunia) [8, 79, 80]. Sexual dysfunction after pelvic radiotherapy has been estimated to affect 50–80 % of women treated for cervical cancer [81, 82]. Radiation causes inflammation of vaginal mucosa, changes to vaginal blood vessels, and damage or destruction of vaginal epithelium [79, 83]. Damage to vaginal epithelial cells results in a decrease in a woman's lubrication response [80, 83]. Vaginal fibrosis and scarring may result in the narrowing or shortening of the vaginal canal [80, 84], and in the worst cases, may result in complete closure, preventing sexual intercourse or vaginal examination [85, 86]. Women undergoing radiation therapy are also at increased risk of persistent sexual dysfunction, such as dyspareunia, postcoital bleeding, difficulties with libido and arousal, decreased lubrication, and overall dissatisfaction with their sexuality [58, 80, 87, 88]. Decreased elasticity of vaginal tissues and altered sensations with sexual stimulation [83] can lead to less sexual activity compared to women treated without radiation therapy [89]. Vaginal stenosis is common after radiation therapy, with rates as high as 88 % [81, 85]. Multiple authors have reported that the incidence of vaginal stenosis is found to be higher if this issue is specifically addressed [81, 85], and women over age 50 may be at an increased risk of developing vaginal stenosis. Radiation therapy may also result in changes to bowel and bladder functioning [79, 81, 83], which may directly or indirectly affect a woman's sexuality. Feelings of unattractiveness, embarrassment related to incontinence, cystitis, diarrhea, and rectal pain may interfere with sexual functioning [84].

One of the most radical but potentially curative procedures for patients with advanced or recurrent gynecologic malignancies is pelvic exenteration—an en bloc resection of the pelvic organs. This radical surgical procedure includes resection of

all (total pelvic exenteration) or most (partial pelvic exenteration) of the pelvic organs, including uterus, adnexa, vagina, cervix, bladder, and sigmoid colon, depending upon the extent of disease [8, 90, 91]. Although prime candidates for this procedure are as young, recurrent cervical cancer patients with pathologically negative surgical margins [90], this does not necessarily mean that older female cancer patients cannot undergo this or any radical procedure. The treating surgeon and physician should individualize surgical technique and treatment for each patient. Pelvic exenteration, in particular, requires a motivated patient with a solid support system to aid in the recovery process [91]. Patients should also be provided with information related to the sexual and other physiological (i.e., ostomy care) changes to their bodies in order to better cope in the postoperative period [91, 92]. Neovaginal reconstruction is often an option either at the time of resection or as a delayed procedure [93]. However, one study noted that only 35 % of patients undergoing pelvic exenteration chose to have this reconstruction [90]. Even with vaginal reconstruction, negative changes to sexual functioning are expected [93]. Women who do not choose immediate reconstruction may be reluctant to undergo additional surgery for reconstruction [91]. Scarring may increase the difficulty of delayed reconstruction operations [93]. Exenterative surgeries often result in ostomies for bowel and/or bladder elimination, which may trigger feelings of shame, embarrassment, or an altered body image for some women [8].

Psychosocial Factors

Depression and anxiety are not uncommon in the cancer setting and among older adults in general. One study reported that up to 79 % of cancer patients were on one or more psychotropic medications [94]. In addition to treating depression and anxiety, these medications may be used for hot flashes, sleep disturbances, or pain [95]. Although helpful at treating these conditions, these medications have side effects that may influence sexuality [96, 97]. As women face the challenges of the cancer experience, they may be confronted with other issues that impact intimacy and lead to the development of depression. Lack of partner availability and support during cancer treatment can result in negative feelings and distress. For older cancer survivors in long-term relationships, this may cause them to fear intimacy or ultimately lose the desire to continue their relationship [98]. Communication between partners is vital when dealing with sexual issues and maintaining a quality relationship.

Regardless of the type or extent of surgery, surgical scars are constant reminders of a woman's cancer experience [79] and can influence her view of herself. Women may equate these losses or changes as an insult to womanhood or femininity. Even though surgical scars may fade over time, many women view their body differently, often as less attractive or desirable [91, 99]. Some may feel disconnected from their bodies or develop a sense of vulnerability, which has the potential to greatly impact their sexual desire and functioning. A woman's view of her sexual self, also known as sexual self-schema, has been found to influence the level of psychological and

sexual morbidity in gynecologic cancer patients [100, 101]. A positive self-schema score has been shown to act as a buffer from depressive symptoms, and women may be more equipped to address and communicate issues of sexual difficulties when they arise [101]. Further insight into this concept of sexual morbidity can possibly set the stage for targeted interventions to identify patients at risk for sexual and psychological issues, to improve confidence, treat sexual difficulties, and enhance overall QOL.

Other Factors

Medications for chronic medical conditions (hypertension, arthritis, and diabetes) are common in older adults and may have negative effects on sexual function and overall health [102]. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are helpful in the treatment of mood disorders and hot flashes but may also interfere with the sexual response [39, 79]. Other medications such as narcotic pain medications, antiemetics, antihistamines, anticholinergics, and sedatives may also have a negative impact on arousal, increase fatigue, and exacerbate vaginal dryness [39, 79]. Prescribed medications as well as over-the-counter supplements and alternative remedies can cause drug interactions, side effects, and organ dysfunction [102]. Therefore, considerations should be taken when prescribing medications to older populations, and patients should be made aware of possible side effects, including sexual dysfunction.

Targeted Vaginal Health Promotion Strategies and Solutions

Vaginal health issues are especially problematic for women with advancing age; however, there are many simple, nonhormonal options to alleviate vaginal estrogen deprivation symptoms on vaginal tissues. Atrophic vaginitis, or vaginal atrophy, commonly causes vaginal itching, discomfort, pain with intercourse, and postcoital spotting [6]. Vaginal estrogen therapy is an effective treatment for vaginal atrophy and dyspareunia, but the use of hormones in the cancer population is not a simple issue due to hormone-sensitive cancers and patient fears [103–106]. Nonhormonal strategies can be safely employed for the treatment of vaginal health. These strategies should be a priority for both sexually and non-sexually active women because of their tremendous effect on vaginal health and overall QOL throughout the cancer continuum.

It is important to distinguish between vaginal moisturizers and vaginal lubricants, and patients as healthcare providers are often confused about the respective uses and administration of these products [6]. Vaginal lubricants are used to aid in vaginal entry or penetration by decreasing dryness and friction and thereby decreasing irritation and pain [6]. Water-based lubricants are recommended as they break

down easily after washing with warm water and soap. Silicone-based lubricants may also be used; these products last longer and therefore may not be washed off as easily. Petroleum-based lubricants (i.e., Vaseline) are not recommended as they may render latex condoms ineffective and increase the risk of vaginal infections [6]. Vaginal moisturizers (creams, gels, suppositories, or ovules) are intended to hydrate the vaginal tissues and improve pH [6, 107]. It is recommended that women insert the moisturizer prior to bedtime for optimal absorption and apply regularly [6]. Recent studies have shown that hyaluronic acid vaginal suppositories and tablets may be beneficial in the treatment of vaginal atrophy [108, 109]. Both of these interventions significantly improved atrophy of the epithelium, pH of the vagina, and vaginal maturation. Although improvements of atrophy and symptoms were found, further research of these products in the cancer population with empirical assessments and patient reported outcomes (PROs) is warranted. Regardless of which vaginal moisturizer a woman prefers, consistency of use is the key factor for achieved benefit. Any abrupt decrease in hormones can increase the experience of vaginal atrophy. With this in mind, administration of vaginal moisturizers approximately every other night, or 3–5 times/week, is suggested to address acute symptoms [6].

Dilator therapy is an important tool for addressing vaginal pain, stenosis, and agglutination. Dilators are available in sets of increasing size, both in terms of width and length, allowing for a gradual stretching process. While regular sexual activity can help to maintain vaginal health, vaginal dilators offer women the ability to rehabilitate the vagina independently if one lacks a partner or does not wish to be sexually active. Although dilators are commonly used after radiation therapy to treat and/or prevent stenosis, it can be extremely useful for patients experiencing pain with intercourse or having difficulty tolerating pelvic examinations [6]. Dilators can assist in gently stretching vaginal tissues, while reducing a woman's anxiety and enhancing confidence that something can comfortably be placed into the vagina without discomfort [6]. Unfortunately, compliance with dilators is a challenge for patients, but women are more likely to be compliant if they believe dilators will make their pelvic exams more comfortable [110].

Dilator therapy may be most helpful when practiced in conjunction with pelvic floor exercises. By practicing contraction and relaxation of pelvic and vaginal muscles, women may find they are able to maintain relaxation of these muscles during penetration, thereby decreasing pain associated with reflexive tightening [111, 112]. Pelvic floor exercises are also beneficial to sexual health [6] by increasing pelvic floor strength and drawing blood flow to the area [6, 113]. Similarly, drawing blood flow by using the arousal response, for example, by self-stimulation and/or with the use of a vibrator, may be helpful as well [6]. Pelvic floor physical therapy and/or biofeedback may be useful for treating vaginal pain and providing feedback on these issues [114].

Vaginal estrogen replacement can be an effective treatment of vaginal atrophy and dyspareunia [6, 104]. The North American Menopause Society (NAMS) recommends that nonhormonal treatments of vaginal atrophy and dyspareunia be used as first-line therapy [104]. If nonhormonal strategies are ineffective, careful consideration of the use of vaginal estrogen may be warranted. If hormonal options are

employed, the lowest possible dose for the shortest duration is recommended [104]. An individualized approach taking into careful consideration a patient's cancer history, individual risk-benefit analysis, and patient preference is suggested. In older women, systemic hormonal therapy may be less favorable due to medical comorbidities. Additionally, past exposure to hormone treatment may also influence the decision-making process [104].

Assessment of Sexual Function in Female Cancer Patient

Maintaining overall vaginal health is essential for the comfort of all women, particularly because gynecological and pelvic examinations are necessary for routine care and cancer surveillance [6]. A comprehensive assessment of a woman's sexual health status, relationship status, and physical issues, such as vaginal health, is needed to identify potential sexual/vaginal health concerns. Future research needs to incorporate comprehensive, validated empirical measures in clinical trials to target patients of all ages, demographics, and lifestyles. Without data addressing the universal prevalence of sexual morbidity, only minimal progress can be made to improve outcomes and develop resources for our patients.

The Gynecologic Oncology Group's (GOG) LAP2 trial that compared laparotomy versus laparoscopy in newly diagnosed endometrial cancer patients included sexual function and QOL items [47, 115]. Analyses of the response patterns showed that younger, married women were more apt to respond to questions regarding sexual activity, and thus, the majority of the sample who were without a sexual partner did not feel the questions were applicable to them (Carter et al., in press). This shows that researchers may not be asking the right questions when assessing vaginal health, especially in regards older patients who may not engage in sexual activity.

Several widely used measures of sexual health, including the Female Sexual Function Index (FSFI), have not been explicitly validated in cancer cohorts until recently [116]. In addition, women who report sexual inactivity on the FSFI tend to score artificially low, which could overestimate the prevalence of sexual dysfunction. An abridged version of the FSFI, known as the FSFI CA-6 SF, has been developed for the general population [117] and investigated in the female cancer population [116], which may not only help reduce patient burden but also provide a more reliable toll to evaluate patients in future clinical trials. Newer measures to assess sexual and vaginal health issues in female cancer patients [118] are emerging as researchers recognize the importance of adding QOL and sexual health components to clinical trials specific to the cancer population. The PROMIS Network (http://www.nihpromis.org/) is another recently established series of innovative tools that measure PROs and sexual function within the oncology setting [118–120]. PROMIS is well into testing their item banks and continues to conduct large-scale item testing, psychometric evaluation, and validation, leading to future translation of findings into brief assessment tools [120].

Conclusion and Future Directions

Cancer diagnosis and treatment in the older gynecological patient can negatively impact sexual functioning in a variety of ways. Sexuality is a complex issue encompassing both physical and emotional components that can remain with women long after their cancer treatment ends. Regardless of whether or not a woman is currently sexually active, assessment of vaginal health is imperative for all women and should be a standard part of clinical care.

Female sexuality experts have made significant efforts to collaborate and advance the field within oncology. The National Scientific Conferences on Cancer and Female Sexuality were held in Chicago in 2010 and New York in 2011, convening researchers, clinicians, and other health professionals from various national and international institutions [121]. These conferences emphasized high-priority areas for research and encouraged collaborative, multi-institutional projects to address the critical need for more evidence-based research. Despite positive changes in the sexual medicine field over the past several decades and commitment to heighten awareness about the importance of sexual and vaginal health, scientific areas of need persist and there is still a paucity of targeted interventions. More prospective research with uniform measures and methods are needed to fully comprehend the impact of gynecologic cancer on sexual function and vaginal health. These issues are crucial among the older population of gynecologic cancer patients and survivors who need and want information and intervention that will help improve their QOL through the cancer continuum.

Resources

American Cancer Society (ACS) www.cancer.org	ACS is a nationwide network of volunteers who work to raise money for cancer research, promote funding opportunities for investigators, and advocate on behalf of cancer patients and survivors through public policy work.
Office of Cancer Survivorship (The National Cancer Institute) (OCS/NCI) http://cancercontrol.cancer.gov/ocs	The OCS promotes cancer research and equips health professionals, patients, and survivors with information to confront the challenges of cancer treatment and survival.
North American Menopause Society (NAMS) www.menopause.org	NAMS provides menopausal management and hormone therapy recommendations.
American Association of Sexuality Educators, Counselors and Therapists (AASECT) www.aasect.org	AASECT provides information regarding human sexuality that is useful for healthcare providers and the public. One can use this website to locate a sexual health professional in their area.

American Psychosocial Oncology Society (APOS) www.apos-society.org	APOS is an organization for those interested in the psychosocial aspect of the cancer experience. APOS works to increase awareness of health professionals and the public, develop effective programs and treatment regimens, and assist the underserved and minority patient populations.
Oncology Nursing Society (ONS) www.ons.org	The ONS is a professional organization for registered nurses and healthcare providers in oncology nursing who are patient caregivers, educators, and/or researchers.

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Chapter 22
End-of-Life Care for Elderly Patients with Gynecologic Cancer

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Abstract In general, the survival outlook for gynecologic cancer patients with advanced disease is poor. Moreover, compared with younger women, older women often present with more advanced gynecological malignancies and are more likely to die from the disease. Symptom management is the most important aspect of care for a patient with advanced disease. The issues involved in providing care directed at excellent symptom management and patient QOL are complex and numerous for elderly gynecologic cancer patients. In this chapter, we discuss some of the end-of-life issues specific to this population as well as issues found more commonly in this population with gynecological cancer and other types of cancer.

This chapter addresses four specific areas of end-of-life supportive care and management strategies for elderly patients with gynecological cancer:

1. Gastrointestinal obstructions, fistula, ascites, and effusions at end of life
2. Pain management issues in elderly patients
3. Fatigue, anorexia, anxiety, and depression
4. Existential issues: dignity, independence, cognition, and attainment of goals

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Cancer is often called the disease of the aging because the incidence of most malignancies, including gynecological cancers, rises dramatically with age. By the year 2030, people over the age of 65 years will account for an estimated 70 % of all cases of cancer in the United States [2]. Among women aged 40–79 years, cancer is the leading cause of death. Nearly 81,000 women were diagnosed with gynecologic malignancies in 2007.

Limited reserve has focused on how to best treat an elderly patient with gynecologic cancer. We are only just beginning to explore outcome differences for older women who undergo extensive tumor reductive surgery or those who experience side effects of chemotherapy. What we do know is that the care of women losing their battle with a gynecologic cancer involves considerations beyond the important areas supportive care professionals traditionally address.

As with all aspects of palliative care, attention focuses on decreasing symptom and improving quality of life (QOL) for patients and their families by relieving suffering and treating physical, psychosocial, and spiritual distress [1]. For patients nearing the end of life, attention may also be on one's acceptance of dying as a normal process. Supportive care can be provided at any point along the cancer treatment process (i.e., in conjunction with life-prolonging therapies), but at the end of life, the focus becomes primarily relieving impaired with distressing symptoms. Supportive care for elderly patients has some important differences that for younger patients. For example, unique aspects of end-of-life care may necessitate the initiation of supportive or palliative care much earlier in the course of cancer treatment for elderly patients. One reason for this urgency of supportive care in the elderly is the presence of multiple comorbidities, the risks associated with polypharmacy, a higher incidence of depression, an inherent increased risk from invasive procedures and or chemotherapeutic side effects, and a lower baseline performance status. In fact, one might argue that for elderly patients with gynecologic cancers, initiating supportive care at diagnosis is imperative in the management of the disease. Indeed, supportive care should be an adjunct to pharmaceutical treatment in order to "tune up" an individual in order to allow her to handle the often grueling but best and most promising treatment options.

In general, the survival outlook for gynecologic cancer patients with advanced disease is poor. Moreover, compared with younger women, older women often present with more advanced gynecological malignancies and are more likely to die from the disease. Symptom management is the most important aspect of care for a patient with advanced disease. The issues involved in providing care directed at excellent symptom management and patient QOL are complex and numerous for elderly gynecologic cancer patients. In this chapter, we discuss some of the end-of-life issues specific to this population as well as issues found more commonly in this population with gynecological cancer and other types of cancer.

Functional Assessment

Influenced by environmental and genetic factors, aging is a process associated with loss of functional reserve and reduced ability to withstand stress. Such changes affect life expectancy and functional capacity and render an individual more susceptible to disease. Although chronological age poorly reflects such age-related changes, the age of 70 years has been identified as a landmark age wherein further evaluation for physiologic age is recommended [3]. No laboratory tests exist that can help determine physiological age, but there are tools that can help clinicians assess elderly women for functional reserve. The multidimensional comprehensive geriatric assessment, for example, is an important tool in designing treatment plans for older patients. This tool helps to estimate a patient's active life expectancy and functional reserve, identifies needs for discharge and home, and provides insight into future needs that may affect the patient's overall therapeutic plan [4]. This tool assesses patient function and physical performance, cognition, number and severity of comorbidities, geriatric syndromes, nutrition, polypharmacy, social support, and living environment [5–7].

A geriatric syndrome can be defined as a multifactorial health condition that can occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges [8]. Some examples are dementia, delirium, falls, incontinence, sensory impairments, sleep disorders, pain, and skin breakdown. One of the goals of good supportive care is to avoid this syndrome.

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Gastrointestinal Obstructions, Fistula, Ascites, and Effusions at End of Life

Once the decision has been made to discontinue active chemotherapeutic treatment (e.g., due to lack of an effective available treatment or declining QOL), symptom management should—if it had not been already—become the main focus of care. One of the most common detriments to QOL in women with advanced gynecologic cancers is bowel obstruction, which may be due to the tumor itself causing luminal occlusion or to intestinal paralysis secondary to involvement of the mesentery or nerves by the tumor. Constipation resulting from dysfunctional motility and pain medications can make partial obstructions more symptomatic. Symptoms of obstruction include nausea and vomiting, bloating, cramping, and occasional passage of

gas or of loose or small stools. Assuming that palliative surgery such as a diverting ostomy is not an option due to poor performance status, surgical contraindications, or near-end-of-life circumstances, interventions could include an attempt at reversal of partial obstructions with medical management and bowel rest. Due to discomfort placement of a nasogastric tube should be avoided in end-of-life circumstances but may be necessary in high-volume-output obstructions. Drugs commonly used to manage bowel obstruction include antiemetics, H2 blockers, analgesics, peristaltic agents, and steroids. The use of metoclopramide, octreotide, and steroids appears to offer some symptomatic relief [9–11]. A patient who is significantly nauseated or vomiting is generally given an antiemetic continuously as prophylaxis during the initial presentation. Haloperidol can be used for nausea in cases of bowel obstruction, but there are no head-to-head studies with other antiemetic agents. Haloperidol can be given intramuscularly or subcutaneously starting at 0.5 mg Q4–6H prn. Also occasionally helpful are lorazepam, diphenhydramine, haloperidol, and metoclopramide (ABHR) rectal suppositories or gels at 2 mg Q6H prn. This combination is limited by extrapyramidal symptoms as side effects and QT prolongation, but incidence is low at doses of up to 2 mg/day.

Ondansetron is often used to prevent nausea or vomiting, as it is less sedating than anticholinergics or phenothiazines. However, ondansetron given intravenously also has been shown to prolong QT when used with other QT-prolonging medications or in patients at increased risk. Its use should be cautioned and started at a low dose for elderly patients taking other QT-prolonging medications or those at risk. Promethazine, an antihistamine, and lorazepam may also be risky in the elderly due to the risk for delirium. If there is a complete bowel obstruction, octreotide may be helpful in decreasing intestinal secretions by inhibiting gastrointestinal hormones, decreasing intestinal motility, and increasing absorption of gastrointestinal fluids.

Octreotide, which resembles natural somatostatin and can be given subcutaneously or intravenously, is available in a short-acting form (every 8 h) or a long-acting (depot) form (monthly). If the depot form is used, a bridge of short-acting octreotide must be used for the first 2–3 weeks. Findings on the use of octreotide in animal studies have been impressive, and trials in noncancer patients with mechanical bowel obstruction have demonstrated improved transit times and less need for surgery [9, 12, 13]. Even so, more clinical studies with elderly cancer patients are needed.

In cases of partial bowel obstruction or crampy pain, metoclopramide is often useful to promote peristalsis. It is best to initially evacuate the rectum with enemas and suppositories to ensure removal of any impaction before drug therapy is begun. H2 blockers and proton pump inhibitors are important in lessening the discomfort associated with esophageal reflux. Lansoprazole is available as an orally disintegrating tablet, and ranitidine can be given subcutaneously if an alternate route is needed. Opioid analgesics are usually necessary for pain relief and occasionally to decrease bowel secretions [10, 14]. Some studies have supported the use of anticholinergics for colicky pain, including scopolamine which can be given intravenously, subcutaneously, or even transdermally [10]. However, compared with younger patients, elderly patients do not tolerate anticholinergics well and experience

common side effects more often, such as drowsiness, dry mouth, and constipation. The lowest effective dose should be used and the patient continually monitored for side effects.

Less studied in this setting is the use of corticosteroids (oral, intravenous, or subcutaneous). A meta-analysis suggested that dexamethasone at 6–16 mg intravenously may resolve partial bowel obstruction more quickly than placebo by decreasing peritumoral edema [15]. Caution is warranted with these patients because of the potential for bacteremia from bowel perforation. Elderly patients also are at higher risk than younger patients for side effects of corticosteroid use, and due to their propensity for comorbidities, the smallest effective dose should be used.

If, after a few days of treatment, the patient has started to pass gas, the diet can be advanced slowly in conjunction with initiation of a potent bowel regimen. If no improvement is seen after at least 3 days, discontinuation of the costly octreotide is recommended. But if this treatment is effective, changing to depot octreotide may be easier to arrange and administer. If resolution does not occur, the next option for patient comfort is insertion of a gastrostomy (G) tube [16, 17]. The G tube is very important in the management of recurrent ovarian cancer as it allows the patient to leave the hospital setting without a nasogastric tube in high-intestinal-output settings [16, 18]. The venting G tube offers patients the ability to deal with intermittent obstructions by using the tube to drain off excess gastric contents. The patient can then be discharged from the hospital with the tube in place. It does not require the use of suction, although occasionally, the family must be taught how to flush the tube. In most cases, the patient will need this device for the remainder of her life.

Side effects of the G tube include leakage of gastric contents around the tube. Maalox or protective ostomy cream can be applied around the tube if there is mild leakage. If there is heavy leakage, the tube could be exchanged for a larger-diameter tube. Most patients can tolerate liquids or even blended meals with a G tube in place and thus partially satisfy the desire to drink or eat small amounts. The tube should be flushed with 20–50 mL of water several times a day to maintain patency. If the tube becomes blocked, the patient may experience nausea and vomiting. Although the G tube can be placed at the time of an aborted attempt to surgically fix a bowel obstruction, a gastroenterologist can place it via an endoscopic procedure, or more likely, it can be placed by an interventional radiologist with ultrasonographic or fluoroscopic guidance. Unfortunately, carcinomatosis, thrombocytopenia, and coagulopathies are relative contraindications to G tube placement [17].

Nutrition and Hydration at End of Life

Nutritional status is an independent predictor of mortality and disability in older people [19]. For the frail older patient, assessment of nutritional status is part of routine clinical evaluation. Poor nutritional status can decrease tolerance to chemotherapy and delay tissue recovery from chemotherapy-induced injury. Malnutrition is an umbrella term for sarcopenia, cachexia, and starvation, and the terms may be

used interchangeably in the literature. Sarcopenia is primarily seen in the elderly and is characterized by loss of muscle mass and strength. The pathophysiology is complex and is thought to be an interplay of internal and external factors. Internal factors may include reduction in anabolic hormones, increase in apoptotic activities in myofibers, changes in mitochondrial function in muscle cells, and declines in motor neurons. External factors include decrease in intake of protein and energy (contributing to further muscle loss), decline in overall function, and acute and chronic medical comorbidities. Cachexia is severe muscle and fat loss as a result of increased protein catabolism secondary to underlying disease, such as cancer chronic heart failure. These syndromes, while studied in general in the cancer population, have not been specifically studied with elderly cancer patients.

For women with advanced gynecologic malignancies who have bowel obstruction, the question of further nutrition and hydration is often raised near the end of life. This desire to discuss this topic is usually born out of the patient's or family member's fear of starvation. Although emotionally and cognitively distressing, in very select cases, such as a patient who has a special event in her life that she wishes to attend, it may be possible to delay death by administering total parenteral nutrition (TPN). Unfortunately, the patient may experience pain, cramping, nausea, vomiting, or fistula formation during this period. Probably the biggest risk to administration of intravenous nutrition is sepsis related to luminal stasis and the presence of a central line for administration of the TPN. Intravenous or subcutaneous hydration, nutrition, or both might be considered, but this decision needs to be based on a fully informed discussion among the patient, her family, and the physician. Unfortunately, parenteral nutrition and hydration are often harder to stop than to start. Furthermore, artificial nutrition and hydration will not reverse the syndrome of cancer anorexia and cachexia [20]. This scenario represents one of the most difficult discussions to have with a patient, and it occurs as the realization surfaces that eating is no longer an option for the patient. In almost all cases and at all ages, hydration at the end of life is not recommended.

Fistulas

Radiation is probably one of the most common causes of fistulas in gynecologic oncology cancer patients. Fistulas can occur for other reasons, such as surgery, malnutrition, and cancer recurrence. Moreover, new agents used in the treatment of ovarian cancer, including bevacizumab, sunitinib, intraperitoneal heated chemotherapy, and paclitaxel, may increase the risk of perforation or fistula formation [21, 22]. The presence of a fistula can lead to a high risk of infection and have a weighty effect on the patient's QOL [23].

At the patient's end of life, it is less important to identify the source of the fistula than to provide protection from odor, skin breakdown, and infection. Supportive pharmacologic agents and ostomy stomal bags are useful in collecting the fistula contents. Because the output can be irritating to the surrounding skin and mucosa,

the skin can be protected with moisture barrier ointments such as zinc oxide or newer preparations which contain a topical anesthetic, such as Calmoseptine or Risamine.

Octreotide can be used to control the volume of luminal content and thus fistula output, but it can elevate liver enzyme levels. If octreotide does not work within the first few days, it will be relatively ineffective [24]. In a prospective study comparing the antisecretory effects of octreotide and scopolamine, octreotide significantly reduced gastric secretions by day 2 ($p=0.016$, 95 % CI 319.5–950.5) [12]. Other studies showed that octreotide reduced the amount of nasogastric tube output to <300 mL and allowed for removal of the tube in patients with small- or large-bowel obstructions [9, 11, 12, 24]. If at all possible, even for an elderly patient at the end-of-life, surgical diversion (ileostomy or colostomy) is preferred to manage the fistulous output. The laparoscopic approach offers a less risky option with potentially QOL-saving effects [18, 25].

The primary goal of care in the setting of fistula at the end of life is symptomatic relief and supportive care. Odors from a fistula can result in great emotional distress and social isolation for cancer patients and their caregivers. Sitz baths and metronidazole gel, oral metronidazole, and charcoal-embedded dressings have all been evaluated with a small number of patients and found to be effective in odor reduction [26, 27]. In our experience, gentle douching with 50 % peroxide and 50 % water can reduce odor.

Most important to remember is that dignity and independence—already difficult issues in elderly populations— are greatly diminished in the setting of advanced cancer with fistula.

Ascites

One of the most frustrating sequelae of gynecologic cancers is repeated bouts of recurrent ascites, pleural effusion, or both [28]. Symptoms of abdominal ascites include bloating, sleep disturbances, early satiety, nausea, burping, constipation, pain, and, for pleural effusions, shortness of breath. Paracentesis and placement of an intraperitoneal or Denver catheter provide significant relief of the most distressing symptoms. In studies of recurrent ascites, placement of catheters reduced symptoms in 78 % of patients, including bloating (42–54 %), anorexia (20–37 %), dyspnea (33–43 %), insomnia (29–31 %), and fatigue (14–17 %) [29, 30]. However, risks include peritonitis, bowel perforation, scarring, loculation of collections, hypoalbuminemia, biochemical disturbances, tumor drainage nodules, peritocutaneous fistulas, and cellulitis [29, 31, 32].

The duration of relief that a patient receives from these procedures depends on the nature of the tumor. If frequent taps are required for symptom management, a semipermanent catheter (suprapubic catheter, intravenous cannula, or PleurX catheter) should be considered for patient comfort and for reduced risk of infection from repeated intervention [30, 33]. Regardless of the type used, the catheter

appears to control ascites with minimal risk to the patient [29]. This said, the longer the catheter is left in place, the greater the chance of peritonitis or catheter malfunction.

Recurrent pleural effusions can be managed by repeated thoracentesis. Like recurrent abdominal cavity effusions, they also can be managed with a chest tube, such as a PleurX, Denver, or pigtail catheter. The recommended drainage volume from the pleura, is no more than 1,000 mL every other day. Pleurodesis via instillation of a sclerosing agent such as asbestos-free talc, bleomycin, or doxycycline could be considered but is rarely effective for management effusion for women with ovarian cancer due to the volume of loculations [30]. Criteria for sclerosis often include daily output of less than 100 mL. Sclerosis is effective for as many as 90 % of carefully chosen patients, but it can be painful, and thus, 1 % lidocaine often is injected into the space first.

The benefits of using a diuretic for the purpose of "drying up" ascites have been inconsistent, and there is no consensus on the use among elderly patients with gynecological cancer. No randomized trials have been completed, and from retrospective data, different and often-suboptimal doses are prescribed. Several studies suggested that using diuretics was effective in 30–40 % of patients [34, 35]. It has been suggested that spironolactone be started at 150 mg/day and the dose increased every few days to a maximum of 450 mg/day, until a response is achieved or clinical features prevent further increase. Furosemide might be substituted for spironolactone. A maintenance dose would most likely be required to prevent re-accumulation. Hypotension and pre-renal dehydration are significant risks and can lead to falls and renal impairment in the elderly population. Caution is emphasized for the use of diuretics for this patient population.

Pain Management

The management of cancer pain is extremely important because pain is reported by more than 60 % of patients with advanced-stage cancer [36], and up to 40 % of these patients are undertreated [37]. In fact, a study found that in the last 3 days of life, more than 40 % of cancer patients experienced severe pain [37].

Pain can be assessed using a numerical rating scale, a faces pain scale, or a pain thermometer, all of which have been validated in this patient population [38, 39]. The verbally administered 0–10 scale is the most often used for elderly patients, but many have trouble responding to it [38]. A visual analog or verbal rating scale can also be used; the latter is preferred for this patient population over other pain intensity scales [38, 40]. When assessing pain in the elderly patient, or indeed any patient, it is important to determine the best assessment tool for that particular individual and to use it consistently. Repeating questions and providing enough time for a response are useful [38, 40]. For those whose cognitive impairment is moderate or severe, it may be helpful to assess the patient by observation or by proxy [40]. Often, pain can manifest as agitation or restlessness in the elderly.

Up to 40 % of elderly patients have undertreated pain [41], which can have multiple contributing factors. Elderly patients might accept pain as part of the aging process, may shy away from informing their physician due to fear of being considered a "bad" patient, and often have comorbid diseases that make pain management challenging [38–40]. Other factors that can contribute to inadequate pain control include fear of addiction to pain medications, fear of the side effects, cognitive impairment, and failure to recognize the need to adjust therapy [38–40].

Pain management for elderly patients can be very challenging because they may be not only more vulnerable to side effects but also extremely sensitive to the effects of medications. The Beers criteria and STOPP (screening tool of older persons' potentially inappropriate prescriptions) are available to assist clinicians in providing appropriate considerations for the pharmacological management of pain in the elderly patient. The STOPP criteria are helpful in identifying potentially inappropriate medications for elderly patients [42]. These tools provide criteria to help identify potentially inappropriate medications for elderly patients.

The World Health Organization recommends non-opioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory (NSAIDs) agents for the initial attempt to control pain. These analgesics are safer options due to less risk of delirium for elderly patients, although as with any medication, caution should be exercised. Acetaminophen is relatively safe except when cirrhosis, hepatitis, or liver cancer are concurrent [43]. The dose should be limited to less than 4 g/day and even less in patients with liver dysfunction. Renal clearance decreases with age and can increase the risk of gastrointestinal side effects and cardiotoxicity associated with the use of NSAIDs [43]. Prolonged use of NSAIDs can also worsen renal clearance and in turn put patients at risk for hyperkalemia [43]. H2 blockers and proton pump inhibitors can be used to minimize gastric side effects if needed. Electrolytes and renal function should be checked periodically when NSAIDS are being used.

Opioids are a viable and often necessary choice for elderly patients, especially for those who are experiencing pain despite use of non-opioid analgesics. Opioids must be introduced slowly and at a low dose to minimize side effects, as several of these drugs have active metabolites that can accumulate due to the elderly patient's reduced renal clearance, which prolongs the effects of the drug [43]. Elderly patients are also more sensitive to the effects of opioids due to decreased clearance and resulting longer duration of action [43]. Elderly women may require increased interval of dosing in addition to a lower starting and overall dose. Drugs like methadone should be used with extreme caution in the elderly due to increased risk of QT prolongation.

Opioids can provide great relief, especially for cancer pain, but they also have a number of side effects that can affect the elderly population. Nausea occurs in up to 30 % of patients taking opioids for cancer pain [44], although it is usually self-limited and may disappear within a week with opioid tolerance. Alternative routes may be considered for patients with persistent nausea or bowel obstruction. Sublingual concentrated morphine can be used if the patient is unable to take anything orally. Although transmucosal and transdermal fentanyl are a popular choice, they are not recommended for the opioid-naïve patient. Dose titration with

transdermal fentanyl can be challenging and should be considered only when a stable dose has been determined. Fentanyl is fat soluble and can have an increased volume of distribution due to an increased ratio of fat to lean body weight with age [43]. One study found that patients >75 years old absorbed more fentanyl from the transdermal patches than did those who were <65 years old [45]. Furthermore, clinical observation has indicated that cachectic patients do not get as much relief from transdermal fentanyl as expected [46]. Other routes that can be used to administer opioids are rectal and subcutaneous, but the availability of various preparations may vary. All opioids that have an injectable formulation can be given subcutaneously. Methadone tends to cause more irritation when given subcutaneously, but adding dexamethasone in the syringe can help alleviate the discomfort. Morphine, hydromorphone, and methadone can be given rectally.

Myoclonus can occur with opioids, especially if not the dose is inappropriate. Elderly patients especially have an increased risk for myoclonus due to faster drug accumulation secondary to reduced renal clearance. Benzodiazepines are used to treat myoclonus but should be initiated only if there is no response to dose reduction or opioid rotation, because benzodiazepines, along with opioids, can increase the risk for falls, disorientation, and confusion. The elderly also may be more prone to urinary retention due to increased anticholinergic sensitivity with age, as are patients who are opioid naïve [43, 47]. Pruritus is a side effect usually seen with intraspinal administration of opioids and is related to histamine release [47]. Opioids should be used with care to avoid adding additional medications in order to manage the side effects from opioids unless absolutely necessary, and these additional medications should be reviewed routinely.

Constipation is one of the most common side effects of opioid use: It occurs in up to 70 % of patients with cancer. Elderly patients are especially prone to constipation due to age-related changes in gastrointestinal tract and neurological processes [43]. Every opioid prescription should be accompanied with a discussion regarding the expected increased constipation, the need for hydration, and the need for daily sennosides. If appropriate, stimulant laxatives should be initiated with the opioid prescription because pelvic pain can be worsened with constipation.

If pain remains uncontrolled or the opioid side effects need to be minimized, adjuvant agents such as antidepressants, anticonvulsants, corticosteroids, or bisphosphonates can be considered. Because antidepressants and anticonvulsants can increase the risk for falls and worsen cognitive function, the risks and benefits of their use must be evaluated; opioid rotation is another approach to minimizing side effects and improves pain control. The patient's renal function, comorbidities, and previous experience with other opioids should be considered in determining the most appropriate rotation. It is important to realize that the risks related to polypharmacy in the elderly are one of the most important contributing factors to increased toxicity in the elderly.

Non-pharmacologic treatment of pain can be useful adjuncts to controlling symptoms. Acupuncture, massage, and cognitive therapy (including relaxation, music therapy, and art therapy) may be considered as well [48].

Special Note: Pain Management in Patients with End-Stage Cervical Cancer

Patients with recurrent, inoperable cervical cancer have a limited life span—often less than 1 year—thus chemotherapy for such a cancer in a previously irradiated field is always palliative. The survival time is affected by a great number of variables, including age, socioeconomic factors, and smoking cessation. For unclear reasons, cervical cancer patients and survivors appear to be at particular risk for negative mood and QOL difficulties compared with other cancer survivors [49].

Discussions with patients who are not expected to live long may need to include management of pain, management of lymphedema, control of odor related to recurrent cervical cancer in the vaginal recurrences, and the use of a permanent percutaneous nephrostomy tube in the setting of urinary obstruction. The fact that cervical cancer is associated with low socioeconomic status means that cervical cancer patients are often without the extensive supportive services that are available to women with other types of cancer. Supportive treatment options for these elderly women might be restricted because of limited "charity" resources and social isolation from the community. An important consideration is that these women, often of minority status, need culturally appropriate discussions designed to build a relationship between the patient and caregiver that is founded on trust, sharing, and informed consent. Such patients need a health care team that includes a social worker, a case manager, a palliative care team, and possibly a member of the clergy or a therapist. This multifaceted approach is essential with cervical cancer—possibly more so than with any other cancer.

Relatively unexplored issues that may be unique to cervical cancer patients pertain to guilt stemming from the fact that cervical cancer is not only a sexually transmitted disease but that it might have been prevented had regular screening recommendations been followed. This guilt may contribute to a form of spiritual pain that has physical consequences. Counseling and triaging for spiritual crisis should be addressed as part of end-of-life pain management.

For difficult cases of physical pain associated with cervical cancer, the following may be considered. For patients with pelvic masses, the risk of urinary obstruction and pain due to retention, fistula, or hydronephrosis should be addressed, although in end-of-life situations, nephrostomy tubes create more inconvenience for the patient and probably offer no additional pain control. If the obstruction lies at the urethra, placement of a suprapubic catheter may also be helpful in relieving genitourinary obstruction and pain. Local control of the disease could be considered, and this is most often in the form of abbreviated external beam radiotherapy. For patients with large, incurable pelvic malignancies that had not been irradiated a "one shot" of 800 cGy or 30 Gy in 10 fractions may be helpful for controlling pain [50].

Another possibility for treating pain due to cervical cancer is the use of blocks. The use of blocks, specifically a superior hypogastric plexus block for this purpose is supported by a few studies; however, no large, well-designed randomized studies have been published. The superior hypogastric plexus is located in retroperitoneal

space L3-L5-S1 and transfers visceral impulses from the upper vagina, cervix, uterus, fallopian tubes, bladder, and right colon through the sympathetic fibers. The block is performed under computed tomographic, fluoroscopic, or ultrasonographic guidance using bupivacaine, ethyl alcohol, or phenol. It has been shown to be effective in reducing pain with a reduction of opioid usage in 43–72 % of the patients who received a neurolytic block and lasted for up to 3 months (60–160 days) [51–53]. In a non-randomized study of 227 patients with gynecologic, colorectal, or genitourinary neoplasias with poorly controlled pelvic pain or intolerable side effects of pharmacological treatment, the effective of superior hypogastric plexus block for pain control was studied. The study results were limited by the presence of heterogeneous cancers and limited opioid availability [53]. The risks and side effects of blocks include transient hypotension and increased intestinal motility; needle injury to visceral, neural, and vascular structures; pain at the injection site; and failure to obtain an analgesic response. Contraindications include bleeding diathesis and local infection, both of which could potentially be a higher likelihood in the elderly population.

Fatigue, Anorexia, Anxiety, and Depression

Fatigue

Cancer-related fatigue is defined as a persistent, subjective sense of exhaustion that is not proportional to recent activity, interferes with usual functioning, and does not usually resolve with rest [54, 55]. It is a multidimensional syndrome that interferes with physical and social activities. This fatigue occurs among about 60–90 % of patients receiving active treatment and 30–75 % of patients who have completed cancer treatment [56–58]. The severity of fatigue is often measured with a numeric scale ranging from 0 to 10, where 0 is no fatigue and 10 is the worst fatigue imaginable [59]. How fatigue relates to the patient's overall function and activities, and QOL is also important in evaluating severity.

Several conditions been reported to be related to fatigue in cancer patients, including anemia, thyroid disorders, depression, sleep disturbances, nutritional problems, and cardiac, lung, kidney and central nervous system disorders. Despite efforts to treat the possible underlying causes of the fatigue, there has been no success in significantly improving the symptom itself. A multimodal approach to managing fatigue is often employed. To date, there is no single drug intervention that has been shown to successfully treat cancer-related fatigue. Pharmacologic agents that have been found to provide some relief include corticosteroids (such as dexamethasone) and psychostimulants (such as methylphenidate and selective serotonin reuptake inhibitors) [60, 61]. Non-pharmacologic measures such as exercise and exposure to natural sunlight have been shown to reduce the severity of cancer-related fatigue [62, 63].

The actual cause of cancer-related fatigue is not known. One of the most consistently evoked factors is the role of cytokines. The cytokine theory posits that when

proinflammatory cytokines (interleukins 1, 2, 6, and 12; interferons alpha and gamma; and tumor necrosis factors alpha and beta) are released and bind to receptors in the central nervous system, neuroendocrine effects on the hypothalamic-pituitary-adrenal axis with subsequent release of nitric oxide and prostaglandin E2 occur, along with changes in the transmission of dopamine, norepinephrine, and serotonin [64, 65].

Anorexia

Anorexia is defined as a loss of appetite or desire to eat and frequently occurs with cachexia or involuntary weight loss with subsequent fat and muscle wasting. The eating disorder occurs in about 80–90 % of patients with advanced cancer [66]. A careful nutritional history is essential. The etiology is multifactorial and complex and is believed to involve interactions between proinflammatory cytokines and hormonal changes. Other conditions that may affect anorexia include severe pain, depression, dental problems, mouth sores, altered sense of taste, nausea, vomiting, early satiety, and constipation.

There is no standard of treatment for anorexia, but addressing the possible causes of it may improve appetite. Medications that decrease gastric emptying time (such as metoclopramide), laxatives to treat constipation, zinc supplementation for dysgeusia, and medications for depression and nausea (such as mirtazapine and olanzapine) may be tried. Appetite stimulation using progestational agents (such as megestrol acetate), corticosteroids, or cannabinoids may be helpful for some patients. Weight gain from use of progestational agents has been in the form of fat and fluid and not lean body mass. Increased risk of thrombosis, hypertension, hyperglycemia, and fluid retention are common side effects of these agents. Corticosteroids are usually reserved for patients with limited life expectancy, as the effects are limited to a few weeks. Dronabinol is approved by the US Food and Drug Administration for treatment of chemotherapy-induced nausea; however, no benefit was shown in a study of cancer patients who received dronabinol and those who received placebo. The side effects limiting its use include sedation, confusion, and disturbances in perception. Other agents under investigation for treatment of anorexia include ghrelin and ghrelin agonists, immune modulators such as thalidomide, nonsteroidal anti-inflammatory drugs, melatonin, myostatin inhibitors, and proinflammatory cytokine antibodies. Nutritional counseling with a dietician can assist with assessment of nutritional status and outlining realistic dietary goals.

Anxiety and Depression

Depression is not a part of normal aging. Even so, it is common among older adults although clinically under-recognized and therefore undertreated. Up to 75 % of

older adults who die by suicide suffered from depression, and most have visited a physician within a month before killing themselves (National Institute of Mental Health).

Thirty to sixty-four percent of women with gynecologic cancer suffer from depression during the first year post surgery [67, 68]. Among older adults, the presentation of depression may be varied and insidious. Such presentations may include depressed mood, anhedonia, change in appetite and weight loss, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue, difficulty in concentration, preoccupation with somatic symptoms or health status, feelings of worthlessness, or recurrent thoughts of death or suicide. Cancer patients at high risk of developing depression include those with a previous history of depression or attempted suicide, a history of alcohol or substance abuse, new stressful losses (such as loss of autonomy, privacy, functional status, or a family member), use of medications associated with risk of depression (such as anticonvulsants, barbiturate, certain beta-adrenergic antagonist, digitalis, and metoclopramide), poor social support, and advanced disease. It is important to that depression be screened for and recognized because its presence affects the treatment plan and outcomes. Depression may be attributed to other comorbid medical conditions such as thyroid disorders, dementia, anemia, diabetes, or substance abuse. It may result in increased use of health care services, increased disability and social isolation, delay and undertreatment of medical illness, noncompliance, and increased mortality.

Several screening tools have been used with geriatric patients. The most commonly used are the Geriatric Depression Scale, Cornell Scale for Depression in Dementia, Center for Epidemiologic Studies of Depression Scale, and Patient Health Questionnaire 9. When time is a limiting factor, the two-item version of the Patient Health Questionnaire has been shown to be as useful as a screening tool with 100 % sensitivity and 77 % specificity. Patients are asked the two questions: During the previous 2 weeks, (1) have you often been bothered by feeling down, depressed, or hopeless and (2) have you often been bothered by having little interest or pleasure in doing things?

The goal of depression therapy is to improve mood, function, and QOL regardless of life expectancy. A combination of pharmacotherapy and psychotherapy is most useful, especially for patients with longer life expectancies [69]. Drug interactions, anticipated life span, dosage adjustments, and presence of other medical comorbidities should be carefully considered when treating patients for depression. The Beers criteria list medications rated by level of appropriateness based on risk-benefit criteria [70]. In general, medications are started at a low dose and slowly increased to the therapeutic goal. Bicyclic antidepressants such as venlafaxine are well tolerated and have few drug interactions. Selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) are also relatively well tolerated by elderly patients. Fluoxetine and paroxetine are less desirable because of their long half-life, potential anticholinergic effect, and increased potential for drug-drug interactions. Of the selective serotonin reuptake inhibitors, citalopram and escitalopram have the fewest drug interactions. Other SSRIs and SNRIs can be used to address coexisting symptoms such as mirtazapine for anorexia, trazodone

for insomnia, and duloxetine and venlafaxine for neuropathic pain. Tricyclics and monoamine oxidase inhibitors are not considered first-line treatments for geriatric patient because of their strong anticholinergic and sedating effect and their potential to cause orthostatic hypotension, hypertensive crises, ventricular conduction delays, and heart block. Psychostimulants such as methylphenidate and modafinil have also been used because their effect is noted earlier than that most other classes of antidepressants. Some forms of psychotherapy used to treat depression are cognitive-behavioral therapy, life review, and interpersonal psychotherapy.

Anxiety often accompanies the experience of receiving bad news but may resolve over several days given support from health care providers, family, and friends. Other conditions that can trigger apprehension and fear include uncontrolled pain and dyspnea, medication side effects, and medication withdrawal. Treating the underlying cause and offering support and reassurance are essential with anxious patients. The use of antianxiety medications may be warranted in certain cases. Benzodiazepines must be used with caution with geriatric patients because it may cause delirium [70].

Communication and Existential Issues: Dignity, Independence, Cognition, and Attainment of Goals

Physician-Patient Communication

Communication is an integral part of the patient-doctor relationship. Whether the goal is to pursue active treatment or to focus on symptom management, effective communication is key in outlining best treatment plans. It is important for clinicians to keep in mind that patients in general would like to be told when prognosis is grave and treatment options are limited and welcome discussions about realistic expectations of survival. Good communication requires that the physician delivers the message in a clear and compassionate manner.

How the message is communicated is as important as the information being delivered [71]. The manner of discussion affects the patient's comprehension of information, level of hopefulness, coping and adjustment, and satisfaction with medical care. Failure to positively reframe hope by helping the patient to "hope" for different goals such as better pain control or peace of mind in the discussion about prognosis may lead to more emotional and psychosocial suffering. It is important for the physician to carefully present medical information while consciously assessing the patient's verbal and nonverbal cues. At a patient's end of life, when distress is high, a myriad of reactions are possible, including anger, shock, denial, and sadness. Physicians need to take time to listen to patients as they express their concerns.

Elderly patients will likely have sensory issues. For patients with hearing loss, the physician should speak slowly, modulate speech to a different frequency or encourage the use of assistive hearing devices to ensure better communication. An

Table 22.1 The six steps of SPIKES

1. *S*—*Setting up* the interview
2. *P*—Assessing the patient's *perception*
3. *I*—Obtaining the patient's *invitation*
4. *K*—Giving *knowledge* and information to the patient
5. *E*—Addressing the patient's *emotions* with empathic responses
6. *S*—Strategy and *summary*

environment where patients can feel safe and validated is important. And in the age of globalization, cultural sensitivity cannot be overemphasized, because culture and belief systems help shape how a person reacts and interacts. In addition, the physician needs to be aware that a patient's coping strategies are products of both cultural and individual experiences.

Evaluating a patient's cognition level is important. A patient's decisional capacity in understanding the disease and the therapeutic goals and plan affects adherence and compliance. Cognitive impairment also makes the assessment of pain and other symptoms difficult. A number of studies have observed some degree of cognitive decline among patients following chemotherapy, which has implications for patient QOL particularly for patients who had demonstrated some cognitive impairment prior to the treatment.

Baile et al. created the six-step protocol SPIKES (Table 22.1) to assist physicians in communicating with their patients, especially in communicating unfavorable medical information [72]. These steps may help the physician who is experiencing anxiety and fear and feels the burden of responsibility for delivering bad news to mentally prepare for these difficult discussions. It is important to keep in mind that such discussions will allow both patients and families to plan for their future.

The meeting should be set up for privacy, adequate time for discussions, and the persons the patient may choose to be present. Giving adequate warning at the start of the conversation that there is bad news can often lessen the shock and grief of the disclosure. Terms that can be easily understood should be used, and very technical and euphemistic terms should be avoided. Open-ended questions will help determine how the patient perceives the medical situation and allows for correction for any misinformation, and the patient's responses will provide insight into the coping strategies the patient may be employing. Throughout the discussion, the physician's empathic responses will offer support and validation. Clear plans can be outlined for the patient with consideration of patient's values and goals [73]. Conflicts may arise when there is a breakdown in communication, when goals are not congruent, and when expectations are not met [74, 75].

Advance Directives at the End of Life

Advance care planning involves discussion about the patient's treatment preferences in anticipation of future deterioration or when the patient becomes unable to make

treatment preferences known to health care providers. Advance directives, also known as living wills, are legal documents that allow patients to continue their autonomy and to provide instructions regarding end-of-life care in case they are unable to make decisions themselves then. A durable power of attorney or health care proxy allows a designated surrogate to make decisions for the patient if the patient becomes incapable of making decisions about medical care.

In a study by Emanuel et al., a significant proportion of patients stated they would discuss advance care planning if the physician brought up the subject [76]. Other studies have shown that persons who had discussed advance care planning or had completed advance directives experienced less fear and anxiety felt they had more control in directing their medical care and believed that their physicians had better understanding of their goals [77, 78]. In addition, the family members of these study subjects were less anxious, especially when there were differences about end-of-life care preferences [77, 78].

Palliative and Hospice Care

Palliative care and hospice care have a shared philosophy. Palliative care can be initiated as early as the time of diagnosis of cancer and aims to control symptoms due to the cancer or its treatment. Hospice enables the patient and family to experience the final stages of life together in a comfortable and meaningful manner. Whether it is palliative care or hospice, care is delivered by an interdisciplinary team that includes trained specialists that focuses on the alleviation of physical, psychosocial, and spiritual suffering [79].

If active cancer treatment is no longer a goal and efforts have been refocused to control symptoms and improve QOL, patients may elect for hospice services. Patients are eligible to receive hospice services after certification by a physician as having a terminal illness with a life expectancy of 6 months or less if the disease would be allowed to take its natural course. Services can continue, even after 6 months, as long as a physician re-certifies eligibility. The most common symptoms that are encountered toward the end of life include pain, fatigue, anorexia, anxiety, and depression [59]. In recent decades, increasing attention has also been placed on spiritual and existential suffering.

Hospice care includes physician services that direct the patient's medical care and regular home visits by the hospice nurse to control symptoms, provide support and identify sources of distress experienced by patients and family that team members can address. Home health aides provide assistance with bathing and dressing. Medical equipment and medications for the relief of pain and other symptoms are also provided [80]. Counseling, spiritual care, and family bereavement services for 13 months after the patient's death are provided by social workers, counselors, and chaplains.

The level of hospice care provided depends on the needs of the patient and family. Care is primarily provided by the family in the home. In the presence of very distressing symptoms that are difficult to control by changes in medication in the

home setting, the patient can avail of crises care services. These care allow a patient to remain at home under the care of a registered nurse for 24 h a day until the symptoms are controlled and care can be resumed by the family. Another option is for the patient to enter into an inpatient hospice unit, hospice-contracted facility staffed by hospice physician and nurses, until symptoms are controlled and the patient can return home. Respite care, where patients can be admitted to hospice-contracted facilities (e.g., nursing homes) so family members can rest and recharge, is also available for a limited number of days.

Specialists of end-of-life care can include a physician, hospice nurse, social workers, case managers, chaplains, and home health aides, all of whom help to make the last stages of life comfortable and meaningful. The services provided by hospice are generally paid for by Medicare, Medicaid, the Department of Veterans Affairs, most private insurances, health management organizations, and many managed care organizations [81, 82].

Existential and Spiritual Distress

The transition from active treatment to palliative care is emotionally and technically challenging for patients and their families. It is important that they be provided effective comprehensive palliative care that focuses the physical, psychosocial, existential, and spiritual sources of distress present at a patient's end of life. The ability to address the physical comfort for patients who are dying is constantly improving, but the ability to provide useful interventions in existential and spiritual suffering remains under-explored.

Elderly patients diagnosed with terminal illness may have several unmet needs. Patients frequently report depression and social isolation, hopelessness, fear of the uncertain future, and fear of being a burden to family and friends. Patients are also confronted with existential concerns such as how to continue to have a sense of hope or how to know that their lives were meaningful and purposeful [83]. Such thoughts and feelings are universal and independent of religion. Part of the goal of end-of-life care is to provide a safe environment for people to explore these issues and find peace or acceptance of their life. This awareness of death, loss of self, and loss of relationships can be alleviated through the creation of life-affirming and transcending purpose and the achievement of an internal sense of control. Engaging and assisting patients in confronting and perhaps resolving those conflicts are crucial to good patient care. Health care providers are obligated to assist patients and families in accepting the dying process as a meaningful process of life.

Several interventions have been developed to relieve existential distress and to enhance the end-of-life experience of terminally ill patients. These interventions include dignity therapy, meaning-centered therapy, supportive-expressive therapy, reflection, and journaling. Dignity therapy is a brief intervention where patients are given the opportunity to reflect on things that matter most to them or on how they

most want to be remembered, enhancing a sense of worth, meaning, and purpose [84, 85]. Patients are encouraged to talk about the importance of the roles they have had in their lifetime, their hopes and dreams, and the legacy they leave behind in the form of life lessons and advice. Meaning-centered psychotherapy aims to help patients find meaning in their experiences with illness. Patients are encouraged to reflect on love, beauty, and relationships as sources of meaning in one's life. Supportive-expressive group therapy is an unstructured group intervention in which participants openly support and discuss death and dying; this approach aims to improve self-worth, decrease isolation, and develop sources of support through the sharing for personal experiences [84].

Other Issues Unique to the Elderly Patient

A number of issues that are unique to the older patient impact the care they receive and the manner by which it is provided. As a consequence of the physiologic changes with aging and presence of comorbidities, functional disabilities may often complicate symptom management. Thus, due to their greater dependence on assistance with basic daily activities, caring for an older patient may be more difficult than caring for a younger patient. Often, patients and their families may require assistance in navigating the complex medical system. As well, inability to pay for custodial care at long-term facilities or for hired home caregivers is an important issue that is encountered by geriatric patients and their families. Caregiver burnout, elder abuse and neglect, institutionalization, and complicated grief are issues to be aware of. The caregiver burden for the "sandwich generation," those adults with children who are also caring for older relatives, can be complex because of multiple competing priorities that can cause negative psychosocial and physical stressors to family members [86]. For some patients, the absence of a caregiver may be a barrier to hospice enrollment. An interdisciplinary approach to these issues is warranted.

Summary

Cytotoxic treatments are now evolving into uniquely tailored plans through the examination of molecular fingerprints of specific cancer types. Similarly, supportive care plans must also be sculpted to specifically address the individual needs of each elderly woman with gynecological cancer. Certain questions need to be considered when designing the best treatment option for particular patient: Is the patient going to die of cancer or with cancer? Will she live long enough to suffer the consequences of cancer? Is she able to tolerate the treatment? Is the patient's social network adequate to support her during the treatment? What are the long-term consequences of cancer treatment for this person? Is there any treatment to improve her QOL? [7]

Medical comorbidities increase with age and are associated with a reduced life expectancy and an increased of morbidity and health care utilization [89]. However, the presence of comorbidities does not predict response to chemotherapy [90]. Pathophysiologic effects of aging should be taken into consideration when treatment is being planned. Reduced organ function and altered body composition occur during aging and may affect the therapeutic and toxicity profiles of some medications. A careful review of all medications, including prescribed, over-the-counter, and natural/herbal supplements, is always recommended because the potential for adverse drug reactions and drug interactions increases with an increasing number of medications. Older patients use more than three times as much medications than younger patients as a result of higher number of concurrent medical conditions [91].

Social support is crucial to the safe and effective management of cancer in the older person. A caregiver not only offers emotional support but also assists the patient in performing certain basic physical functions, identifies and reports early side of adverse effect or toxicity to treatment, and advocates for the patient.

The Comprehensive Geriatric Assessment and other prognostic indices have been used in the clinical discussion on treatment plans for older patients. Such indices are useful in determining prognosis without using an arbitrary age cutoff. Clinical decisions are influenced by the mortality risks and the patient's preferences. These tools allow for a more holistic approach by physicians to explore other medical issues that may reduce the patient's life expectancy and QOL by exploring questions on terminal disease and other health issues: Will prognosis be altered with additional treatment? How will the patient's QOL be with or without treatment? What are the patient's goals and priorities? [7]. Often during these discussions, patients and families look to the physician for guidance. Central to these talks are careful and truthful discussions about the goals of care, risks and benefits of treatment, and preservation of functional independence and acceptable QOL.

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Chapter 23
Palliative Surgery

Lisa A. dos Santos and Andrew W. Menzin

Abstract The trajectory of a patient's illness may lead to a time when oncologic care focuses not on therapeutics but rather on symptom control and quality, not quantity, of life. Most often, interventions in this setting are pharmaceutical or psychosocial. However, in selective circumstances, surgery may be employed as a palliative tool. The most common clinical scenarios in which palliative surgery is considered include bowel obstruction, fistulas, urinary obstruction, and recurrent pleural effusion. We will review the relevant issues and management options for these common gynecologic oncology situations.

Keywords Palliative surgery • Gynecological oncology • End-of-life issues • Bowel obstruction • Fistulas • Urinary obstruction • Pleural effusion

Ethical Dimensions

The practice of clinical medicine may be seen as a crossroads of the bioethical principles of autonomy, beneficence, non-maleficence, and justice. Nearly every circumstance one encounters can be viewed through a prism of each principle, and balancing one, several, or all may prove a challenge without clear resolution, particularly in the setting of palliative care and especially when surgical intervention is considered.

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Table 23.1 American College of Surgeons: statement of principles of palliative care

Respect the dignity and autonomy of patients, patients' surrogates, and caregivers
Honor the right of the competent patient or surrogate to choose among treatments, including those that may or may not prolong life
Communicate effectively and empathically with patients, their families, and caregivers
Identify the primary goals of care from the patient's perspective, and address how the surgeon's care can achieve the patient's objectives
Strive to alleviate pain and other burdensome physical and nonphysical symptoms
Recognize, assess, discuss, and offer access to services for psychological, social, and spiritual issues
Provide access to therapeutic support, encompassing the spectrum from life-prolonging treatments through hospice care, when they can realistically be expected to improve the quality of life as perceived by the patient
Recognize the physician's responsibility to discourage treatments that are unlikely to achieve the patient's goals, and encourage patients and families to consider hospice care when the prognosis for survival is likely to be less than a half year
Arrange for continuity of care by the patient's primary and/or specialist physician, alleviating the sense of abandonment patients may feel when "curative" therapies are no longer useful
Maintain a collegial and supportive attitude toward others entrusted with care of the patient

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Surgery is a therapeutic tool. Surgeons practice the art of using that tool to the desired end. As Hofmann and colleagues noted, "surgery is a physical (invasive) procedure that is expected to enable relief of physical suffering" [1, p. 804]. They go on to acknowledge surgery's effect on mental processes. In 1998, recognizing the central role of surgeons throughout the course of a patient's illness, the American College of Surgeons (ACoS) initially issued a "statement of principles guiding care at the end of life." The Task Force on Surgical Palliative Care and the Committee on Ethics of the ACoS subsequently in 2005 put forth the "statement of principles of palliative care" (Table 23.1). This document provides a guide with which to approach patients who require a consideration of palliative intervention, and translates the core ethical principles into a practical framework that a surgeon may use at the bedside [2].

Surgery in the Patient Who Is DNR

The consideration of surgery as a potential palliative intervention creates a challenging scenario for patients who have expressed a wish not to be resuscitated (DNR). Anesthetic care and cardiopulmonary resuscitation may be seen as representing a continuum of therapeutics. Angelos and Dunn [3] reviewed this ethical dilemma and offer the technique of "required reconsideration," described by Cohen and Cohen [4], as a model for managing this circumstance. Essentially, a thorough review of the proposed intervention and possible consequences takes place, with a consideration of acceptable interventions in the context of the patient's wishes and goals for care. A clear understanding by all stakeholders (patient, family, caregivers, and other hospital staff) is critical, as is a description of the agreed upon parameters in the patient's chart.

Clinical Scenarios

Malignant Bowel Obstruction

Malignant bowel obstruction (MBO) is a common clinical problem in patients with gynecologic malignancy, particularly in cases of recurrent and progressive disease. In the natural history of advanced epithelial ovarian cancer, carcinomatosis frequently leads to progressive encasement of the bowel and mesentery, causing obstruction and eventual death. While bowel obstruction is the most common cause of death in ovarian cancer, this process may also occur in patients with metastatic disease from other primary gynecologic malignancies. In the absence of widespread carcinomatosis, MBO may be related to localized extrinsic compression or intrinsic involvement of the bowel adjacent to a pelvic mass, such as occurs in advanced or recurrent cervical and endometrial carcinoma. While malignant bowel obstruction may sometimes be a presenting symptom at initial diagnosis and be treated as part of initial surgical therapy, it is most commonly encountered in recurrent and progressive disease and hence it is frequently considered in the realm of palliative surgery.

While intestinal obstruction in patients with advanced disease may occasionally be due to a benign etiology such as postoperative adhesions or incisional hernia, the majority of cases are due to tumor-related factors. Direct mechanical obstruction by carcinomatosis involving the bowel wall and mesentery is most common. Other factors contributing to obstruction include impaired gastrointestinal motility, ascites, hypersecretion, electrolyte disturbances, and resultant adynamic ileus. MBO may be partial or complete, unifocal or multifocal, and involve the small bowel, the large bowel, or both. Each of these factors must be evaluated in the consideration of palliative surgery, as they affect the likelihood of successful surgery. Radiographic evaluation with cross-sectional imaging such as CT scan can approximate the extent and resectability of obstructive tumor masses and determine whether there are multiple points of obstruction. Depending on the clinical scenario, endoscopy or colonic evaluation with contrast enema may be indicated in order to establish patency of the distal gastrointestinal tract.

Defining Palliation in the Context of Bowel Obstruction

The primary goal of palliative surgery for MBO is mitigation of the patient's symptoms, which most frequently include intractable nausea, vomiting, abdominal distension, and significant abdominal pain, in order to provide an improved quality of life. Other quality of life factors are also relevant, including the ability to consume food and drink and freedom from the continuous discomfort of a nasogastric tube. While there is no standardized consensus regarding the definition of successful palliation after surgery for MBO, the ability to tolerate a diet of solid food at 60 days postoperatively has been used as a desired outcome [5, 6].

The role of surgery in the management of MBO in the palliative setting involves complex decision-making. In the majority of cases, a trial of medical management with analgesia, fluid resuscitation, antiemetic medication, pharmacologic agents, and decompression with a nasogastric tube is indicated. In cases of bowel perforation, or suspected impending perforation, surgical intervention may be considered emergently. In most cases, however, failure of conservative management after a period of time leads to a discussion regarding the feasibility of surgical options.

As with any palliative procedure, realistic and honest conversation with the patient and their family regarding expectations and goals of treatment is crucial. The patient's desires must be clearly articulated, and a mutual agreement should be made between surgeon and patient regarding the expectations and goals of the procedure. The patient's overall disease status must be considered, including performance status, life expectancy, and availability of potential options for further chemotherapy. The significant risks of morbidity and mortality of the planned surgical procedure must be taken into account, and the undesirable possibility of a prolonged postoperative hospital stay in a patient with a limited life expectancy should be considered. In the elderly patient, these issues are often amplified by poor performance status and medical comorbidities, making surgical intervention a decision deserving extremely careful consideration.

Patient Selection and Prognostic Factors

The goals of palliative surgery can most often be successfully accomplished through careful patient selection. Numerous attempts have been made by various authors to identify a subset of patients who will derive benefit from palliative surgery [7–10]. Proposed prognostic factors have included age, performance status, nutritional status, albumin level, extent of disease, presence or absence of ascites, interval since primary surgery, and prior therapy. No clear set of guidelines has been established to date, and the decision remains highly individualized to the particular patient [11].

The vast majority of published data relevant to MBO in gynecologic oncology is limited to epithelial ovarian cancer, is retrospective, and uses overall survival or nonstandardized quality-of-life endpoints. However, several series have suggested potential benefit in a subset of patients. Pothuri and coauthors retrospectively evaluated 64 patients who underwent surgery for recurrent ovarian cancer and found that surgical correction was attained in 84 % of cases. Of these, successful palliation was achieved in 71 % of cases, as defined by tolerance of a regular or low-residue diet at least 60 days postoperatively [5]. Chi and colleagues prospectively followed a cohort of 74 recurrent ovarian cancer patients undergoing palliative operative (resection, bypass, or diversion) or endoscopic interventions (PEG, colonic stent) for MBO. At 30 days post-procedure, improvement or resolution of symptoms was achieved in 88 % of patients. At 60 days post-procedure, 71 % of operative intervention patients and 50 % of endoscopic intervention patients maintained symptom control. At 90 days, 64 % of the operative intervention patients demonstrated

continued symptom control. Overall, patients selected for operative intervention had a longer median survival than those who underwent endoscopic procedures [12].

The morbidity and mortality of palliative procedures for MBO in this patient population is significant. Kolomainen and colleagues described a series of 90 women undergoing palliative surgery for MBO in recurrent ovarian cancer, with operative mortality and morbidity rates of 18 and 27 %, respectively [6].

Types of Procedures

In metastatic gynecologic malignancy, MBO may occur at any point in the gastrointestinal tract. Therefore, surgical management is highly individualized to the particular patient's clinical situation as well as the anatomic characteristics of the obstruction. A thorough intraoperative evaluation of the entire tract is warranted, and a thoughtful and creative approach to multifocal obstruction is often necessary for surgery to be successful. The importance of establishing the patency of the distal tract cannot be overemphasized, particularly if anastomosis or bypass is under consideration.

Isolated small bowel obstruction (SBO) may be treated with primary resection of the obstructing mass followed by primary anastomosis. In cases of multifocal small bowel obstruction, it is important to carefully identify the most proximal and distal points of obstruction or impending obstruction in order to restore the continuity of the gastrointestinal tract and reduce the rate of early recurrence of symptoms. The post-procedural length of residual functional small bowel is an important factor to consider, as short bowel syndrome can be severely symptomatic and limiting to the patient's quality of life. In cases of obstruction due to multifocal disease and/or an unresectable tumor mass, a bypass procedure is often most appropriate. In these cases, it is crucial to maintain a route of egress for secretions from the bypassed segment in order to avoid a closed loop obstruction.

In some cases, due to proximal obstruction or very extensive disease, continuity of the gastrointestinal tract cannot be safely reestablished, and intestinal diversion is the most appropriate management. It is crucial to establish the most proximal site of obstruction. An ileostomy or jejunostomy may then be performed proximal to the obstruction but conserving as much proximal intestine as is technically feasible in order to maximize residual small bowel surface area. In cases of proximal jejunal or duodenal obstruction, a gastrostomy tube is most appropriate for definitive management. A gastrostomy tube may also be placed as an adjunct to the procedures outlined above in order to provide temporary or intermittent proximal drainage. In cases of known proximal obstruction definitely requiring a gastrostomy tube in the palliative setting, the procedure can often be accomplished endoscopically (percutaneous endoscopic gastrostomy, PEG). This approach can spare the patient and the morbidity of a major procedure.

Large bowel obstruction (LBO) may be a unifocal event, most commonly occurring in the rectosigmoid region due to pelvic tumor, or it may be multifocal or occur

in combination with small bowel obstruction. In cases where the obstruction is limited to the large intestine, primary resection of the obstructing mass with colonic anastomosis may be feasible. Temporary diverting ileostomy is sometimes performed in selected cases. Obstruction is also frequently encountered at the ileocecal level, which may be treated with ileocecal resection and ileocolonic anastomosis. In cases of unresectable right lower quadrant tumor, an ileocolonic bypass may be considered. In cases of very extensive disease or unresectable pelvic tumor, diverting colostomy is most appropriate.

The use of colorectal stents in the management of MBO in gynecologic malignancies has increased in recent years and in selected cases provides a viable alternative to major surgery. Caceres et al. reviewed a series of 35 gynecologic oncology patients undergoing colonic stent placement and found that 77 % of patients were successfully stented at initial procedure. Of these, one-third eventually required additional procedures to relieve obstruction, and the median overall survival after stent placement was 7.7 months [13].

Fistulas

The development of intestinal fistulas to the skin, bladder, vagina, and perineum is a phenomenon related to treatment-related effects as well as the tumor itself. In patients with inoperable tumors or otherwise not suitable for surgical resection, palliative treatment may be offered to mitigate the significant symptoms that may be adversely affecting the patient's quality of life. In these cases, intestinal diversion may provide relief and decrease the infectious complications associated with these lesions. In selected cases, the procedure may be performed in a minimally invasive fashion in order to minimize the surgical morbidity and maximize quality of life [14, 15].

Urinary Obstruction

Urinary obstruction in the end-stage gynecologic cancer patient may arise from a variety of causes, either intrinsic or extrinsic to the urinary tract. An evaluative plan to identify the cause should be systematic and consider distal and proximal sites of blockage. While typically diagnosed on ultrasound, CT scan or MR imaging, additional investigation with renal function assessment using isotope scanning provides a quantitative determination of function and may influence further therapeutic decisions. Dedicated ultrasound may also provide adjunctive information, particularly regarding bladder size or dilatation of the ureter and renal pelvis.

Uncomplicated obstruction of the urinary tract may be asymptomatic, and a thoughtful decision should be made as to the goal of intervention in the absence of relevant sequelae. When a palliative procedure is deemed appropriate, various options may be considered.

Outlet obstruction due to urethral compromise by a mass lesion, infiltration of the periurethral tissues, or compression against the pubic bone from a pelvic mass may be associated with dilatation of the bladder and, at times, the proximal urinary tract. Simple decompression with a Foley catheter may provide immediate relief. If passage of a transurethral catheter is not technically feasible, a placement of a suprapubic catheter will also accomplish rapid mitigation of what may be significant symptomatology. With continued bladder decompression, secondary ureteral dilatation may abate as well.

Ureteral obstruction may occur at any site along the course of the ureter, but common locations include the pelvic brim as the ureter traverses the iliac vessels and along the pelvic sidewall where compression may occur from a peritoneal mass or bulky retroperitoneal adenopathy. Retrograde contrast imaging can provide a determination of the level of the blockage, and relief of the obstruction may be achieved in many cases with cystoscopic placement of a ureteral stent. Should the retrograde approach prove unsuccessful or technically impossible, renal decompression via placement of a percutaneous nephrostomy, usually under the direction of an interventional radiologist, is an excellent alternative. Subsequent antegrade passage of a ureteral stent may be considered depending on the goals of treatment.

Major surgical intervention for management of a urinary obstruction is usually avoided in the setting of end-stage malignancy. Fistulous communications can often be treated with percutaneous decompression and drainage. Post-obstructive infections are also best dealt with in this fashion.

Recurrent Pleural Effusion

Metastatic disease in the pleural space typically presents clinically as an effusion, which may compromise pulmonary function. The symptomatic manifestation of a pleural effusion is often an acute and significant challenge for the patient. The accompanying shortness of breath creates a sense of suffocation, anxiety, and an inability to communicate effectively with loved ones and caregivers.

Palliation in this setting may be accomplished by bedside or image-guided thoracentesis, but recurrent symptomatic effusion is common. A Cochrane review concluded that thoracoscopic pleurodesis was superior compared to other methods and noted that talc was associated with more effective results than other sclerosants [16]. Therapeutic discussions should focus around the trade-off of greater efficacy of thoracoscopy with the increased invasiveness and the need for general anesthesia.

Concluding Remarks

The aim of palliative surgery in the gynecologic cancer patient is to alleviate symptoms and optimize quality of life. As Angelos and Dunn note: “these goals are directly related to how the patient experiences the illness” [3, p. 452]. It has long

been said in general surgery that "not everyone needs to die with an incision." As oncology surgeons, we must continually strive to develop palliative management strategies that offer the patient the maximum optimization of quality of life, with or without a surgical procedure.

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