Ministry of Health - Italy

MEDITERRANEAN BOOKLETS SERIES

TUNISIA

Feminine cancer prevention and treatment.

Materials forwarded during three training stages at Campus Bio-Medico University - 2009-2010

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1. Breast cancer update

1.1. American Cancer Society recommendations for early breast cancer detection in women without breast symptoms

Women age 40 and older should have a mammogram every year and should continue to do so for as long as they are in good health.

Current evidence supporting mammograms is even stronger than in the past. In particular, recent evidence has confirmed that mammograms offer substantial benefit for women in their 40s. Women can feel confident about the benefits associated with regular mammograms for finding cancer early. However, mammograms also have limitations. A mammogram can miss some cancers, and it may lead to follow up of findings that are not cancer.

Women should be told about the benefits and limitations linked with yearly mammograms. But despite their limitations, mammograms are still a very effective and valuable tool for decreasing suffering and death from breast cancer.

Mammograms should be continued regardless of a woman's age, as long as she does not have serious, chronic health problems such as congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease, and moderate to severe dementia. Age alone should not be the reason to stop having regular mammograms. Women with serious health problems or short life expectancies should discuss with their doctors whether to continue having mammograms.

Women in their 20s and 30s should have a clinical breast exam (CBE) as part of a periodic (regular) health exam by a health professional preferably every 3 years. Starting at age 40, women should have a CBE by a health professional every year.

CBE is done along with mammograms and offers a chance for women and their doctor or nurse to discuss changes in their breasts, early detection testing, and factors in the woman's history that might make her more likely to have breast cancer.

There may be some benefit in having the CBE shortly before the mammogram. The exam should include instruction for the purpose of getting more familiar with your own breasts. Women should also be given information about the benefits and limitations of CBE and breast self-examination (BSE). The chance of breast cancer occurring is very low for women in their 20s and gradually increases with age. Women should be told to promptly report any new breast symptoms to a health professional.

Breast self-examination (BSE) is an option for women starting in their 20s. Women should be told about the benefits and limitations of BSE. Women should report any breast changes to their health professional right away.

Research has shown that BSE plays a small role in finding breast cancer compared with finding a breast lump by chance or simply being aware of what is normal for each woman. Some women feel very comfortable doing BSE regularly (usually monthly after their period) which involves a systematic step-by-step approach to examining the look and feel of one's breasts. Other women are more comfortable simply feeling their breasts in a less systematic approach, such as while showering or getting dressed or doing an occasional thorough exam. Sometimes, women are so concerned about "doing it right" that they become stressed over the technique. Doing BSE regularly is one way for women to know how their breasts normally look and feel and to notice any changes. The goal, with or without BSE, is to report any breast changes to a doctor or nurse right away.

Women who choose to use a step-by-step approach to BSE should have their BSE technique reviewed during their physical exam by a health professional. It is okay for women to choose not to do BSE or not to do it on a regular schedule such as once every

month. However, by doing the exam regularly, you get to know how your breasts normally look and feel and you can more readily find any changes. If a change occurs, such as development of a lump or swelling, skin irritation or dimpling, nipple pain or retraction (turning inward), redness or scaliness of the nipple or breast skin, or a discharge other than breast milk (such as staining of your sheets or bra), you should see your health care professional as soon as possible for evaluation. Remember that most of the time, however, these breast changes are not cancer.

Women at high risk (greater than 20% lifetime risk) should get an MRI and a mammogram every year. Women at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram. Yearly MRI screening is not recommended for women whose lifetime risk of breast cancer is less than 15%.

Women at high risk include those who:

- Have a known BRCA1 or BRCA2 gene mutation
- Have a first-degree relative (parent, brother, sister, or child) with a BRCA1 or BRCA2 gene mutation, and have not had genetic testing themselves
- Have a lifetime risk of breast cancer of 20% to 25% or greater, according to risk assessment tools that are based mainly on family history (see below)
- Had radiation therapy to the chest when they were between the ages of 10 and 30 years
- Have Li-Fraumeni syndrome, Cowden syndrome, or hereditary diffuse gastric cancer syndrome, or have one of these syndromes in first-degree relatives

Women at moderately increased risk include those who:

- Have a lifetime risk of breast cancer of 15% to 20%, according to risk assessment tools that are based mainly on family history (see below)
- Have a personal history of breast cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH)
- Have extremely dense breasts or unevenly dense breasts when viewed by mammograms

If MRI is used, it should be in addition to, not instead of, a screening mammogram. This is because although an MRI is a more sensitive test (it's more likely to detect cancer than a mammogram), it may still miss some cancers that a mammogram would detect.

For most women at high risk, screening with MRI and mammograms should begin at age 30 years and continue for as long as a woman is in good health. But because the evidence is limited regarding the best age at which to start screening, this decision should be based on shared decision-making between patients and their health care providers, taking into account personal circumstances and preferences.

It is recommended that women who get a screening MRI do so at a facility that can do an MRI-guided breast biopsy at the same time if needed. Otherwise, the woman will have to have a second MRI exam at another facility when she has the biopsy.

There is no evidence right now that MRI will be an effective screening tool for women at average risk. While MRI is more sensitive than mammograms, it also has a higher false-positive rate (it is more likely to find something that turns out not to be cancer). This would lead to unneeded biopsies and other tests in many of the women screened.

The American Cancer Society believes the use of mammograms, MRI (in women at high risk), clinical breast exams, and finding and reporting breast changes early, according to

the recommendations outlined above, offers women the best chance to reduce their risk of dying from breast cancer. This approach is clearly better than anyone exam or test alone. Without question, a physical exam of the breast without a mammogram would miss the opportunity to detect many breast cancers that are too small for a woman or her doctor to feel but can be seen on mammograms. Mammograms are a sensitive screening method, but a small percentage of breast cancers do not show up on mammograms but can be felt by a woman or her doctors. For women at high risk of breast cancer, such as those with BRCA gene mutations or a strong family history, both MRI and mammogram exams of the breast are recommended.

1.2. Clinical practice guidelines for the management of early breast cancer

Early breast cancer has been defined as tumours of not more than five centimetres diameter, with either impalpable or palpable but not fixed lymph nodes and with no evidence of distant metastases. This corresponds to tumours that are T1-2, N0-1, M0 as currently defined by the International Union Against Cancer (UICC).

The aim of surgery for primary breast cancer is to eradicate the primary tumour and any local extension in the hope of achieving total disease control. Indirect evidence suggests that surgical intervention may extend survival from the time of clinical detection. In an historical comparison, women treated by radical mastectomy appeared to survive longer than women whose breast cancer was untreated,185 and in the long-term follow-up of women treated by radical mastectomy, about 30 per cent of women were alive 30 years after surgical treatment.

There have been two randomised trials involving women over 70 not having surgery. In the first, women were randomised to either tamoxifen 40mg daily or tamoxifen plus optimal surgery. At a median follow-up of 34 months, many women on tamoxifen alone had progressed to surgery, but there was no demonstrable difference in quality of life or survival rate. The trial is continuing. However, a number of women over the age of 70 years are of good performance status and good prognosis and should probably be treated along standard treatment lines, which in most circumstances would be wide local excision followed by post-operative radiotherapy. There is no evidence to suggest that these patients have any greater difficulty coping with such treatment. In the second trial,188 women were randomised to either wedge resection or tamoxifen 40mg daily. At a mean follow-up of 65 months, significantly more women in the tamoxifen group had progression of their cancer. There was no difference in overall survival, cause of death, the rate of metastases or the site of initial metastasis.

Further evidence supporting the value of surgical excision is provided by randomised controlled trials of screening mammography. Women offered mammographic screening and treatment of screen detected cancers have significantly lower mortality than women in unscreened control groups in

population-based trials of mammographic screening

The surgical treatment of primary breast cancer has devolved into two basic procedures:

- complete local excision (CLE) with axillary dissection
- total mastectomy with axillary dissection

1.2.1. Breast conserving surgery

Breast conserving surgery demands CLE, which by definition means clear histological margins with a rim of normal breast tissue around the periphery of the primary tumour on all sides. This procedure is suitable for tumours which are unifocal and in which clear margins can be obtained, if necessary by including overlying skin. All the requirements of treatment must be taken into account when planning the incision. There is no absolute limit to the size of a tumour which can be

locally excised without incurring a high risk of recurrence; 3–4cm is often regarded as a practical limit. The aim of treatment is to maximise control of the disease and decrease the impact of breast cancer on the woman's quality of life. However, the relativity of tumour size to breast size and the achievement of an acceptable cosmetic result are equally important considerations.

A breast conserving protocol comprises CLE in which clear margins are obtained by any surgical technique (including segmentectomy and quadrantectomy), combined with axillary dissection and followed by adjuvant radiation therapy to the breast (see below). Completeness of excision minimises the risk of local recurrence. There are no reliable data to show a definite width of margin that is necessary for complete excision, but re-excision should be considered where the tumour extends to and or involves the margin. For specimens of impalpable lesions that are accompanied by a specimen radiograph, it is essential to correlate the radiological and histological appearances. Blocks should be selected from the area of the radiological abnormality which can be identified, by either slicing or repeating an X-ray of the slices or by using a localisation device in which a grid reference is used to locate the areas of interest. Either method is acceptable. Any lesion present within the specimen should be described and its maximum dimension recorded in millimetres. The relationship of the lesion to the excision margins should be recorded and the distance to the nearest margin or margins, measured. Very small, well differentiated tumours are associated with decreased levels of axillary involvement, and in such cases after discussion, consideration may be given to omission of axillary dissection. It should be noted that even in T1b tumours (6–10mm), the probability of lymph node involvement approaches 20 per cent. Studies of sentinel node biopsy may help to resolve this.

When the omission of axillary dissection from a breast preserving protocol is considered, the woman should be fully informed of the risk of axillary node metastases being undetected. Radiotherapy could be offered as an alternative.

1.2.2. Total mastectomy

In clinical trials conducted in the 1960s, total mastectomy combined with axillary dissection or radiation treatment to the axilla achieved survival rates similar to those achieved by the Halsted radical mastectomy.192 Later studies confirmed this and there is now essentially no role for Halsted therapy in modern care of breast cancer. The surgical protocol for a total mastectomy includes complete excision of the breast parenchyma with preservation of the underlying pectoral muscles. Total mastectomy is an appropriate treatment for women whose tumours extend widely within the breast, have ill defined margins which defy CLE, directly involve the nipple or overlying skin, or who do not choose breast conservation. Nipple involvement does not always preclude breast conservation. In such cases, excision of the central breast tissue, including the nipple, is often feasible. It is reasonable to reconstruct the nipple as a secondary procedure.

Skin sparing and nipple preserving mastectomy with immediate reconstruction may have a place in the treatment of early breast cancer. Although no long-term results of this technique are yet available, early data suggest no increase in the risk of local recurrence when tumours of comparable size are treated by skin sparing mastectomy as opposed to total mastectomy.

1.2.3. Comparison of breast conserving surgery with mastectomy

Pre-operatively, about 70 per cent of mammographically detected cancers and 50 per cent of clinically detected cancers appear suitable for breast conservation, and this option should be discussed with the woman. Numerous randomised, controlled clinical trials have demonstrated no difference in distant metastases or survival among women with operable breast cancer treated by

mastectomy compared with those treated by breast conserving surgery when both have included axillary dissection.

The incidence of local recurrence is 1–2 per cent per year in women who have breast conserving surgery followed by radiotherapy.204 In comparable tumours, the incidence of local recurrence following mastectomy is 3–5 per cent at 10 years, or less than 0.5 per cent per year. The choice of surgery is an individual one and each woman should be fully informed of her options, including the risks and benefits of each procedure. The woman should be informed that local recurrence can occur even in surgery properly performed and she should be made aware of the potential need for further surgery if the margins are positive. The cosmetic result of breast conserving surgery has a high level of

acceptance, gives an opportunity to preserve the breast shape, avoids the need for a prosthesis or reconstructive surgery, facilitates a better fit of clothing and in general is associated with less impact on body image and sexuality. These are factors which may influence a woman's decision in favour of breast conserving surgery. In discussion of choice between breast conserving surgery and mastectomy, women should be informed that body image is better preserved with conservation surgery.

1.3. Management of the axilla

Management of the axilla has several aims:

- eradication of metastatic disease within the axillary nodes
- assessment of nodal status for evaluation of prognosis
- assessment of nodal status to determine adjuvant therapy

Both dissection and irradiation are used in managing the axilla. The best approach needs to be considered, as there are side effects from both axillary dissection and axillary irradiation—in particular, lymphoedema. Reported estimates of rates of lymphoedema following axillary surgery (sampling or dissection) and/or axillary irradiation vary widely, reflecting the methodological weaknesses of many of the studies that have investigated the prevalence of lymphoedema following treatment for breast cancer. Rates of between 0 per cent and 58 per cent for axillary dissection alone (six studies); between 0 per cent and 11 per cent for axillary sampling (two studies) and 8 per cent for women who received axillary irradiation alone (one study) have been reported. When both axillary surgery (dissection or sampling) and irradiation are given, reported rates of lymphoedema range between 6 per cent and 60 per cent. However, analysis of the significance of much of this research is complicated by the lack of comparability between studies and measurement methods, small sample sizes, poor differentiation of subgroups and methodological problems in individual studies.

1.3.1. Axillary dissection

The extent of axillary dissection can be defined with reference to the pectoralis minor muscle:

- level 1: lower axilla up to the lower border of pectoralis minor
- level 2: axillary contents up to the upper border of pectoralis minor
- level 3: axillary contents extending to the apex of the axilla

All nodes removed should be sent to the pathologist for examination.

1.3.2. Survival

The benefits of axillary dissection in prolonging survival are unclear; studies have reported different effects on survival and most have some methodological flaws. For example, the NSABP 04 trial found that there was no difference in survival between women who had simple mastectomy and those who had radical mastectomy (including axillary dissection). However, 33 per cent of women

in the non-dissected group had undergone some form of limited axillary surgery and the power of the study may have been insufficient to demonstrate a clinically significant difference between the groups. Other studies have found overall long-term benefits in survival when axillary dissection was carried out.192,217,218 For example, Cabanes' study of lumpectomy plus breast and axillary irradiation without axillary dissection, versus lumpectomy plus breast irradiation with axillary dissection, showed a small but significant improvement in survival in women who had axillary surgery (92.6% vs 96.6%, p=0.014).217 However, interpretation of these results is difficult since a significant proportion of the axillary dissection group received adjuvant systemic therapy based on their nodal status.

1.3.3. Prognostic information

Axillary dissection also provides information about nodal status for both prognosis and the planning of adjuvant treatment. Axillary lymph node status is the most powerful single variable in the estimation of prognosis for primary breast cancer. Prognosis is related to the *number* of axillary nodes which contain metastases—this relationship applies to both disease-free interval and to survival. As a means of selecting women for adjuvant systemic therapy, the number of nodes involved is important since the benefits of therapy are expressed as a reduction in risk. The probability of lymph node involvement is related directly to the size of the primary tumours. Larger tumours are more likely to have metastasised to axillary lymph nodes than smaller ones. But even in small primary tumours (T1a), the risk of nodal metastases approaches 20 per cent. In the presence of nodal involvement adjuvant radiotherapy has been shown to have a significant influence on disease-free survival, to reduce locoregional recurrence and, in a few studies, to improve overall survival.220,221. At this time, axillary dissection is the only reliable technique for determining lymph node status. Axillary sampling is an ill-defined procedure and is not recommended as an alternative to axillary dissection. Axillary sampling may imply the removal of a single lymph node for histological examination, or a dissection of the axillary contents extending to level 1. Although there is now some evidence from randomised controlled trials which shows that this technique produces qualitative information about whether an axilla is histologically involved under some circumstances, the accuracy of the procedure has not been validated by other centres. At this time axillary sampling is considered unreliable in assessing the presence of axillary lymph node metastases because of the high false negative rate.

1.3.4. Sentinel node biopsy

Sentinel node biopsy is being studied,225,226 but is not currently considered an alternative to axillary node dissection and the procedure should only be performed as part of a controlled study or as a prelude to dissection. In the future, after appropriate controlled randomised trials have been completed, sentinel node biopsy technologies may modify the approach to the axilla.

1.3.5. Axillary irradiation

The selective use of radiotherapy in patients with increased risk of recurrence is beneficial. Two studies have shown a survival benefit for post mastectomy radiotherapy that included the axilla (and the internal mammary chain and supraclavicular fossa), and another trial has shown a trend towards improved survival. However, a large overview failed to demonstrate a survival benefit for post-operative radiotherapy.

1.3.6. Axillary irradiation following dissection in women with limited nodal involvement

Relevant data are provided by extrapolation of results from several large randomised trialswhich compared breast conserving therapy and mastectomy. They suggest that there may be little benefit from adding

axillary irradiation among women who have had axillary dissection and who have only a small number of involved lymph nodes. For example, the NSABP-B06 trial reported that 90 per cent of patients had less than four lymph nodes positive in a dissected axilla. Local axillary relapse in this entire series is low, at around 1–3 per cent. It is unlikely that the addition of radiotherapy will confer much benefit where rates of relapse are already very low. This conclusion is supported by a strong body of retrospective data. Data from the Mayo Clinic suggest isolated locoregional recurrences (that is, recurrences on the chest wall or lymphatic areas) of only around 8 per cent of women with less than four lymph nodes involved suggest isolated locoregional recurrences of 7 per cent in this group. Of the 634 patients analysed in this study, only 1.3 per cent recurred in the axilla alone and another 1.3 per cent in multiple sites that included the axilla—that is, the total axillary recurrence rate was only 2.6 per cent. Fisher analysed patterns of recurrence in 320 patients who had been treated for Stage II or III breast cancer with surgery and chemotherapy without locoregional radiation therapy. Twenty-one isolated axillary recurrences were found (6.6 per cent) at a median follow-up of 77 months. The number of axillary nodes involved was not predictive of recurrence.

1.3.7. Axillary irradiation following dissection in women with greater lymph node involvement or remaining disease in the axilla

While these data suggest that there is little to be gained by axillary irradiation in women with only a small number of involved lymph nodes, it seems that there may be benefit from the addition of radiotherapy when it is likely that there is remaining disease in the axilla—for example, when the surgeon believes that macroscopic disease was left behind or transected, or when the pathologist indicates positive margins. The addition of axillary irradiation with greater nodal involvement is more controversial. When there is greater nodal involvement, local relapse rates will be increased for surgery alone. For example, data from the Mayo Clinic suggest isolated locoregional recurrences at three years of 14 per cent among women with 4–7 positive nodes and 22 per cent for women with eight or more positive nodes. Similar data have been reported by Fowble *et al*. However, not all of these relapses are axillary. Most studies have shown at least 50 per cent to be on the chest wall. These studies are unrandomised. The three randomised trials noted above which showed an improvement in survival in high-risk disease for patients irradiated to the entire lymphatics and chest wall, showed a reduction in locoregional relapse from 32 per cent to 9 per cent at ten years. Again, the distribution of local relapses was not given, but more than half were on the chest wall. Axillary recurrences remain uncommon even in patients with heavy nodal involvement. Not all analyses have demonstrated increased axillary relapse rates with increasing numbers of involved nodes. It is important, however, to consider the role of axillary irradiation in patients at high risk of local recurrence. Not all axillary recurrences can be salvaged. It is particularly difficult to salvage axillary recurrence with radiotherapy where the axilla has been previously selectively excluded from the chest wall and supraclavicular fossa volume. The prevention of recurrence is therefore a preferable option, although it carries the cost of increased risks of lymphoedema.

1.4. Clinical practice guidelines for the management of advanced breast cancer

Locally advanced breast cancer represents 10–20 per cent of all cases of breast cancer at presentation. It is less common than it used to be, presumably because of greater awareness of breast cancer.

Surprisingly, most women with locally advanced disease do not have evident systemic disease, although it is often suspected. Despite common belief, the prognosis is not inevitably poor. With multimodality therapy, five-year survival rates for stage IIIA disease (T0–2, N2, M0

and T3, N1–2, M0) of 84 per cent and for stage IIIB disease (T4, N1–3, M0, and T1–4, N3, M0) of 44 per cent have been reported. Likewise, four-year disease-free and overall survival rates for inflammatory cancer — often erroneously considered to have a uniformly dire prognosis — have been reported as 54 per cent and 74 per cent respectively.

The prognosis may be such that even if mastectomy is required, women could be informed that a form of reconstruction may be possible, and this should be discussed with the woman if she wishes.

1.4.1. Diagnosis

The initial assessment of locally advanced breast cancer is the same as for any woman presenting with advanced breast cancer. It must include confirmation of the clinical diagnosis by biopsy, as well as tests to determine the extent and nature of any metastases.

1.4.2. Treatment

The best outlook for patients with stage III breast cancer is obtained by using combined modality therapy with surgery, radiotherapy and systemic therapy (chemotherapy and/or hormone therapy). Treatment of local disease in women with locally advanced breast cancer must be more intensive than in women with early breast cancer, because the tumour is larger or involves tissue other than breast soft tissue. Due to the potential complexity of the treatment program, patients with stage III breast cancer need to be seen by the various specialists, so the order of treatments can be agreed upon, ideally in a multidisciplinary clinic. As a consequence of the paucity of randomised controlled trials involving women with locally advanced disease, there is considerable uncertainty as to the optimum order of these treatments and whether all four treatments are required for the best results. There is some evidence and reasonable agreement that if multimodality treatment is considered the best option, then the optimal program could entail:

- chemotherapy (known as neoadjuvant chemotherapy if given before radiotherapy or surgery);
- local therapy (either surgery or radiotherapy);
- then more chemotherapy;
- then consideration of further local therapy - whichever was not used previously; and
- endocrine therapy (for example, tamoxifen if the tumour is oestrogen receptive, for at least five years

Regular clinical follow-up is recommended because of the relatively high risk of local relapse.

1.4.3. Chemoterapy

Even though there is no evidence that any particular combination is superior in locally advanced breast cancer, it is common practice to use a combination which includes an anthracycline. Anthracyclines should be avoided if chemotherapy is to be given at the same time as radiotherapy, because of the risk of potentiating the radiation reaction.

Neoadjuvant chemotherapy, preceding local therapy may reduce the tumour to such an extent than an operation, even breast conserving surgery (particularly for T3 lesions) is feasible in women whose lesion would not initially have allowed this option. Appropriate local therapy — radiotherapy, or surgery followed by radiotherapy — is often followed by further adjuvant chemotherapy.

Endocrine therapy should also be considered for women with locally advanced breast cancer, particularly for those with hormone receptor positive tumours (either oestrogen receptor or progesterone receptor positive). Tamoxifen 20mg daily for five years is suitable for pre- or post-menopausal women; ovarian ablation should also be considered for pre-menopausal women. This recommendation is based on the efficacy of

ovarian ablation and tamoxifen in reducing the risks of recurrence and death in women with early breast cancer and on their efficacy in women with advanced breast cancer rather than on evidence in women with locally advanced breast cancer.

1.4.4. Surgery

In most cases involving surgery, mastectomy is required. If surgery is chosen as the form of treatment for the axilla, a level III (full) dissection should be performed to decrease risk of regional relapse. Breast reconstruction techniques may be applicable in selected patients. Breast conserving surgery may be feasible after neoadjuvant chemotherapy.

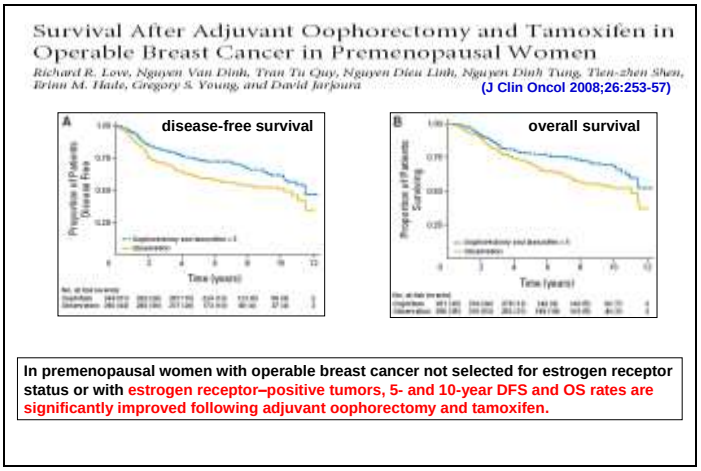
If radiotherapy is given first, surgery for known or anticipated residual disease should be delayed until the radiation reaction has settled down. This may take six to eight weeks.

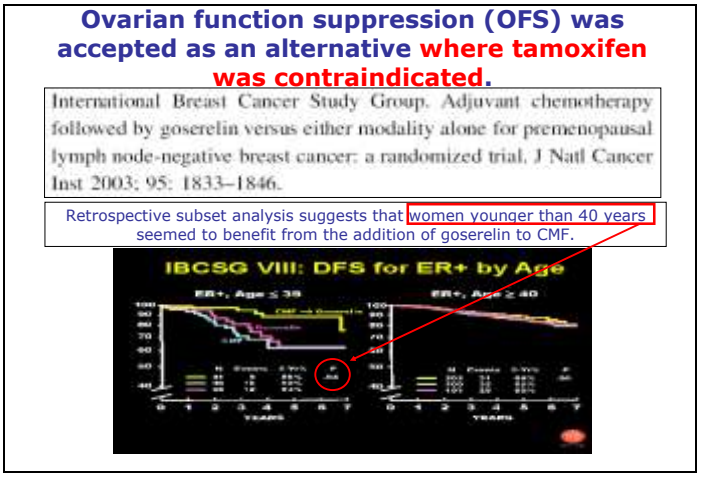
1.4.5. Radiotherapy

Radiation therapy needs to be given in appropriately high doses to the entire breast tissue and nodal areas. However, due to the implications for lymphoedema, irradiation of the axilla should only be conducted if the completeness of surgery is in doubt. If there is doubt about axillary clearance or there is residual macroscopic disease after surgery, the axilla should be irradiated. Consultation with a radiation oncologist is appropriate in the planning of treatment. In addition, areas of palpable disease will require further radiation, either with external beam or possibly a brachytherapy implant.

For most locally advanced carcinomas, conventional fractionation of two Gray per fraction is considered adequate, but this can be modified if the history is that of a rapidly growing tumour.

Tissue equivalent build-up material to bring up the radiation dose to the skin surface may be required for local control in the presence of peau d'orange, ulceration or any skin involvement. This will make the skin reaction more florid and is likely to cause temporary desquamation.

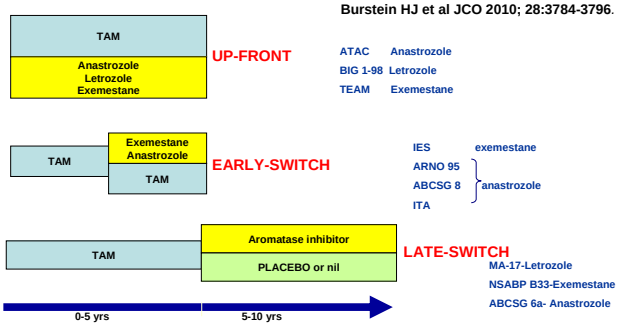




Adjuvant endocrine therapy in postmenopausal pts

AIs vs TAM :Phase III randomised trials

Burstein HJ et al JCO 2010; 28:3784-3796.



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Effect of Body Mass Index on Recurrences in Tamoxifen and Anastrozole Treated Women: An Exploratory Analysis From the ATAC Trial

Ivana Sestak, Wolfgang Dowsett, John F. Forbes, Mitch Dowsett, Anthony Howell, and Jack Cuzick

CONCLUSION

These results confirm the poorer prognosis of obese women with early-stage breast cancer.

Recurrence rates were lower for anastrozole than tamoxifen for all BMI quintiles.

Our results suggest that the relative efficacy of anastrozole compared to tamoxifen is greater in thin postmenopausal women and higher doses or more complete inhibitors might be more effective in overweight women, but this requires independent confirmation.

STRATEGIES: (P)-PRIMARY; (S)-SEQUENTIAL; (E)-EXTENDED

Clinical setting	Options	Recommended duration of tamoxifen	Recommended duration of AI	Recommended total duration of endocrine therapy
If patient is commencing adjuvant endocrine therapy; (patient may have just finished surgery or chemotherapy) (P/S)	*AI monotherapy*	N/A	5 years	5 years
	Tamoxifen → AI	2-3 years	2-3 years	5 years
If patient in middle of tamoxifen (S)	*Tamoxifen → AI*	2-3 years	2-3 years	5 years
If patient in middle of AI (S)	*AI → tamoxifen*	2-3 years (administer second)	2-3 years (administer first)	5 years
If patient finishing five years of tamoxifen (E)	*Tamoxifen → AI*	5 years	3-5 years	8-10 years
If patient is pre- or peri-menopausal	*Tamoxifen*	5 years	NR	5 years

Burstein HJ et al JCO 2010; 28:3784-3796.

Lancet Oncology 2010

Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial

David Azria, Yazid Belkacemi, Gilles Romieu, Sophie Georges, Marion Gutowski, Khalil Zarnani, Carmen Oscar Mercanda, Chantal Lemanski, Michael Coffin, Barry Rosenstein, Pascal Fenoglietto, Nigel B A Symonds, Mahrous Ghadban

INTERPRETATION

AT A MEDIAN FOLLOW-UP OF 26 MONTHS (RANGE 3–40)

LETROZOLE CAN BE SAFELY DELIVERED SHORTLY AFTER SURGERY AND CONCOMITANTLY WITH RADIOTHERAPY.

LONG-TERM FOLLOW-UP IS NEEDED TO INVESTIGATE CARDIAC SIDE-EFFECTS AND CANCER-SPECIFIC OUTCOMES.

META-ANALYSIS OF AI'S VS TAM

- **Monotherapy: ATAC, BIG 1-98/IBCSG 18-98**
  - **9856 pts with 50,000 women-years of f/u for 5 years**
  - **2.7% decrease in relapse, p=0.00004**
  - **1% reduction in death, p=0.28**
- **Switching: ABCSG 8, ARNO 95, IES/BIG 2-97, ITA:**
  - **9015 pts with 33,000 women-years of f/u for 5 years**
  - **3.5 % decrease in relapse, p<0.00001**
  - **1.6% reduction in death, p=0.02**
- **Benefit not affected by PR, age, grade and node**

Dowsett M et al. JCO2009

ANTICANCER RESEARCH 29: 4791-4796 (2009)

Retrospective Analysis of Concurrent *vs.* Sequential Administration of Radiotherapy and Hormone Therapy Using Aromatase Inhibitor for Hormone Receptor-positive Postmenopausal Breast Cancer

MAKOTO IRITOKI, YOSHIFUMI KUMOKE, KAZUYOSHI MOTOMURA, HIROKI KUYAMA, KINJI NISHIYAMA and HIDEO INAJI

Departments of Breast and Endocrine Surgery, and Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakaochi, Higashinari-ku, Osaka 537-8511, Japan

Patients were grouped as concurrent (aromatase inhibitors given during radiotherapy followed by continued aromatase inhibitors; 113 patients) and sequential (radiotherapy followed by aromatase inhibitors; 151 patients).

RESULTS: At a median followup of 2.9 years, there were no differences in the breast cancer outcomes and treatment-related complications between the two treatment groups.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Early Discontinuation and Nonadherence to Adjuvant Hormonal Therapy in a Cohort of 8,769 Early-Stage Breast Cancer Patients

Dawn L. Hershman, Lawrence H. Kushi, Theresa Shao, Dorothy Buono, Aaron Kershenbaum, Wei-Yann Tsai, Lawrence Fehrenbacher, Scarlett Lin Gomez, Sandra Miles, and Alfred I. Neugut

CONCLUSION

Only 49% of patients with BC took adjuvant hormonal therapy for the full duration at the optimal schedule.

Younger women are at high risk of nonadherence.

Interventions to improve adherence and continuation of hormonal therapy are needed, especially for younger women.

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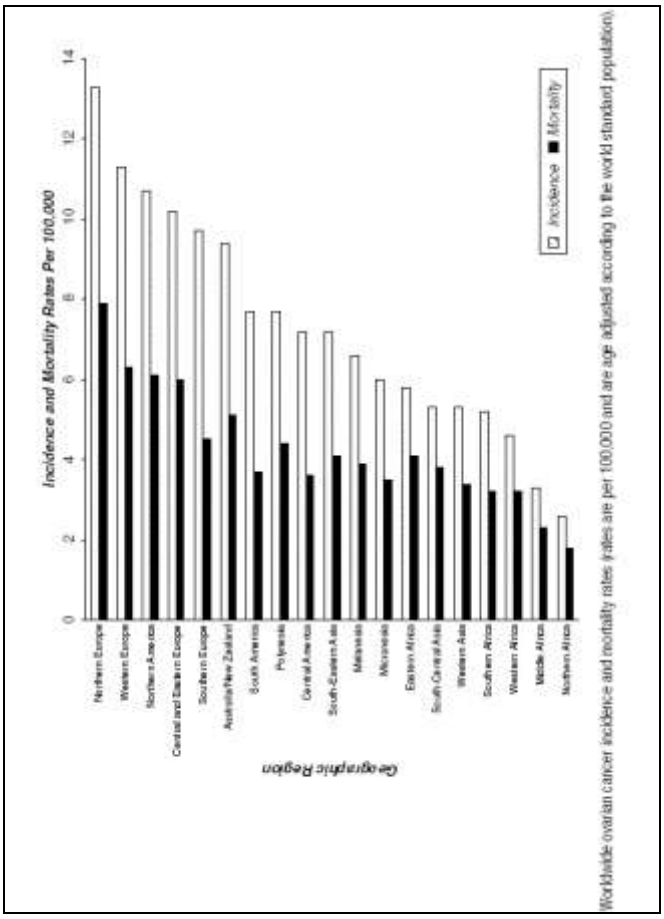
2. Ovarian carcinoma: update

2.1. Epidemiology

Ovarian cancer is the sixth most commonly diagnosed cancer among women in the world, accounting for nearly 4% of all female cancers. Ovarian cancer also represents the second leading gynecologic cancer, following cancer of the uterine corpus, and causes more deaths per year than any other cancer of the female reproductive system. An estimated 1 in 70 women in the United States will develop ovarian cancer in their lifetime.. On a worldwide basis, an estimated 204,000 new cases are diagnosed and 125,000 women die of ovarian cancer annually. In 2007, approximately 22,430 new cases of ovarian cancer will be diagnosed and 15,280 ovarian cancer-related deaths are expected in the United States. Mortality is high because women typically present with late-stage disease when the overall 5-year relative survival rate is 45%. Thus, the public health burden is significant. Despite the high incidence and mortality rates, the etiology of this lethal disease is not completely understood. Research to identify the causes of ovarian cancer is sorely needed, as such knowledge could inform strategies for risk assessment, prevention, surveillance, early detection, and treatment. Ovarian cancer incidence exhibits wide geographic variation . The highest age-adjusted incidence rates are observed in developed parts of the world, including North America and Western and Northern Europe, with rates in these areas exceeding 10 per 100,000, except for Japan (6.4 per 100,000). Rates are intermediate in South America (7.7 per 100,000), and lowest in Asia and Africa. Migration from countries

with low rates to those with high rates results in greater risk, underscoring the importance of nongenetic factors. However, even within the United States, racial differences in risk are apparent that mimic the observed international variation. Rates are highest among whites (14.3 per 100,000), intermediate for Hispanics (11.5 per 100,000), and lowest among blacks (10.1 per 100,000) and Asians (9.7 per100,000). In most parts of North America and Europe, the incidence of ovarian cancer was constant in the decades prior to the 1990s, and has gradually declined since that time. In the United States, there has also been a gradual decline in ovarian cancer-related mortality for all races combined. Several reasons have been proposed to explain both the geographic variation in incidence rates and the trends in incidence and mortality. Such reasons include differences in oral contraceptive (OC) use practices and pregnancy history along with variations in the frequency of prophylactic oophorectomy. Additionally, changes that have impacted medical care such as improvements in diagnosis and treatment, better access to care for minorities and underserved populations, and improved levels of general health awareness may explain the trends. The incidence of ovarian cancer increases with age, with a median age at diagnosis of 63 years. Over 80% of ovarian cancers occur after age 45 years.



2.2. Hystopathology

The task forces of FIGO endorse the histologic typing of ovarian tumors as presented in the WHO publication no. 9, 1973, and recommend that all ovarian epithelial tumors be subdivided according to a simplified version of this. The types of tumors classified are as follows: serous, mucinous, endometrioid, clear cell (mesonephroid), undifferentiated and unclassified.

• Serous tumors

– Benign serous cystadenomas

– Of borderline malignancy: serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)

– Serous cystadenocarcinomas

• Mucinous tumors

– Benign mucinous cystadenomas

– Of borderline malignancy: mucinous cystadenomas with proliferating activity of the epithelial cells

and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)

– Mucinous cystadenocarcinomas

• Endometrioid tumors

– Benign endometrioid cystadenomas

– Endometrioid tumors with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)

– Endometrioid adenocarcinomas

• Clear cell tumors

– Benign clear cell tumors

– Clear cell tumors with proliferating activity of the epithelial cells and nuclear abnormalities, but with no in.ltrative destructive growth (low potential malignancy)

– Clear cell cystadenocarcinomas

• Brenner

– Benign Brenner

– Borderline malignancy

– Malignant

– Transitional cell

• Undifferentiated carcinomas: a malignant tumor of epithelial structure that is too poorly differentiated to be placed in any other group.

• Mixed epithelial tumors: these tumors are composed of two or more of the five major cell types of common epithelial tumors (types should be specified).

• Cases with intraperitoneal carcinoma in which the ovaries appear to be incidentally involved and not the primary origin should be labeled as extra-ovarian peritoneal carcinoma.

Histopathologic grade (G)

• GX: Grade cannot be assessed

• G1: Well differentiated

• G2: Moderately differentiated

• G3: Poorly or undifferentiated

2.3. Staging

2.3.1. Rules for classification

Ovarian cancer is staged surgically. There should be histologic confirmation of the disease. Operative findings, prior to tumor debulking, determine stage, which may be modified by histopathologic as well as clinical or radiological evaluation. Laparotomy and resection of the ovarian mass, as well as hysterectomy, form the basis for staging. Biopsies of all suspicious sites, such as omentum, mesentery, liver, diaphragm, pelvic and paraaortic nodes, are required. The final histologic findings after surgery (and cytologic ones when available) are to be considered in the staging. Clinical studies include routine radiology of the chest. Imaging studies and serum tumor markers may be helpful in both initial staging and follow-up of the tumors.

Evaluation of surgical staging

Laparotomy and biopsy of all suspected sites of involvement provide the basis for staging. Histologic and cytologic data are required.

Postsurgical treatment – pathologic staging

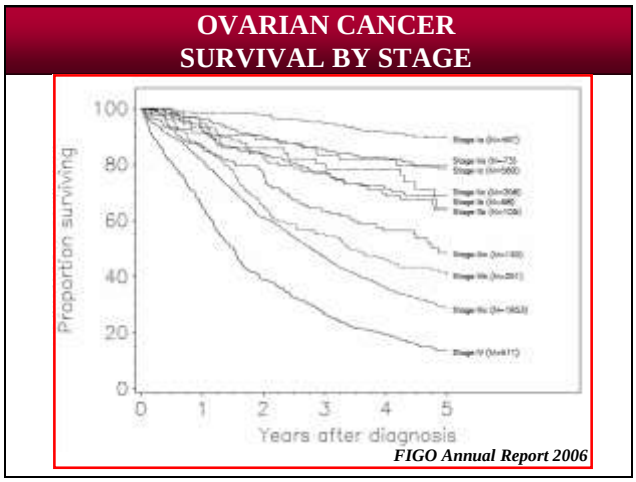
This should include laparotomy and resection of ovarian masses, as well as hysterectomy. Biopsies of all suspicious sites, such as the omentum, mesentery, liver, diaphragm and pelvic and para-aortic nodes, are required. Pleural effusions should be aspirated for cytology.

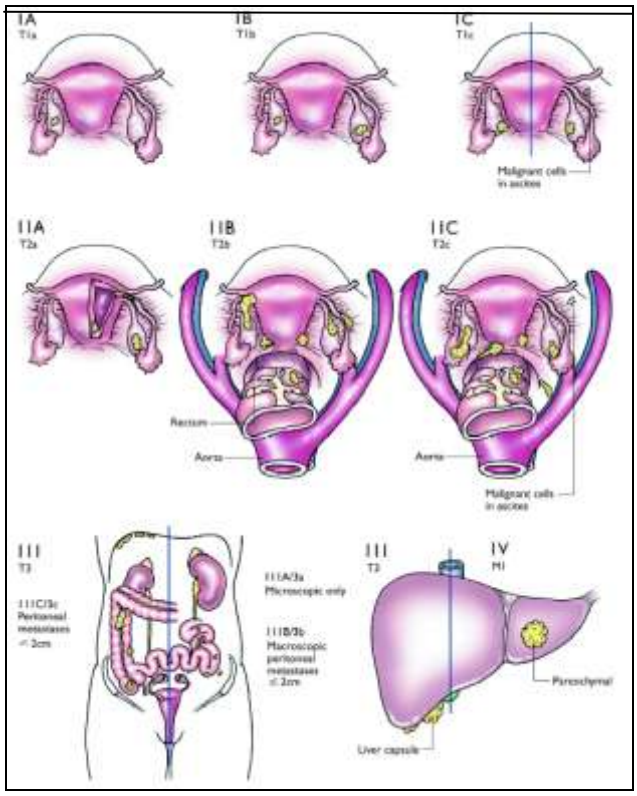
2.3.2. Surgical staging classification

FIGO nomenclature (Rio de Janeiro, 1988)

Staging is based on findings made mainly at surgical exploration. Clinical evaluation and imaging studies should be done as appropriate. These findings may affect final

staging. The histology is to be considered at staging, as is cytology as far as effusions are concerned.





Carcinoma of the ovary. Staging ovarian cancer: primary tumor and metastases (FIGO and TNM).

2.4. Surgical management

2.4.1. CA125 Estimation

Preoperative serum CA125 levels can be used to predict disease bulk, and may be of benefit in identifying patients in whom optimal cytoreductive surgery is feasible. CA125 levels are higher in serous rather than mucinous tumours, as well as in postmenopausal compared to premenopausal patients. The sensitivity and specificity of CA125 in predicting the possibility of cytoreductive surgery range from 62 to 78% and 73 to 83% respectively. It is not possible to determine if a particular preoperative CA125 level can be used to predict whether optimal cytoreduction is possible. CA125 may be elevated in women who have had a recent laparotomy

2.4.2. Other tumour markers

Carcinoembryonic antigen (CEA) is a tumour marker found in the blood of patients suffering from colorectal cancer. There is no correlation between the CEA level and the FIGO stage of ovarian carcinoma. Measurement of a fetoprotein (AFP) and human chorionic gonadotropin (hCG) in younger women can help exclude non-epithelial ovarian tumours.

Human epididymis protein 4 (HE4) is a novel marker for ovarian cancer. HE4 exhibits a high sensitivity to detect ovarian cancer and can be used with CA125 as a predictor of malignancy. Additional uses of HE4 are as an aid of monitoring response to therapy for patients with invasive ovarian cancer and as a marker to detect recurrences in the follow-up after treatment of the primary tumour.

OVARIAN CANCER TREATMENT

MAJOR CONTRIBUTION TO
IMPROVED RESULTS AND QUALITY OF LIFE

- **CHEMOTHERAPY**
  Platinum-taxane based combinations….
- **CYTOREDUCTIVE SURGERY**

- **PATIENTS SELECTION & MANAGEMENT CARE**

OVARIAN CANCER TREATMENT

MAJOR CONTRIBUTION TO
IMPROVED RESULTS AND QUALITY OF LIFE

- **CYTOREDUCTIVE SURGERY**

- **Subspecialty physician training**
- **Extraperitoneal approach**
- **Upper abdomen debulking**
- **Automatic stapler devices(endogia)**
- **Low colorectal anastomosis**
- **New electro surgical device (biclamp, ultracsion, ligasure, gyrus, tissue link)**

2.5. Management of early disease

Early disease refers to disease confined to the ovaries. There are two clinical scenarios where early disease could be encountered:

- the first is where the gynaecologist is alerted to the possibility of malignancy being present prior to the laparotomy;
- the second is where the gynaecologist had no suspicion of cancer being present prior to surgery.

To minimise the risk of the gynaecologist encountering the second scenario, use should be made of the RMI scoring system if an isolated pelvic mass is discovered on preoperative imaging. In young women the possibility of a non-epithelial ovarian tumour being present should also be considered.

The surgical dilemma in early disease is how comprehensively to stage a case and in particular whether to assess retroperitoneal nodes and take random peritoneal biopsies. The presence of positive retroperitoneal nodes or peritoneal implants upstages the case to stage III.

Proponents of comprehensive staging argue that it is important to give accurate prognostic information to a patient and that choice of chemotherapy regimen might be influenced by knowledge of the stage of disease. Descriptive studies have reported that at least 15% of patients thought to have disease confined to the ovaries are found to have positive lymph nodes. The opponents of comprehensive staging argue that it cannot be recommended as routine practice due to the lack of RCT data demonstrating any survival benefit conferred to those who undergo full staging including retroperitoneal nodal assessment.

The publication of the ICON 1 and ACTION chemotherapy trials means that it is unlikely that future studies will be designed to answer the role of comprehensive staging in early disease.

In the ACTION chemotherapy trial one third of patients were optimally staged. Adjuvant chemotherapy in this group of patients was not associated with a statistically significant improvement in overall and disease-free survival. The validity of a subgroup analysis in this study is questionable given the small number of patients involved. When the data from the ACTION trial were combined with that from the ICON 1 trial (in which the majority of patients were not optimally staged) platinum-based adjuvant chemotherapy resulted in an 8% improvement in overall survival and an 11% improvement in disease-free survival.

The guideline development group suggest the following to ensure that cases of suspected stage I disease are thoroughly assessed:

- staging should be through a mid-line incision to allow palpation of all peritoneal surfaces;

- assessment of peritoneal cytology, hysterectomy, removal of ovaries and Fallopian tubes and infracolic omentectomy should be performed, capsular rupture during surgery should be avoided.

2.5.1. Fertility conserving surgery

In women who wish to conserve their fertility, adequate staging (excluding disease involving the liver, spleen, peritoneum, retroperitoneal nodes, appendix and diaphragm) is required and the risk of recurrent disease developing must be discussed.

No data from RCTs were found. One cohort study reported a 9% risk of recurrence (involvement of contralateral ovary or extraovarian disease) in women treated with fertility sparing surgery. In this study 56 women aged under 40 years with histologically confirmed ovarian cancer (Grades 1, 2 and 3, *see* underwent fertility sparing surgery which involved adequate staging (unilateral salpingo-oophorectomy, omentectomy, appendectomy, biopsies from peritoneal cavity and retroperitoneal lymph node sampling) The mean age of the women was 29 years and 32 had FIGO 1A disease, two had FIGO 1B disease and 22 FIGO 1C disease). Five women developed recurrence (9%) and in two of these women recurrence involved the residual ovary (3.6%). Metastatic endometrial cancer was found at a second look operation in one woman.

In another publication the risk of endometrial cancer being present (metastatic involvement or synchronous tumour) has been reported to be as high as 14%, particularly when the ovarian tumour is of endometriod or clear cell subtypes.

2.6. Optimal surgery for advanced disease

Advanced disease refers to cases where the disease has spread beyond the ovaries (FIGO stage Ic and above). Treatment for these cases involves surgery and chemotherapy. This section addresses the issue of surgery before the initiation of chemotherapy. Imaging with ultrasound prior to surgery can identify advanced disease. It is unclear whether additional imaging with computerised tomography is necessary with every case of advanced disease).

There are two surgical scenarios:

- aggressive surgical cytoreduction with the aim of leaving no residual disease
- optimal cytoreduction where residual tumour deposits are no more than 2 cm in diameter.

As complete resection of all tumour deposits (aggressive cytoreduction) is usually impossible in advanced disease, surgical treatment for the majority of these patients involves performing optimal cytoreductive surgery.

Three meta-analyses demonstrated a strong correlation between optimal cytoreduction and survival. None of the meta-analyses determined whether the improved survival and the feasibility of aggressive cytoreduction were related to intrinsic tumour biology.

One meta-analysis looked at the independent contribution of both cytoreductive surgery and platinum based chemotherapy on overall survival. Each 10% increase in maximal cytoreductive surgery was associated with a 4.1% increase in median survival time. Platinum-based chemotherapy produced an estimated 53% rise in median survival time. In this analysis patients were treated with non-platinum based therapy as well as platinum-based therapy hence the magnitude of benefit induced by chemotherapy is likely to be exaggerated. A subsequent meta-analysis has confirmed this. The question of specialty of surgeon has been addressed in a retrospective population-based review of 1,866 women treated in Scotland over five non-consecutive years. The review reports on 1,032 patients operated on by general gynaecologists, 351 by specialist gynaecologists and 216 by general surgeons.

The demographics of the three patient groups were different: those cared for by the general gynaecologists had an expected better prognosis after surgery than those operated on by the specialist gynaecologists and the group cared for by the general surgeons were the poorest prognostic group. An attempt was made to correct these differences by adjusting for patient age, histology, tumour differentiation, presence of ascites and socioeconomic status. The results were analysed for each FIGO stage and the endpoint for analysis was death by three years. Of those with stage III disease, those operated on by specialist gynaecologists had a 25% reduction in death compared to those operated on by general gynaecologists (P=0.005). Those operated on by general surgeons had the lowest survival rates. Similar trends were found in the other FIGO stages, but were not significant. These data are supported by a similar retrospective review of 12,316 patients in which patient survival was significantly better in the group operated on by specialist 'gynaecological oncologists' compared to 'obstetrician gynaecologists' and general surgeons.

Patients with stage IV disease are increasingly being treated with chemotherapy prior to surgery when there is no doubt that the primary tumour is ovarian. A multidisciplinary team should manage these cases.

TREATMENT OPTION IN ADVANCED OVARIAN CANCER

- **PRIMARY DEBULKING SURGERY + CT**
- **Suboptimal SURGERY + (NA)CT + IDS (with optimal intent) + CT**
- **NACT (after explorative LPS/LPTM) + RS**
- **CHEMOTHERAPY**

INFLUENCE OF TUMOR VOLUME BEFORE SURGERY AND CYTOREDUCTIVE OUTCOME ON SURVIVAL

Covariate	RR	95% CI	P value
Sum of rankings			
0-5	1.00		0.05
6-10	1.24	1.16-2.44	
≥ 11	1.44	1.34-3.08	
Cytoreductive outcome			
Absent RT	1.00		0.001
≤ 1 RT	2.32	1.20-5.37	
> 1 RT	2.98	1.74-5.23	

Complete cytoreduction has more significant influence on survival than the extent of the disease before surgery. Rankings of specific anatomic sites did not independently influence survival

Eisenkop et al, Gynecol Oncol 2003

FEASIBILITY OF OPTIMAL DEBULKING BY SURGEONS

SPECIALIZED IN GYNECOLOGIC ONCOLOGY

Author	No of Pts	Optimal debulking rate %
Piver 1986	50	76
Eisenkop 1998	163	98.8
Benedetti Panici 2002	255	91
TOT	368	88.6%

NOT SPECIALIZED IN GYNECOLOGIC ONCOLOGY

	Optimal debulking rate %
Gynecologists	40%

ADVANCED OVARIAN CANCER

Survival by treating physicians

	Gynecol oncol	Gynecol	General surgeon
Relative Risk of death	1	1.25	1.33

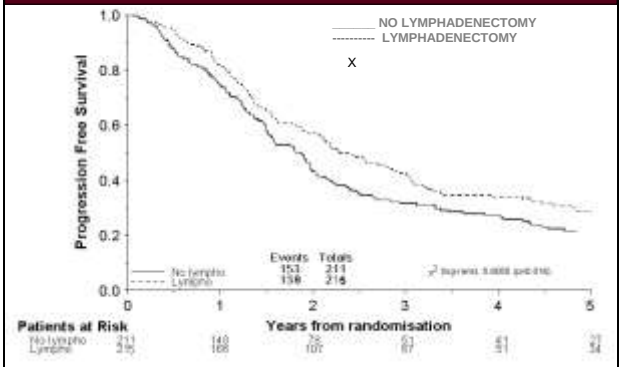
Junor EJ. 1999

SITES OF BOWEL RESECTION IN ADVANCED OVARIAN CANCER

AUTHORS	SMALL BOWEL (%)	COLON (A.T.D.)(%)	RECTOSIGMOID COLON (%)
Jaeger 2000	56/194 (28.9%)	75/194 (38.7%)	110/194 (56.7%)
Tamussino 2000	64/180 (36 %)	27/180 (15 %)	117/180 (65%)
Gliette-Cloven 2001	26/104 (25%)	47/104 (45%)	75/104 (72%)
Benedetti Panici 2005	38/429 (9%)	93/429 (21%)	167/429 (39 %)
Hoffman 2005	25/144 (18%)	36/144 (25 %)	81/144 (56%)
Cai 2007	9/97 (9.2%)	5/97 (5.1%)	38/97 (39%)
TOT	181/789 (22.9%)	203/789 (25.7%)	421/719 (58.5%)

REVIEW OF LITERATURE

ADVANCED OVARIAN CANCER- Lymphadenectomy trial PROGRESSION FREE SURVIVAL



Benedetti Panici et al JNCI 200

ASSOCIATED SURGICAL PROCEDURE Lymphadenectomy trial (n= 427)

PROCEDURES	LYMPHADENECTOMY NO (211) %	YES (216) %
Pelvic peritonectomy	75	67
Small bowel resection	6	3
Large bowel resection	39	39
Diaphragmatic nodule resection	30	23
Bulky nodes resection	42	28

Benedetti Panici et al JNCI 2005

Randomised trial of the EORTC-GCG and NCIC comparing primary debulking surgery with neoadjuvant chemotherapy in Stage IIIc-IV ovarian, fallopian tube and peritoneal cancer.

I Vergote, Oslo, JE Sardi, F Amant, Oslo, Vancouver, N Johnson, RHM Verheijen, MEL van der Burg, AJ Lacave, P Benedetti Panici, Leiden, A. Casado, C. Mendiola, C. Coens, S. Pecorelli, N. Reed

Stage IIIc-IV ovarian, fallopian tube and peritoneal cancer.

- Arm A: PDS + CT (6 course CDDP-TAXOL)
- Arm B: NACT (3 course CDDP-TAXOL) + IDS + CT (3 course CDDP-TAXOL)

718 patients were randomised
Median follow-up was 4.7 years

N Engl J Med 2010

ARTICLES

Systematic Aortic and Pelvic Lymphadenectomy Versus Resection of Bulky Nodes Only in Optimally Debulked Advanced Ovarian Cancer: A Randomized Clinical Trial

JNCI

Pierluigi Benedetti Panici, Angelo Maggioni, Neville Hacker, Fabio Landoni,

STUDY DESIGN

P.I.: P. BENEDETTI PANICI

FIGO STAGES IIIB, IIIC, IV (pleural)
≤ 1 cm INTRAPERITONEAL RESIDUAL TUMOR
≤ 75 yrs AGE

RANDOM

- SYSTEMATIC AORTIC AND PELVIC LYMPHADENECTOMY
- NO LYMPHADENECTOMY*

PLATINUM-BASED CHEMOTHERAPY

- *AORTIC NODES ≥ 15 PELVIC NODES ≥ 25
- *BULKY NODES RESECTION ONLY

FOLLOW-UP

JNCI 2005

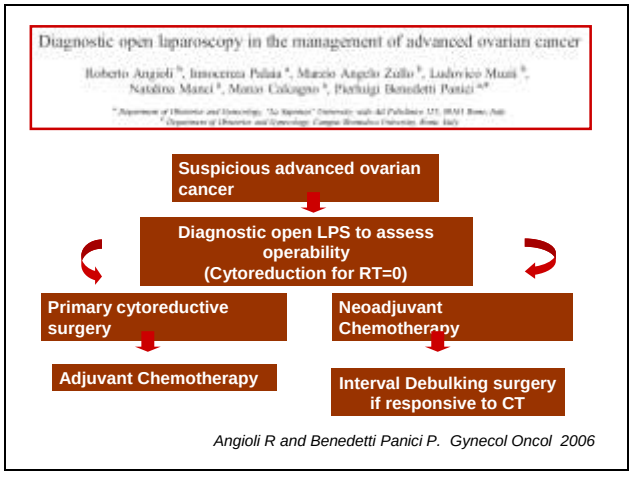
Randomised trial of the EORTC-GCG and NCIC comparing primary debulking surgery with neoadjuvant chemotherapy in Stage IIIc-IV ovarian, fallopian tube and peritoneal cancer.

	Arm A	Arm B	Hazard Ratio
Median overall survival (Intention to treat analysis)	29 month	30 month	(HR: 0.98; CI: 0.85-1.14),
Median PFS	11 month	11 month	(HR: 0.99; CI: 0.87-1.13).

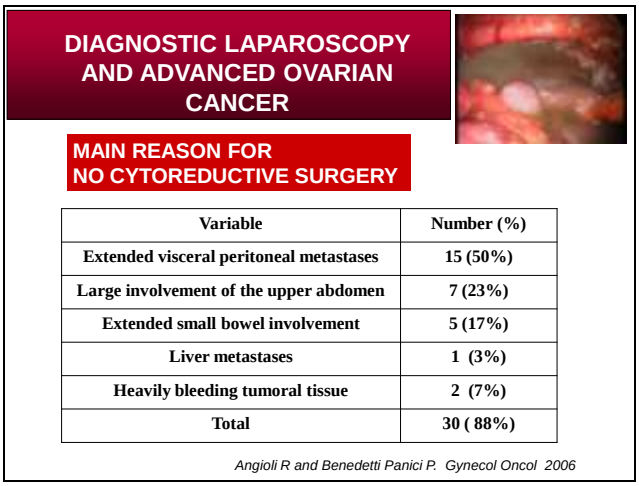
2.7. Interval debulking surgery

Interval debulking surgery (IDS) refers to surgery performed in women whose tumour mass has decreased following three courses of chemotherapy and who have previously been suboptimally cytoreduced.

The potential role for IDS has been examined in three RCTs, with two of these studies demonstrating different results. The first did not demonstrate a statistically significant improvement in survival in the group of women who underwent IDS, whilst the second reported an increase of six months median survival for those who had IDS. In the second study 127 women who had IDS were followed up. Following three courses of chemotherapy 83 of the women had tumours greater than 1cm. Of these 83, only 37 had tumours measuring less than 1cm left behind after IDS. It is not possible to identify the characteristics of the small group who responded to chemotherapy and who were left with a decreased tumour load after IDS. Preliminary results from the third RCT suggest that when the first operation is done by a gynaecological oncologist IDS is not recommended even if optimal cytoreduction was not achieved.

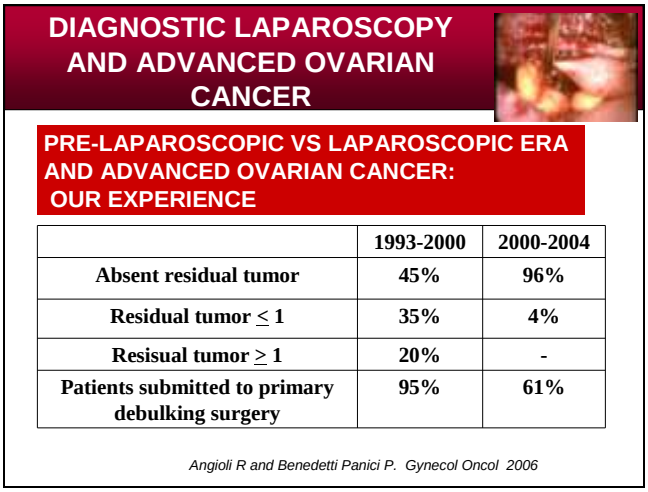


Angioli R and Benedetti Panici P. Gynecol Oncol 2006



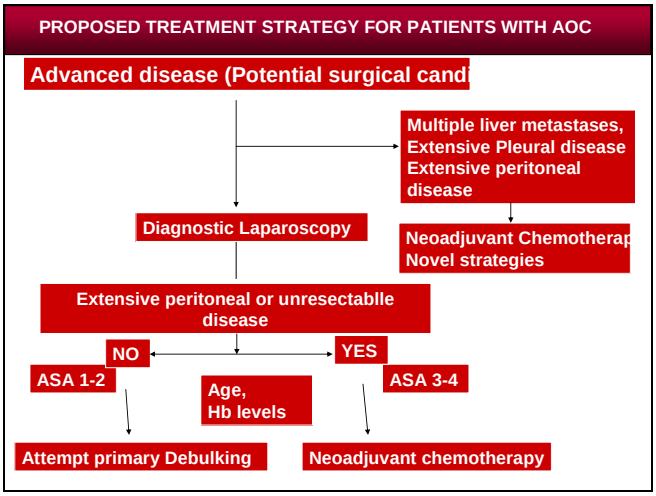
Variable	Number (%)
Extended visceral peritoneal metastases	15 (50%)
Large involvement of the upper abdomen	7 (23%)
Extended small bowel involvement	5 (17%)
Liver metastases	1 (3%)
Heavily bleeding tumoral tissue	2 (7%)
Total	30 (88%)

Angioli R and Benedetti Panici P. Gynecol Oncol 2006



	1993-2000	2000-2004
Absent residual tumor	45%	96%
Residual tumor ≤ 1	35%	4%
Resisual tumor ≥ 1	20%	-
Patients submitted to primary debulking surgery	95%	61%

Angioli R and Benedetti Panici P. Gynecol Oncol 2006



2.8.The future

It is expected that subsequent workshops will still wish to consider four specific areas:

1. Early diagnosis. The benefit of early diagnosis has been identified but the specific mechanism to do so remains subject to investigation. This will include consideration of the role of proteomics as well as molecular markers. There should also be an assessment of the role of diagnostic imaging including PET scanning in women with ovarian cancer.

2. First-line therapies. This will likely remain as a focus of interest over the next decade and require ongoing review. This should include a consideration of the role of optimal radiation therapy both in first-line and salvage therapy.

3. Maintenance/consolidation. The question will likely remain as to whether one should consider novel therapies in this regard and what should the valid end points be in this setting.

4. Post-recurrence/progression therapy. This area will undoubtedly remain as a major issue. The question should consider treatment selection (as relates to prediction of response and resistance), appropriate surgery, measures of symptom control/quality of life, survivorship, end points. The issue of whether there should be a standard protocol for women with progressive disease after first-line therapy merits consideration.

The final area to be addressed is the impact that this and earlier consensus workshops have had on current practice. Although this issue is important to understand, it is one that is very difficult to quantify. If the intent is to influence the standard of practice, then one could consider that the shifts in 5-year survival rates as documented by FIGO are markers of this impact. During the period from 1988–2003, the 5-year survival rate for women diagnosed with stage III ovarian cancer has increased from 22.9% to a high of 49.2% (range 28.9% to 49.2%) [1]. Although numerically modest, this is a significant gain at a global level. However, there are multiple confounding factors in this correlation that may consider the relationship only as coincidental. If the intent of the consensus process is to provide support to the effective conduct of clinical trials, then the impact may be evaluated by a record of successful completion of international phase III trials in the population of women with a diagnosis of ovarian cancer. This is more readily quantified as since the previous consensus conference, there have been at least four randomized clinical trials completed assessing the first-line treatment of women with a diagnosis of advanced ovarian cancer that include accrual from more than one national cooperative clinical trials group. In aggregate form, these trials and others have confirmed the role of a platinum compound with a taxane as standard therapy for women with ovarian cancer, recognized the option of single-agent carboplatin as a standard therapy and demonstrated the lack of benefit of an anthracycline

to the above-mentioned regimens [2–6]. This may be viewed as a marker of positive impact on the global consensus process. However, it is important that future consensus workshops have included a process of evaluation in order to effectively measure the impact of this process on the burden of ovarian cancer. Additionally, in considering the consensus process, it is apparent that the generation of new data so frequently presented in the setting of publications and/or meetings does not necessarily

lead to better information. Furthermore, it is even less often that better information promotes new knowledge or practices. As new data become available, they must be considered in the context of how this might be effectively adopted into practice. Future international consensus workshops on the treatment of women with ovarian cancer should consider the impact of previous workshops on the outcome of women affected by ovarian cancer. The relevant questions must be derived from a direct

correlation of the issues with the desired outcomes and an opportunity created for discussion and consensus.

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3. Cervical cancer: update

3.1. Incidence

Cervical cancer is the most common gynecologic cancer in women and ranks second among all malignancies for women, with only breast cancer occurring more commonly.

In 2001, the WHO estimated 471.000 new cases were identified globally and 233.000 deaths were recorded.

In general, higher incidences are found in developing countries, and these countries contribute 83% of reported cases annually, whereas economically advantaged countries add only 3.6 % of new cancers.

This incidence disparity highlights successes achieved by cervical cancer screening programs in which Papanicolaou (Pap) test are regularly obtained.

In 2006, the American Cancer Society estimated 9,710 new cases and 3,700 deaths from this malignancy. Within the United States, cervical cancer is the third most common gynecologic cancer and the sixth most common solid malignant neoplasm among women.

In the European Union the incidence is 13.2/100 000 and the mortality rate is 5.9/100000 women/year; in Italy are registered about 3700 new cases every years.

The age at which cervical cancer develops is in general earlier than that of other gynecologic malignancies, and the median age at diagnosis ranges from 40 to 59 years. In women aged 20 to 39 years, cervical cancer is the second leading cause of cancer deaths.

3.2. Risk factors

In addition to demographic risks, behavioral risks have also been linked with cervical malignancy. Most cervical cancers originate from cells infected with the human papillomavirus (HPV), which is sexually transmitted. Early coitarche, multiple sexual partners, and increased parity are associated with a substantially greater incidence of cervical cancer (see Table 1).

In addition, smokers are at greater risk, although the mechanism underlying this risk in not known. The greatest risk for cervical cancer is the lack of regular Pap-test screening. Most communities that have adopted such screening have documented decreased incidences of this cancer.

Tab. 1 Cervical Cancer Risk Factors

Older age	**2**
Residency in asia, africa, certain latin american	**2-6**
Lower level of education or income	**2-3**
Black, Hispanic, american indian	**2**
Multiparity	**2-4**
Early age at first sexual intercourse	**2-4**
Multiple sexual partners	**2-5**
Presence of HPV	**4-40**
Hx. STDs	**2-10**
Long-term smoking	**2-4**
Long-term use of OCPs	**1.5-2**
No prior regular pao smear screening	**2-6**
Diets low carotene, vitamin C	**2-3**

3.3. HPV infection

More than 100 HPV types have now been identified. Clinically, HPV types are classified as high-risk (HR) or low-risk (LR) (see Table 2).

The role of this virus in the genesis of essentially all cervical neoplasia and a significant portion of vulvar, vaginal, and anal neoplasia is firmly established. Human papillomavirus is a nonenveloped DNA virus with a protein capsid.

The most common HR HPV types (16, 18, 45, and 31) found in cervical cancer are also the most prevalent in the general population. Specifically, HPV 16 is the dominant cancer-related HPV, accounting for 40 to 70 percent of invasive squamous cell cervical cancers worldwide. This serotype is also the most

common HPV found among low-grade lesions and in women without neoplasia.

Like HPV 16, viral types 18, 45, and 56 are also highly oncogenic. The prevalence of HPV 18 is much lower than that of HPV 16 in the general population, but it is found in up to 25 percent of squamous cell carcinomas, and in an even higher proportion of cervical adenocarcinomas and adenosquamous carcinomas.

The presence of high-risk HPV is a marker for the risk of diagnosis of CIN 2,3+; only 1 in 10 to 1 in 30 HPV infections are associated with abnormal cervical cytology results, with an even smaller proportion associated with CIN 2,3+. Among women with negative cytology test results and a positive HPV test result, only 15%

will have abnormal cytology results within 5 years. However, high-risk HPV is necessary for the development and maintenance of CIN 3. Persistent high-risk HPV is a necessary but not sufficient condition for the development of almost all types of invasive cervical cancer. Conversely, the risk of cervical cancer in women who do not harbor oncogenic HPV is extremely low.

When HPV is present, smoking doubles the risk of progression to CIN 3. From a clinical perspective, it is important to distinguish which intraepithelial neoplastic lesions will progress to invasive cancer if left untreated. However, the diagnostic categories currently available have only modest predictive value, and that value decreases as the lesions become less severe.

The likelihood of progression to cancer is higher and the time to progression is shorter as the grade of dysplasia increases. Although expression of the presence of HPV as CIN can occur within months of viral acquisition , the time course from CIN 3 to invasive cancer averages between 8.1 years and 12.6 years. The slow pace of these changes in immunocompetent women means that accurate estimates of progression risk require long follow- up periods. Perhaps more relevant for clinical practice are estimates of regression to normal status. A review of the literature from 1950 to 1992 noted the likelihood of regression to be 60% for CIN 1 and 40% for CIN 2.

Infection with HPV is suspected by the appearance of clinical lesions and through the results of cytology, histology, and colposcopy, all of which are subjective and often inaccurate. Therefore, a definitive diagnosis can be made only by the direct detection of HPV DNA. This can be done histologically by in situ hybridization, by nucleic acid amplification via polymerase chain reaction (PCR), or by hybrid capture (HC) techniques. Currently, Hybrid Capture 2 is the most common technique in clinical use. It is a chemiluminescent test that uses a mixture of RNA probes for the detection of 13 oncogenic HPV types.

Clinical HPV testing by HC 2 can be carried out by collection of cervical cells using a small brush device or in conjunction with liquid-based cytology. Routine testing for HPV is not currently indicated outside of cervical cancer screening and triage or surveillance of abnormal cytologies. Human papillomavirus DNA positivity is much more prevalent in women aged 18–22 years (71%) versus those older than 29 years

Tab. 2 HPV Type

HPV Type	Cancer Risk
6,11,42-44	**Low to negligible**
16,18	**High risk Implicated in most cervical and other anogenital cancers**
31,33,35,39,45,51,53,55, 56,58,59,63,66,68	

3.4. Cervical cytology

Cervical cytology screening programs are associated with a reduction in the incidence of and mortality from invasive squamous cancer. Conventional cytology is reported to be 30–87% sensitive for dysplasia. A meta-analysis of conventional cervical cytology studies

suggested a sensitivity of 58% when used for population screening. Another meta-analysis comparing the performance of ThinPrep with conventional cytology screening methods found sensitivity rates, relative to histology, were 68% (conventional) and 76% (ThinPrep), and specificity rates were 79% (conventional) and 86% (ThinPrep).

Because the range of sensitivity (30–87%) is so broad, all abnormal cytology results must be evaluated, although the vast majority of results do not represent underlying CIN 2,3+. In the ASC-US LSIL Triage Study (ALTS), the quality control reviewer at the National Cancer Institute and the university-based cytopathologist at the study site agreed on an ASC result in 43% of 1,473 cases, on an LSIL result in 68% of 1,335 cases, and on an HSIL result in 47% of 433 cases.

3.5. Bethesda system

The 2001 Bethesda System terminology (see Table 3) is used to describe the categories of epithelial cell abnormalities, including atypical squamous cells (ASC), low-grade or high-grade squamous intraepithelial lesions (LSIL or HSIL), and glandular cell abnormalities, including atypical glandular cells (AGC) and adenocarcinoma in situ (AIS). Histology diagnoses of abnormalities are reported as cervical intraepithelial neoplasia (CIN) grades 1–3. Both LSIL and CIN 1 reflect the cytologic and pathologic effects of infection with HPV. Most of these lesions will never progress to cancer. However, as many as 28% of women with cytologic LSIL harbor CIN 2 or CIN 3, approximately two thirds of which is identified by colposcopy. CIN 3 and AIS are cervical cancer precursors. CIN 2 lesions are more heterogeneous, and their significance is less clear than that of CIN 3. CIN 2 is more likely to progress to CIN 3 and cancer than CIN 1. However, many CIN 2 lesions will regress without therapy.

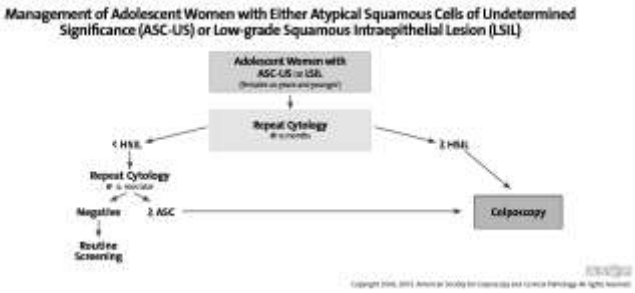
Tab. 3 Bethesda System Terminology

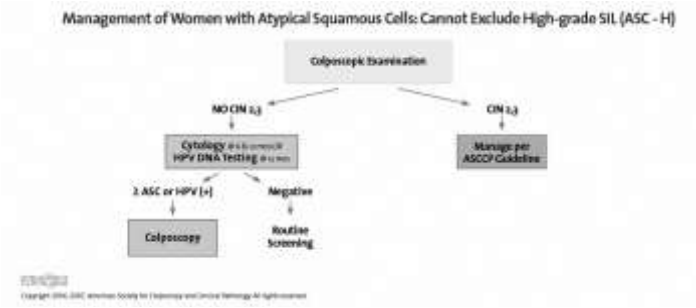
Squamous Cell
• Atypical squamous cell
— Of undetermined significance
— Cannot exclude high-grade squamous intraepithelial lesions
• Low-grade squamous intraepithelial lesions—encompassing human papillomavirus, mild dysplasia, and CIN 1
• High-grade squamous intraepithelial lesions—encompassing moderate and severe dysplasia, carcinoma in situ, CIN2, and CIN3
• Squamous cell carcinoma
Glandular Cell
• Atypical glandular cells (specify endocervical, endometrial, or not otherwise specified)
• Atypical glandular cells, favors neoplasia (specify endocervical or not otherwise specified)
• Endocervical adenocarcinoma in situ
• Adenocarcinoma

3.6. Colposcopy with and without directed biopsy

Colposcopy with directed biopsy has been the criterion of disease detection and remains the technique of choice for treatment decisions. Evaluation of colposcopy sensitivity has, until recently, focused on populations with identified lesions sufficient to produce abnormal cytology. Some recent studies have used colposcopy with endocervical curettage and blind four-quadrant ectocervical biopsies or loop electrosurgical excision procedure (LEEP) as the diagnostic criteria. This approach permits a more realistic evaluation of the sensitivity of colposcopy with directed biopsy. The presence of CIN 2,3+ was missed on directed biopsy but detected on the random

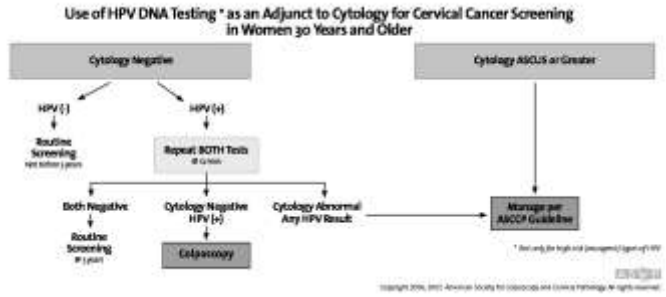
four-quadrant biopsies in 18.6–31.6% of CIN 2,3+ cases. Similar conclusions are reported in ALTS. Women with a previous LSIL or ASC-US HPV-positive test result and a CIN 1 biopsy were offered LEEP after 2 years of follow-up. Of the 189 women with CIN 2,3+ diagnosed during the 2-year study in the ”immediate colposcopy” arm of the trial, only 106 (56%) women received the diagnoses on the initial colposcopy. The other cases were identified after HSIL cytology, an exit colposcopy, or LEEP. Results of these studies indicate that biopsies of all visible lesions are warranted, regardless of colposcopy impression, and that follow-up should include multiple colposcopy examinations over time for those women with abnormal cytology or histology results who have persistent low-grade abnormalities or persistently test positive for HPV.

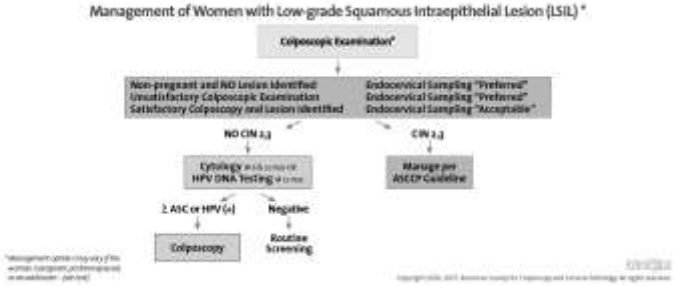


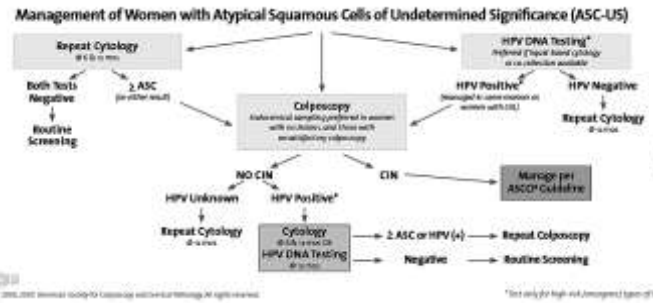


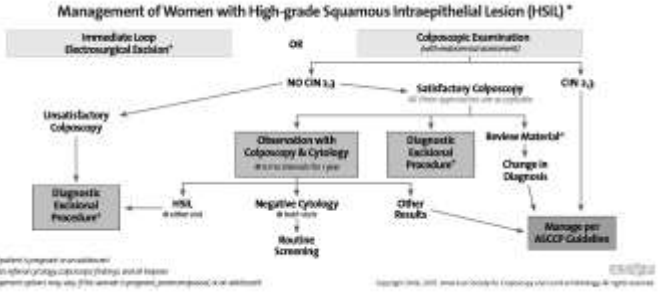
3.7. ACOG 2008 recommendations

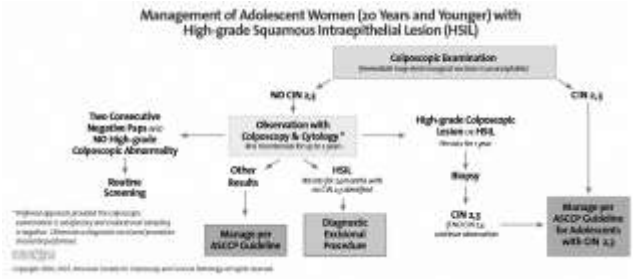
The best management approach is show in the follow algorithms:

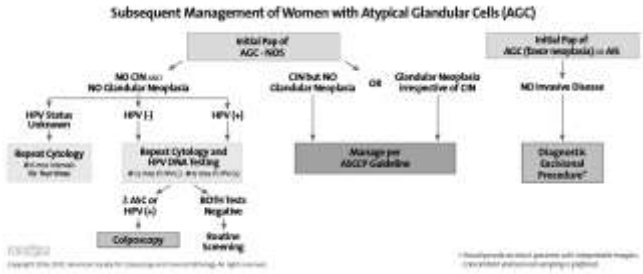












The recommended management of CIN 1 is follow-up without treatment for at least 2 years during which regression of many of the lesions is expected. After 2 years, the patient may be treated, but continued follow-up is acceptable. Treatment options include cryotherapy, laser ablation, laser conization, knife conisation (see Fig 1-2), and loop electrosurgical excision. Although studies in general have been small and may have difficulty in distinguishing subtle differences among treatments, various treatments appear to be similarly efficacious in eradicating preinvasive disease.

Selection of the appropriate treatment modality depends on the operator's experience, equipment availability, lesion size, and other factors. Alternatively, if the lesion extends onto the vagina, laser ablation may be more appropriate than other treatment because it can be tailored to encompass the entire lesion with excellent depth control. When microinvasive cancer or AIS is suspected, then conization provides a histology specimen for assessment. Ablative treatments (eg, cryotherapy or laser vaporization) should be used only after rigorously excluding invasive cancer. When endocervical assessment shows CIN, the colposcopy result is not satisfactory, cytology or colposcopy examination suggests cancer, or after prior therapy, cancer may be present but unseen and ablative therapy is not appropriate. Laser and loop electrosurgical excision minimize blood loss by thermal cautery during excision but may cause thermal artifact that impairs the interpretability of a specimen. This may be clinically significant at a focus of possible microinvasion or AIS. In these cases, knife conization may be preferable.

CIN 3 generally is considered to be a cancer precursor, although not all lesions will progress to cancer. The prevalence of CIN 3 peaks between ages 25 years and 30 years, and progression to cancer usually takes at least a decade longer The risk of progression of CIN 3 is unclear because most experts consider the risk too high to justify observation. A biopsy diagnosis of CIN 3 may miss occult invasive cancer and apparent progression after a colposcopy biopsy diagnosis may reflect missed prevalent cancer. One review found that the likelihood of CIN 3 progressing to invasion was 12%, with 33% of patients regressing and the remainder having stable disease. Smaller lesions with fewer colposcopy features are more likely to regress, whereas larger lesions with coarse vascular changes are less likely to regress. CIN 2-3 lesions associated with HPV 16 genotype are less likely to regress. The significance of CIN 2 is unclear. The risk of progression to CIN 3 and cancer appears greater for women with CIN 2 than for women with CIN 1. However, many women with CIN 2 will have regression of their lesions without therapy. In one review, CIN 2 progressed to cancer in 5% of patients and to

CIN 3 in 20% of patients, persisted in 40% of patients, and regressed in 40% of patients. No accepted tests are available to distinguish CIN 2 that reflects an exuberant HPV infection from that with true malignant potential. The cutoff between CIN 1 and CIN 2 and between CIN 2 and CIN 3 is arbitrary. Because of the moderate cancer risk associated with CIN 2, the decision among leaders in colposcopy and cervical cancer prevention in the United States has been to consider CIN 2 the threshold for treatment for most U.S. women.

However, there are exceptions. The risk of progression to invasive cancer is low before age 21 years, and some CIN 2-3 lesions regress, especially in younger women. For this reason, observation of adolescents and young women appears to be a safe and reasonable approach, provided cancer has been ruled out. When a histology diagnosis of CIN 2 is specified, observation is preferred. One study found unsuspected cancerous lesions in 8% of women undergoing hysterectomy for CIN 2-3, which suggests that prior conization is mandatory to exclude malignancy. For these reasons, hysterectomy is unacceptable as the primary therapy for CIN 2-3.

Although the overall incidence of AIS is increasing, it remains relatively rare compared with CIN 2-3. In 1991–1995, the overall incidence of squamous carcinoma in situ of the cervix among white women in the United States was 41.4 per 100,000, whereas the incidence of AIS was only 1.25 per 100,000. Because cytology screening and colposcopy detection of AIS are so challenging and the clinical behavior of AIS is so different from CIN 2,3, the principles involved in the management of AIS differ from what is the norm for squamous disease. The colposcopy changes associated

with AIS can be minimal or unfamiliar to most colposcopists. Adenocarcinoma in situ frequently is multifocal, may have "skip lesions," and frequently extends for a considerable distance into the endocervical canal, making complete excision difficult. Thus, negative margins on a diagnostic excisional specimen do not necessarily mean that the lesion has been completely excised.

Hysterectomy continues to be the treatment of choice for AIS in women who have completed childbearing. However, an excisional procedure is still curative in most of these patients. A comprehensive review of the published literature conducted in 2001 identified 16 studies that included a total of 296 women with AIS who were treated with a diagnostic excisional procedure. The overall failure rate was 8% . Margin status and endocervical sampling at the time of an excisional biopsy are clinically useful predictors of residual disease. Excisional biopsy is required in all women with AIS before making any subsequent management decisions. Conservative management is acceptable if future fertility is desired. If conservative management is planned and the margins of the specimen are involved or endocervical sampling obtained at the time of excision contains CIN or AIS, re-excision to increase the likelihood of complete excision is preferred. These women should be reevaluated at 6 months using a combination of cervical cytology, HPV DNA testing, and colposcopy with endocervical sampling. Long-term follow-up after treatment is recommended for all women with AIS.

Fig.1

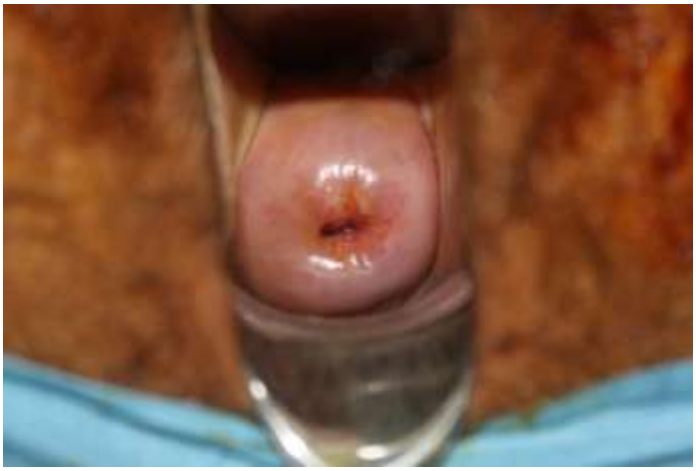


Fig 2

3.8. Cervical cancer presentation

Women may present asymptomatically when their disease is detected as a result of abnormal cervical cytology. In more advanced lesions, there are usually symptoms

raising the possibility of cervical cancer. These include post-coital bleeding, postmenopausal bleeding and offensive blood-stained vaginal discharge. If there is abnormal bleeding during pregnancy, then a cervical lesion needs to be excluded. In some women presenting with late disease, there may be backache, leg pain/oedema, haematuria, bowel changes, malaise and weight loss.

3.9. Staging

Staging should include gynecological examination under anaesthetic which should include a combined recto-vaginal assessment and biopsy of the suspicious area; CXR(chest X-ray) and IVU (intravenous urogram). Cystoscopy and Sigmoidoscopy should be considered. Other imaging as indicated and according to facilities available. These might include computerized axial tomography (CT) scan and Magnetic Resonance Imaging (MRI) scan. MRI is superior to CT scan for tumor extension assessment and MRI is equal to CT scan for nodal assessment. MRI should be preferred to CT scan and include pelvic and abdominal imaging. A thoracic CT scan may be included for metastasis assessment

Surgical pelvic and para-aortic nodal staging are optional and PET is under evaluation. The most widely used classification is FIGO, based on clinical examination (see Tab.4).

Tab 4 FIGO staging of cervical cancer

Stage I

Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded. The diagnosis of both Stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion.

- **Stage IA**: Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
- **Stage IA1**: Stage IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm diameter.
- **Stage IA2**: Stage IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
- **Stage IB**: Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA. All gross lesions even with superficial invasion are Stage IB cancers.
- **Stage IB1**: Stage IB1: Clinical lesions no greater than 4 cm in size.
- **Stage IB2**: Stage IB2: Clinical lesions greater than 4 cm in size.

Stage II

Stage II is carcinoma that extends beyond the cervix, but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.

- **Stage IIA**: No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina.
- **Stage IAB**: Obvious parametrial involvement, but not into the pelvic sidewall.

Stage III

Stage III is carcinoma that has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney are

Stage III cancers.

- **Stage IIIA**: No extension into the pelvic sidewall but involvement of the lower third of the vagina.
- **Stage IIIB**: Extension into the pelvic sidewall or hydronephrosis or non-functioning kidney.

Stage IV

Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

- **Stage IVA**: Spread of the tumour into adjacent pelvic organs.
- **Stage IVB**: Spread to distant organs.

3.10. Histologic types

3.10.1. Squamous Cell Carcinoma

The two most common histologic subtypes of cervical cancer are squamous cell and adenocarcinoma. Of these, squamous cell tumors predominate, comprise 85 percent of all cervical cancers, and arise from the ectocervix. Over the past 30 years, there has been a decrease in the incidence of squamous cell cancers and an increase in the incidence of cervical adenocarcinomas. These changes may be attributed to an improved method of screening for early squamous lesions of the cervix and an increase in the prevalence of HPV Evidence describing the prognosis of these two cell types is contradictory. For example, a randomized study of stage IB and IIA cervical cancer by Landoni and colleagues (1997) showed a statistically significant lower overall survival in those with adenocarcinoma compared with squamous cell carcinoma. However, the Gynecologic Oncology Group (GOG) in a subsequent study found that overall survival in women with stage IB squamous and adenocarcinomas of the cervix is similar (Look, 1996). Moreover, the 1998 International Federation of Obstetricians and Gynecologists (FIGO) annual report, which reported more than 10,000 squamous carcinomas and 1,138 adenocarcinomas, noted no difference in survival in stage I cancers. However, with advanced stage disease, evidence suggests that cervical adenocarcinomas (stage IIB to IVA) may portend a poorer overall survival risk compared with that of squamous cell carcinomas (Eifel, 1990; Lea, 2002).

3.10.2. Adenocarcinomas

Adenocarcinomas are a group of cervical cancers comprised of the subtypes. In contrast to squamous cell cervical carcinoma, adenocarcinomas comprise 10 to 15 percent of cervical cancers and arise from the endocervical mucus-producing glandular cells. Because of this origin within the endocervix, adenocarcinomas are often occult and may be advanced before becoming clinically evident. Adenocarcinomas exhibit a variety of histologic patterns composed of diverse cell types. Of these, mucinous endocervical adenocarcinomas are the most common. Endometrioid adenocarcinomas are the second most frequently identified and display glands resembling those of the endometrium. Minimal deviation adenocarcinoma is characterized by cytologically bland glands that are abnormal in size and shape. They contain an increased number of glands positioned at a deeper level than normal endocervical glands.

3.10.3. Mixed Cervical Carcinomas

These cervical malignancies are rare and histologically classified as adenosquamous, adenoid cystic, adenoid basal epithelioma, and glassy cell carcinoma. Adenosquamous carcinomas do not differ grossly from adenocarcinomas of the cervix. The squamous component is poorly differentiated and shows little keratinization. Glassy cell carcinoma describes a form of poorly differentiated adenocarcinoma in which cells display cytoplasm with a ground-glass appearance and a prominent nucleus with rounded nucleoli. Adenoid cystic carcinoma usually presents as a hard friable mass. Histologically this tumor resembles adenocarcinoma with

adenocystic differentiation. Lastly, of this rare group of mixed tumors, adenoid basal epitheliomas typically behave in a benign fashion. Histologically, these tumors are characterized by nests and cords of small oval cells with a peripheral palisading arrangement.

3.10.4. Neuroendocrine Tumors of the Cervix

These malignancies include large cell and small cell tumors of the cervix. Large cell neuroendocrine tumors are highly aggressive and even early stage cancers have a relatively low disease-free survival rate despite treatment with radical hysterectomy and adjuvant chemotherapy (Albores-Saavedra, 1997). In contrast, small cell neuroendocrine carcinoma contains a uniform population of small cells with a high nuclear:cytoplasm ratio and resemble small cell carcinoma of the lung. Uncommonly, endocrine and paraendocrine tumors are associated with these neuroendocrine tumors.

3.10.5. Other Malignant Tumors

Rarely, the cervix may be the site of sarcomas and malignant lymphomas. Most of these tumors present as a bleeding cervical mass. Initially, differentiation of cervical sarcomas from primary uterine sarcoma requires careful pathologic examination and localization of the tumor's primary bulk. Cervical leiomyosarcomas and cervical stromal sarcomas have a poor prognosis, similar to uterine. Because these tumors are rare, statements regarding treatment of cervical sarcomas are limited. Most cases are managed with multimodality treatment.

3.11. Treatment

3.11.1. FIGO stage IA1

Standard treatment consists of conization with free margins or simple hysterectomy (according to patient age) [III, B]. In the case of lympho-vascular space involvement, pelvic lymphadenectomy is recommended [III, B]. In patients with pelvic node involvement, standard treatment consists of complementary concomitant chemoradiation [I, B].

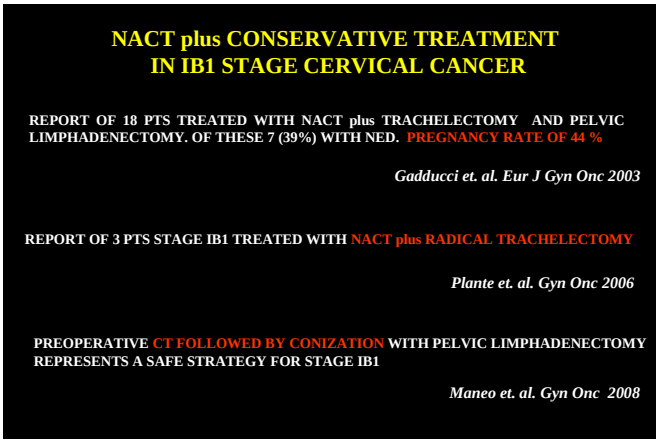
3.11.2. FIGO stage IA2

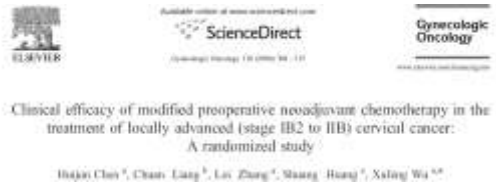
Surgery is the standard. Options consist of conization or trachelectomy in young patients and simple or radical hysterectomy in other patients [III, B]. Pelvic lymphadenectomy is required [III, B]. In patients with pelvic node involvement, standard treatment consists of complementary concomitant chemoradiation [I, B].

3.11.3. FIGO stage IB1

There is no standard treatment. Options consist of surgery, external irradiation plus brachytherapy or combined radiosurgery [III, B]. Standard surgery consists of radical hysterectomy, bilateral oophorectomy and pelvic lymphadenectomy.

Conservative surgery can be proposed for a tumor with excellent prognostic factors. Combined radio-surgery usually consists of preoperative brachytherapy followed 6–8 weeks later by surgery. In patients treated with upfront surgery or preoperative brachytherapy followed by surgery presenting pelvic node involvement, standard treatment consists of complementary concomitant chemoradiation [I, B].





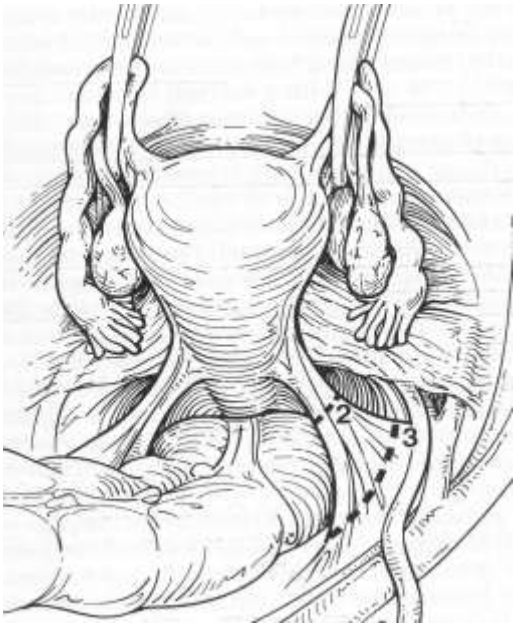
- NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADICAL SURGERY IS A VALID OPTION FOR LOCALLY ADVANCER CERVICAL CANCER
- IN ORDER TO ACHIEVE THE BEST RESULTS, THIS TREATMENT MODALITY NEEDS TO BE CARRIED OUT BY REFFERAL CENTERS AND BY A MULTIDISCIPLINARY TEAM
- SEVERAL QUESTIONS STILL REMAIN OPEN REGARDING THE BEST DRUGS AND THE BEST SURGICAL TECHNIQUE TO ADOPT
- ONGOING TRIALS ARE PRESENTLY COMPARING THE USE OF CT-RT vs NACT + SURGERY IN LOCALLY ADVANCED CERVICAL CANCER
- IN THE FUTURE, IT IS HOPEFUL THAT PROGNOSTIC FACTORS WILL AID PHYSICIANS TO BEST DIRECT THE OPTIMAL TREATMENT
- NACT MAY BE REDUCED THE INCIDENCE OF BULKY LYMPH NODE
- NACT FOLLOW BY ANTERIOR PELVECTOMY SHOULD BE CONSIDERED IN STAGE IV

➢ THE USE OF PREOPERATIVE NEOADJUVANT CHEMOTHERAPY (NAC) IN LOCALLY ADVANCED CERVICAL CANCER (LACC) WAS HINDERED BY THE DISADVANTAGES OF A DELAY OF CURATIVE TREATMENT FOR NONRESPONDERS AND THE DEVELOPMENT OF RADIORESISTANT CELLS.

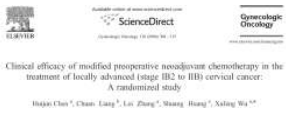
➢ HOWEVER, THESE DISADVANTAGES MAY BE OVERCOME BY A DQUICKT HIGH-DOSE SCHEME ADMINISTERED IN A SHORT PERIOD BEFORE SURGERY.

Chen Gynecol Oncol 2008

THE POINT OF TRANSECTION OF THE UTEROSACRAL AND CARDINAL LIGAMENTS IN CLASS II AND III RADICAL HYSTERECTOMY



QUICK SCHEME CHEMOTHERAPY



➢ **Cisplatin 100 mg/m2 intravenously (IV) given on Day 1, mitomycin C 4 mg/m2 intramuscular (IM) from Day 1 to Day 5, and 5-fluorouracil 24 mg/kg/day intravenously (IV) from Day 1 to Day 5.**

➢ **Two cycles of NAC were initially given at 14-day intervals.**

➢ **Only patients with good response received the third cycle.**

Chen Gynecol Oncol 2008

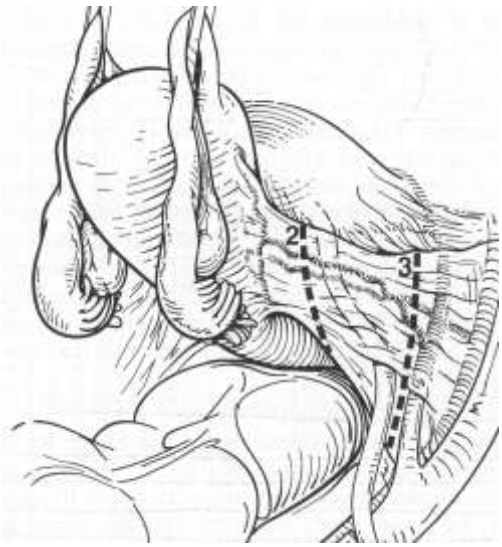
CHEMORADIATION IN LACC

CONSENSUS CONFERENCE ON CERVICAL CARCINOMA 1996

"THERE IS NO EVIDENCE THAT HYDROXYUREA OR ANY OTHER CONCOMITANT CHEMOTHERAPY AGENT SHOULD BE INCORPORATED INTO STANDARD PRACTICE"

NCI CLINICAL ANNOUNCEMENT 1999

"STRONG CONSIDERATION SHOULD BE GIVEN TO THE INCORPORATION OF CONCURRENT CISPLATIN BASED CHEMOTHERAPY IN WOMEN WHO REQUIRE RADIATION THERAPY FOR TREATMENT OF CERVICAL CANCER"



3.11.4. FIGO stage IB2–IVA

Concomitant chemoradiation represents the standard [I, A]. This modality is superior to radiotherapy alone for local control, metastasis rate, disease-free and overall survival, with an increase in toxic (gastrointestinal and haematological) side-effects [I, A]. Patients with advanced stage III and IVA may benefit less than patients with stage IB2–IIA/B. Platinum-based regimens for chemoradiation remain the standard. External irradiation is combined with brachytherapy and the total treatment duration should remain <55 days [III, B]. Complementary extrafascial hysterectomy

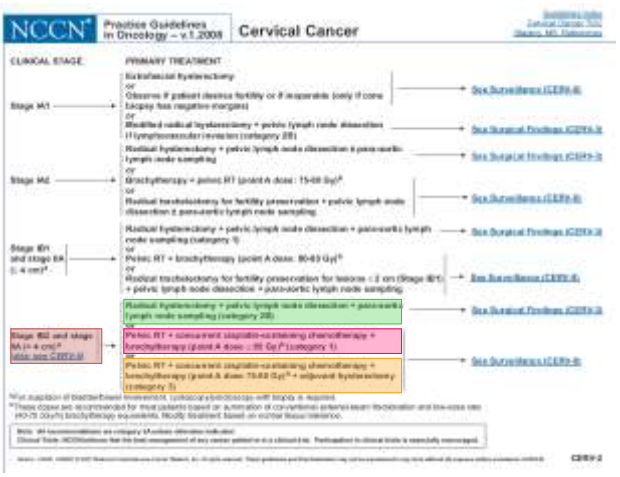
is an option. Neoadjuvant chemotherapy remains controversial and is currently under investigation by the EORTC (55994).

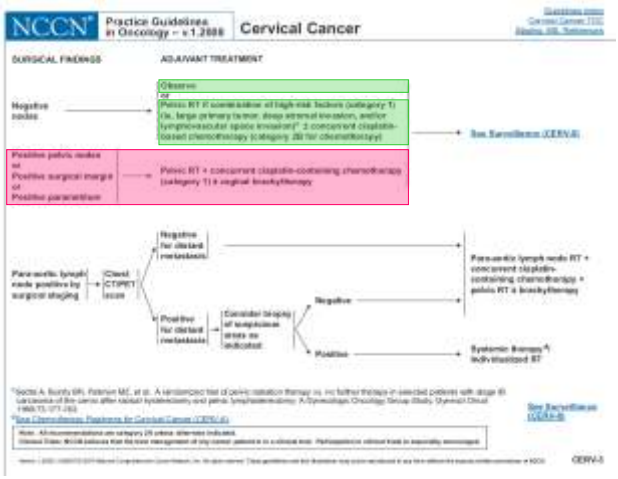
3.11.5. FIGO stage IVB

Platinum-based combination chemotherapy has potential benefit [III, B].

3.11.6. Locoregional and metastatic recurrence

For most patients palliative chemotherapy is the standard option. Pelvic surgery (exenteration in most cases) and radiotherapy are an option in selected cases.





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Annexes – Programmes of the training stage

Coopération tuniso-italienne
COURS DE FORMATION ET DE PROFONDEUR
"Le cancer cervical et le cancer du sein: prévention, diagnostic et traitement"

			MER 21	**JEU 22**	**VEN 23**	**SAM 24**
19-24 jan			**Arrivèe**	**Accueil et prèsentation du stage**	**Master « Breast surgery and breast reconstruction »**	**Master « Breast surgery and breast reconstruction »**
	LUN 26	**MAR 27**	**MER 28**	**JEU 29**	**VEN 30**	**SAM 31**
26-31 jan	**Radiologie: mammographie et repères chirurgicaux**	**Salle opératoire de la chirurgie plastique/du sein**	**Salle opératoire de la chirurgie plastique/du sein**	**Salle opératoire de la chirurgie plastique/du sein**	**FNA/ radiothérapie**	
	LUN 02	**MAR 03**	**MER 04**	**JEU 05**	**VEN 06**	**SAM 07**
02-07 feb	**Cours théorique et pratique: la chirurgie du sein oncoplastique (Siena)**	**Cours théorique et pratique: la chirurgie du sein oncoplastique (Siena)**	**5th international congress on controversies in senology (Siena)**	**5th international congress on controversies in senology (Siena)**	**5th international congress on controversies in senology (Siena)**	**De retour à Rome**
	LUN 09	**MAR 10**	**MER 11**	**JEU 12**	**VEN 13**	**SAM 14**
09-14 feb	**Consultations externes pour le cancer du sein**	**Matin : consultations externes** **Après-midi : présentation de cas cliniques de la salle opératoire**	**Salle opératoire oncologique pour le sein**	**Salle opératoire oncologique pour le sein**	**FNA**	
Dim 15	**LUN 16**					
Diner social	**Dèpart**					

Coopération tuniso-italienne
COURS DE FORMATION ET DE PROFONDEUR
"Le cancer de l'ovaire, du col de l'utérus et le cancer du sein: prévention, diagnostic et traitement"

	LUN	MAR	MER	JEU	VEN	SAM
I semaine	Matin: Consultation externes pour la prévention du cancer du col de l'utérus	Matin : Echographie préopératoire et l'enseignement de cas cliniques	Salle opératoire	Matin : Salle opératoire Après midi : Cours théorique et pratique de diagnostic de la pathologie de l'ovaire	Matin : Consultation externes Après midi : Présentation de cas cliniques du cancer de l'ovaire	
	LUN	**MAR**	**MER**	**JEU**	**VEN**	**SAM**
II semaine	Diagnostic de la pathologie de l'ovaire: L'écographie et la tomodensitométrie	Matin : consultation externes de la prévention du cancer du col de l'utérus : Colposcopie et biopsies Après midi : Cours théorique et pratique sur la prévention du cancer du col de l'utérus	Salle opératoire de la gynécologie oncologique	Matin : Salle opératoire de la gynécologie oncologique Après midi : Présentation de cas cliniques du cancer du col de l'utérus	Consultation externes de la prévention du cancer du col de l'utérus : pap-test + colposcopie	
	LUN	**MAR**	**MER**	**JEU**	**VEN**	**SAM**
III semaine	Matin: Salle opératoire Après midi : Pathologie : examen microscopique	Matin : Consultation externes de la prévention du cancer du col de l'utérus : pap-test + colposcopie Après midi : Enseignement sur le follow-up du cancer gynécologique	Matin : Salle opératoire de la gynécologie oncologique Après midi : Examen microscopique	Workshop sur la prévention et le traitement des cancers gynécologiques	Workshop sur la prévention et le traitement des cancers gynécologiques	Workshop sur la prévention et le traitement des cancers gynécologiques
	LUN	**MAR**	**MER**	**JEU**	**VEN**	**SAM**
IV semaine	Matin: Radiologie: mammotome et microbiopsies Après midi: Chirurgie du sein : consultation externes	Matin : Chirurgie du sein : consultation externes et présentation des cas cliniques de la salle opératoire Après midi : Enseignement sur le follow-up du cancer gynécologique	Matin : Radiologie : Microbiopsie + chirurgie du sein : salle opératoire Après midi : Pathologie : Examen microscopique	Matin : Day surgery – chirurgie du sein Après midi : Enseignement sur le traitement de la pathologie mammaire	Matin : Radiologie : Examen des cas cliniques Après midi : Chirurgie du sein : Consultation externes	

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"Cancer du col utérine et le cancer du sein: prévention, diagnostic et traitement"

	LUN 04	MAR 05	MER 06	JEU 07	VEN 08	SAM 09
04 - 10 oct	Matin: Visite au Ministère de la Santé h.13.00 lunch buffet h.14.30 Workshop. Après-midi: Visite à l'hôpital.	Workshop: "Locally Advanced Ovarian Cancer and Early Breast Cancer"	Workshop: "Locally Advanced Ovarian Cancer and Early Breast Cancer"	Matin: Salle opératoire Oncologique de la gynécologie Après-midi: Salle opératoire de la chirurgie plastique	Matin: cas cliniques + échographie gynécologique Après-midi: radiologie diagnostique	
	LUN 11	**MAR 12**	**MER 13**	**JEU 14**	**VEN 15**	**SAM 16**
11-17 oct	Radiologie: mammotome et micro-biopsies	Matin: Ambulatoire de sénologie et présentation de cas cliniques Après-midi: Présentation de cas cliniques + salle opératoire (chirurgie plastique)	Matin: Salle opératoire oncologique pour le sein/ échographie obstétricale Après-midi: Salle opératoire Oncologique de la gynécologie	Salle opératoire oncologique pour le sein en régime de "day surgery"/ Salle opératoire Oncologique de la gynécologie Après-midi: Salle opératoire de la chirurgie plastique	Radiologie diagnostique	