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Surgical shortcuts

Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis

Ghaem-Maghami, S. (Lancet Oncol 2007;8:985–93) undertook a meta-analysis of studies published between January 1, 1960 and January 31, 2007 that examined the risk of posttreatment disease (i.e., CIN of any grade or invasive cancer) in relation to completeness of excision. Studies were included if they described treatment of CIN by excision, numbers of women with involved margins, and prevalence of and numbers of women with posttreatment disease in relation to margin status. Criteria for posttreatment disease had to be stated as a defined abnormal cytology or histology. Studies were excluded if they described treatment of cervical glandular intraepithelial disease (CGIN), if all or nearly all women had reflex hysterectomy done soon after initial treatment, if women were immunosuppressed (e.g., if they were HIV-positive), or if no control group with disease-free margins was used. The endpoint of the analysis was the relative risk (RR) of posttreatment disease in those whose treatment histology suggested that excision was complete compared with those in whom excision was incomplete or uncertain. RR meta-analysis was done by use of a random effects model.

The initial Medline search identified 1,756 publications, from which 125 publications were short-listed. Sixty-five of these plus one unpublished study met our inclusion criteria; therefore, 66 studies were included in this meta-analysis. These studies described findings in 35,109 women of whom 8,091 (23%) had at least one margin of the excision biopsy involved with disease. After incomplete excision, RR of posttreatment disease of any grade was 5.47 (95% CI 4.37–6.83) and RR of high-grade disease (i.e., CIN 2 or 3, or high-grade squamous intraepithelial lesion) was 6.09 (3.87–9.60) compared with the reference group who had complete excision. High-grade posttreatment disease occurred in 597 of 3,335 (18%) women who had incomplete excision versus 318 of 12,493 (3%) women who had complete excision.

The authors conclude that incomplete excision of CIN exposes women to a substantial risk of high-grade posttreatment disease. Some of these women would be safer with a second treatment, especially if deep margins are involved, but most will need close follow-up for at least 10 years. Every effort should be made to avoid incomplete excision. Adding extensive ablation in the treatment crater to compensate for inadequate excision should be avoided because this might delay detection of inadequately treated invasive disease and because the effectiveness of additional ablation to destroy any residual CIN cannot be assessed. Furthermore, extensive ablation does not decrease any risk of preterm delivery in subsequent pregnancies.

Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial

Krag D.N. et al. (Lancet Oncol 2007;8:881–8) conducted the B-32 trial to establish whether sentinel-lymph-node (SLN) resection can achieve the same therapeutic goals as conventional ALND but with decreased side-effects, and they reported on the technical success and accuracy of SLN resection plus ALND versus SLN resection alone.

In the trial 5,611 women with invasive breast cancer were randomly assigned to receive either SLN resection followed by immediate conventional ALND (n=2807; group 1) or SLN resection without ALND if SLNs were negative on intraoperative cytology and histological examination (n=2804; group 2) in the B-32 trial. Patients in group 2 underwent ALND if no SLNs were identified or if one or more SLNs were positive on intraoperative cytology or subsequent histological examination. Primary endpoints, including survival, regional control, and morbidity, will be reported later. Secondary endpoints include accuracy and technical success and are reported here.

Data for technical success were available for 5,536 of 5,611 patients; 75 declined protocol treatment, had no SLNs removed, or had no SLN resection done. SLNs were successfully removed in 97.2% of patients (5,379 of 5,536) in both groups combined. Identification of a preincision hot spot was associated with greater SLN removal (98.9% [5,072 of 5,128]). Only 1.4% (189 of 13,171) of SLN specimens were outside of axillary levels I and II. Of all SLN specimens 65.1% (8,571 of 13,171) were both radioactive and blue; a small percentage was identified by

palpation only (3.9% [515 of 13,171]). The overall accuracy of SLN resection in patients in group 1 was 97.1% (2,544 of 2,619; 95% CI 96.4–97.7), with a false-negative rate of 9.8% (75 of 766; 95% CI 7.8–12.2). Differences in tumour location, type of biopsy, and number of SLNs removed significantly affected the false-negative rate. Allergic reactions related to blue dye occurred in 0.7% (37 of 5,588) of patients with data on toxic effects.

The authors reported excellent balance in clinical patient characteristics between the two randomised groups and that the success of SLN resection was high. These findings are important because the B-32 trial is the only trial of sufficient size to provide definitive information related to the primary outcome measures of survival and regional control. Removal of more than one SLN and avoidance of excisional biopsy are important variables in reducing the false-negative rate.

Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause

Rocca W.A. et al. (Neurology 2007;69:1074–83) studied the association of oophorectomy performed before the onset of menopause with the risk of subsequent cognitive impairment or dementia.

The authors included all women who underwent unilateral or bilateral oophorectomy before the onset of menopause for a noncancer indication while residing in Olmsted County, MN, from 1950 through 1987. Each member of the oophorectomy cohort was matched by age to a referent woman from the same population who had not undergone oophorectomy. In total, we studied 813 women with unilateral oophorectomy, 676 women with bilateral oophorectomy, and 1,472 referent women. Women were followed through death or end of study using either direct or proxy interviews.

Women who underwent either unilateral or bilateral oophorectomy before the onset of menopause had an increased risk of cognitive impairment or dementia compared to referent women (hazard ratio [HR] = 1.46; 95% CI 1.13–1.90; adjusted for education, type of interview, and history of depression). The risk increased with younger age at oophorectomy (test for linear trend; adjusted $p<0.0001$). These associations were similar regardless of the indication for the oophorectomy and for women who underwent unilateral or bilateral oophorectomy considered separately.

The authors conclude that both unilateral and bilateral oophorectomy preceding the onset of menopause are associated with an increased risk of cognitive impairment or dementia. The effect is age-dependent and suggests a critical age window for neuroprotection.

Hysterectomy and risk of stress-urinary-incontinence surgery: nationwide cohort study

Altman, D. et al. (Lancet 2007;370:1494–9) did a nationwide, population-based, cohort study from 1973 to 2003 in Sweden and selected 165,260 women who had undergone hysterectomy and a matched control group of 479,506 individuals who had not had this procedure.

During the 30-year observational period, the rate of stress-urinary-incontinence surgery per 100,000 person-years was 179 (95% CI 173–186) in the exposed cohort versus 76 (95% CI 73–79) in the unexposed cohort. Correspondingly, individuals in the exposed cohort were at increased risk for stress-urinary-incontinence surgery compared with those in the unexposed cohort (hazard ratio 2.4; 95% CI 2.3–2.5), irrespective of surgical technique. Risk for stress-urinary-incontinence surgery varied slightly with time of follow-up: the highest overall risk was recorded within 5 years of surgery (2.7; 95% CI 2.5–2.9) and the lowest risk was seen after an observation period of 10 years or more (2.1; 95% CI 1.9–2.2).

The authors conclude that hysterectomy for benign indications, irrespective of surgical technique, increases the risk for subsequent stress-urinary-incontinence surgery. Women should be counselled on associated risks related to hysterectomy, and other treatment options should be considered before surgery.

Human papillomavirus and Papanicolaou tests to screen for cervical cancer

Naucler, P. et al. (N Engl J Med 2007;357:1589–97) investigated whether screening for cervical cancer based on testing for human papillomavirus (HPV), although increasing the sensitivity of detection of high-grade (grade 2 or 3) cervical intraepithelial neoplasia, represents overdiagnosis or protection against future high-grade cervical epithelial neoplasia or cervical cancer.

In a population-based screening program in Sweden, 12,527 women 32–38 years of age were randomly assigned at a 1:1 ratio to have an HPV test plus a Papanicolaou (Pap) test (intervention group) or a Pap test alone (control group). Women with a positive HPV test and a normal Pap test result were offered a second HPV test at least 1 year later, and those who were found to be persistently infected with the same high-risk type of HPV were then offered colposcopy with cervical biopsy. A similar number of double-blinded Pap smears and colposcopies with biopsy were performed in randomly selected women in the control group. Comprehensive registry data were used to follow the women for a mean of 4.1 years. The relative rates of grade 2 or 3 cervical intraepithelial neoplasia or cancer detected at

enrollment and at subsequent screening examinations were calculated.

At enrollment, the proportion of women in the intervention group who were found to have lesions of grade 2 or 3 cervical intraepithelial neoplasia or cancer was 51% greater (95% CI 13–102) than the proportion of women in the control group who were found to have such lesions. At subsequent screening examinations, the proportion of women in the intervention group who were found to have grade 2 or 3 lesions or cancer was 42% less (95% CI 4–64) and the proportion with grade 3 lesions or cancer was 47% less (95% CI 2–71) than the proportions of control women who were found to have such lesions. Women with persistent HPV infection remained at high risk for grade 2 or 3 lesions or cancer after referral for colposcopy.

The authors conclude that the addition of an HPV test to the Pap test to screen women in their mid-30s for cervical cancer reduces the incidence of grade 2 or 3 cervical intraepithelial neoplasia or cancer detected by subsequent screening examinations.

Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer

Mayrand et al. (N Engl J Med. 2007;357:1579–88) investigated in a randomized trial whether testing for DNA of oncogenic human papillomaviruses (HPV) is superior to the Papanicolaou (Pap) test for cervical-cancer screening.

They compared HPV testing, using an assay approved by the Food and Drug Administration, with conventional Pap testing as a screening method to identify high-grade cervical intraepithelial neoplasia in women ages 30–69 years in Montreal and St. John's, Canada. Women with abnormal Pap test results or a positive HPV test (at least 1 pg of high-risk HPV DNA per milliliter) underwent colposcopy and biopsy, as did a random sample of women with negative tests. Sensitivity and specificity estimates were corrected for verification bias.

A total of 10,154 women were randomly assigned to testing. Both tests were performed on all women in a randomly assigned sequence at the same session. The sensitivity of HPV testing for cervical intraepithelial neoplasia of grade 2 or 3 was 94.6% (95% CI 84.2–100), whereas the sensitivity of Pap testing was 55.4% (95% CI 33.6–77.2; $P=0.01$). The specificity was 94.1% (95% CI 93.4–94.8) for HPV testing and 96.8% (95% CI 96.3–97.3; $P<0.001$) for Pap testing. Performance was unaffected by the sequence of the tests. The sensitivity of both tests used together was 100%, and the specificity was 92.5%. Triage procedures for Pap or HPV testing resulted in fewer referrals for colposcopy than did either test alone but were less sensitive. No adverse events were reported.

As compared with Pap testing, HPV testing has greater sensitivity for the detection of cervical intraepithelial neoplasia.