Journal Reviews

Clinical Breast Cancer

Intraglandular technique for breast tumours located in upper outer quadrant

The aim of any breast cancer surgery is to remove the tumour with safe surgical margins and preserve the natural contour of the breast. In the current practice, tumours ≤5cm in size (T1 and T2) are candidates for breast conserving surgery (BCS). However, traditional BCS techniques may not adequately meet the goals of breast cosmesis at all times. Therefore, in such situations, breast oncoplastic surgery (OPS) can be a useful alternative. The goals of OPS warrants similar oncological outcomes compared to BCS and better cosmetic results. To achieve good cosmetic outcome in patients with medium and small size breasts that do not require reduction mammoplasty, expanding the breast parenchyma with volume replacement technique such as an intraglandular flap to cover the area of defect can be a suitable option. This paper describes a local experience of using of such a flap to cover breast defects following excision of T1 and T2 breast tumours from the upper outer quadrant in a 47-patient series. The mean tumour size reported was 2.53 ± 0.8 cm. The volume of resected specimen recorded was 185 ± 29 cm^3. The mean distance from the tumour to the nearest surgical margin was 1.65 ± 0.4cm. A complication rate of 4% was recorded for fat necrosis and 4.2% for hematoma, other complications like seroma, glandular and flap necrosis were not observed. The authors conclude that using intraglandular technique with racket incision for T1 and T2 outer quadrant tumours in small and medium size breast is an easy and safe technique in terms of oncological outcomes and complications. Furthermore, with this technique, breast cosmetic results from the patients were superior in terms NAC displacement and wide tissue defects.

Reviewer's opinion: This paper highlights the use of an intraglandular flap, mobilized within the same breast to cover defects occurring as a result of outer quadrant tumour excisions in small and medium size breast. This is a short patient series that shares the local experience of using the technique, complications rates and oncological outcomes associated with it. The paper also evaluates the relation between breast density and complications with the technique and concludes higher chances of glandular necrosis with fatty breasts, wide skin flaps and wide mobilization method. However, this technique has oncological safety, low rates of fat necrosis rates and seroma complications with a shorter learning period. In conclusion, this is an interesting series which provides readers an opportunity to familiarise themselves with a new technique of breast mobilization OPS for small and medium size breasts. – TH

Intraglandular flap technique for tumors located in the upper outer quadrant of the breast.
Dogan L, Gulcelik MA, Karaman N, Camlibel M, Serdar GK, Ozaslan C.
CLINICAL BREAST CANCER
2012;Jun;12(3):194-8.

Unanswered questions about the role of ALNC with positive sentinel lymph node metastasis

Axillary lymph node status in breast cancer patients helps in disease staging and is a powerful independent predictor of survival and disease recurrence. Historically axillary lymph node clearance (ALNC) was carried out to obtain axillary status; however, with the widespread use of breast screening, number of patients with negative axillary nodes has increased. Therefore, to spare patients from ALNC morbidity without losing the prognostic information, sentinel lymph node biopsy (SLNB) was introduced as an alternative. SLNB, from its selective sampling of the first draining lymph node(s) for purposes of staging, allows clinicians to offer clearance with further surgery or axillary radiotherapy in presence of macro-metastasis (≥ 2mm tumour deposit). However, with the recently published results of the ACSOG Z0011 trial showing no 5-year overall survival (OS) (ALNC vs SLNB; 91.8% vs 92.5%) or disease free survival (DFS) (82.2% vs 83.9%) benefits in 891 women with T1-T2 invasive breast cancer having 1 or 2 positive sentinel lymph nodes randomised to ALNC or only SLN biopsy. Questions have been raised about the need for further surgery or radiotherapy of the axilla in these patient groups. Findings of the loco-regional failure (LRR) rate in the Z-0011, when compared with the NSABP-04 study, however, showed a marked variation (NSABP-04 vs Z-0011; 19% vs 0.9%). This discrepancy with respect to the LRR between the 2 trials can be explained by the pertinent differences between the 2 patient groups in terms of their receptor status, tumour size, operative procedures carried out, systemic therapies and follow-up duration. Nevertheless, comparing Z-0011 with NSABP-04 highlights some important facts such as the need for a longer follow up data from Z-0011 patients, clarity on the role of axillary status to decide adjuvant systemic therapy and the role of radiation technique employed for the whole breast radiation in sanitising the axilla inadvertently. Answers to these questions and similar results of the OS, DFS and LRR rates from future trials will ease clinicians' concerns in adopting minimally invasive axillary techniques alone as the routine standard of care for the early breast tumours.

Reviewer's opinion: This is a good review paper presenting some important points by comparing the differences in the LRR failure rates of the Z-0011 and NSABP-04 trials. Since the results of the Z-0011 have been published, clinicians on either side of the Atlantic seem to be divided on the role of ALNC in women with positive SLNB. This paper compares the findings of high rate of LRR in the NSABP-04 to low rates seen in the Z-0011 trial. Authors raised several important points, such as longer follow-up period, no systemic therapy, larger tumour size, more triple negative patients, higher rate of mastectomies and aggressive axillary management for the patients in the NSABP trial, which could be the reasons behind such discrepancies. Furthermore, authors also highlighted an important point that those patients with multiple sentinel node metastasis or with lymphovascular and pericapsular invasion and triple negative breast cancer should be considered for a complete ALNC, based on the unanswered questions on the method of radiation delivery, possibility of administration of Herceptin therapy and pending a long-term follow up data from the Z-0011 trial. – TH

Unanswered questions about the role of axillary dissection in women with invasive breast cancer and sentinel node metastasis.
Murthy V, Ballehaninna UK, Chamberlain RS.
CLINICAL BREAST CANCER
2012;Oct;12(5):305-7.

Outcome of Ipsilateral Breast Tumour Recurrence following Accelerated Partial Breast Irradiation in Early-Stage Breast Cancers

Accelerated partial breast radiation (APBI) is a technique that delivers biologically equivalent radiation doses to conventional radiotherapy treatment but to a limited radiation target (tissue that surrounds the surgical cavity), with a variable margin. Furthermore, treatment times with APBI are reduced to 1 week or less in contrast to the conventional breast adjuvant radiation therapy treatment times of 6 to 7 weeks. Limited data is available on outcomes after ipsilateral breast tumour recurrence in patients treated with APBI. In this study, a total of 534 patients with early-stage breast cancer treated with APBI were analysed for clinical outcomes, such as ipsilateral breast tumour recurrence (IBTR), regional recurrence, DFS, cause-specific survival and OS at the end of 5-year follow up. Eighteen (3.3%) patients developed IBTR; 14 (77.8%) recurrences were thought to represent new primary cancers. Thirteen (72.2%) patients were managed with salvage mastectomy and 4 (22.2%) with second attempt at breast conserving surgery (BCS). The 5-year rates of DFS, cause-specific survival and OS after salvage mastectomy for IBTR were 81, 100 and 100%, respectively. In the 4 patients who had second attempt at BCS, no IBTR, axillary failure, regional recurrence, or distant metastases were noted at 5 years. In conclusion, the IBTRs following APBI were comparable with those observed after whole-breast radiation with excellent clinical outcomes.

Reviewer's opinion: This is a good case series of 534 early-stage breast cancer patients treated with APBI with 5-year follow-up data. Evidence from prospective RCTs on the usefulness of APBI in early stage breast cancer vs whole breast radiation (WBI) is lacking. Currently, the NSABP B-39/RTOG 0413 phase III trial is recruiting patients with invasive and non-invasive breast cancers to randomise them to receive APBI or WBI. Until the results from the RCT are available, evidence on the usefulness of APBI to achieve loco-regional control, DFS and OS can be obtained from case series studies, such as above. However, as the author points out, one of the limitations of this study, despite large numbers of patients, is that the numbers of failures were relatively small, limiting the analysis. Data from a longer follow-up period will be required to fully assess the loco-regional failure rates with APBI therapy. – TH

Outcome after ipsilateral breast tumour recurrence in patients with early-stage breast cancer treated with accelerated partial breast irradiation.
Shah C, Wilkinson JB, Jawad M, Wobb J, Berry S, Mitchell C, Wallace M, Vicini FA.
Clin Breast Cancer.
2012;Dec; 12(6):392-7.

Clinical Oncology

Randomised controlled trial to evaluate role and optimal fractionation schedule of radiotherapy following breast conserving surgery

Radiation treatment (whole breast, tumour bed boost, chest wall and supraclavicular fossa [SCF]) as adjuvant therapy is standard practice following breast conserving surgery and after mastectomy (post-mastectomy radiotherapy) in selected patients. It helps to prevent local regional recurrence and improves overall survival. In this randomised controlled study, patients with stage I and II breast cancers were randomised to receive radiotherapy or no radiotherapy treatment following breast conserving surgery. Those receiving radiotherapy were further randomised to long (50 Gy in 25 daily fractions over 5 weeks) and short course (40 Gy in 15 daily fractions over 3 weeks) regimens. The main end-point was to study time to first loco-regional relapse. The study included 707 women recruited between 1985 and 1992, of which 68% were post-menopausal with a median tumour size of 2cm. Findings after 16.9 years of median follow-up showed 271 patients had relapsed, 110 in the radiotherapy group and 161 in the no radiotherapy group. The site of first relapse was locoregional in 68% and distant relapse in 36%. There was an estimated 24% reduction in the risk of any competing event (local and distant relapse and death) with radiotherapy (HR-0.76; 95% CI: 0.65-0.88; $p<0.001$) across all prognostic groups. No difference was seen between either radiotherapy fractionation schedules. The study confirmed better locoregional control and improved survival with radiotherapy treatment. Furthermore, 40 Gy fractionation schedule was an efficient and effective regimen compared to the International Convention regimen of 50Gy in 25 daily fractions.

Reviewer's Opinion: This study reinforces the message that radiotherapy is an essential component in breast cancer treatment, highlighting the clinical effectiveness (loco-regional control) and survival benefits with radiotherapy treatment following breast conserving surgery. Similar studies had shown higher rates of loco-regional recurrences across all breast cancer subgroups not receiving immediate radiotherapy compared to surgery alone in both node positive and node negative disease. However, as a focally targeted local therapy within specific breast cancer subgroups is yet to be established, immediate postoperative treatment should be offered routinely to all patients following breast conserving surgery. This study also highlighted the effectiveness of using short course regimen rather than long course to achieve similar results for loco-regional and distant relapses at the end of 5 and 17 years. – TH

Spooner D, Stocken DD, Jordan S, Bathers S, Dunn JA, Jevons C, Dodson L, Morrison JM, Oates GD, Grieve RJ.
A Randomised Controlled Trial to Evaluate both the Role and the Optimal Fractionation of Radiotherapy in the Conservative Management of Early Breast Cancer.
CLINICAL ONCOLOGY
2012;24(10):697-706.

Clinical Colorectal Cancer

Preoperative Radiation Therapy for Upper Rectal Cancer T3,4/Nx: Selectivity Essential

This readable and balanced review from the University of Arizona sheds light on a grey area surrounding neoadjuvant treatment of rectal cancer – is preoperative radiotherapy of value in locally advanced tumours above the peritoneal reflection? A brief recap of the major trial data from the Swedish Rectal Cancer Trial, the Dutch TME trial, the smaller German Rectal Cancer Study Group and the CR07 trial summarises what is already known: preoperative radiotherapy halves the local recurrence (LR) rate following subsequent surgery and has substantially lower acute and chronic toxicity than selective postoperative radiotherapy. However, whilst the data is robust for lower- and middle-third tumours, the picture is much less clear with upper-third tumours. This is partly due to less accurate staging. The German study relied on endorectal ultrasound (ERUS), technically difficult in upper-third tumours, which comprised as a result only 15% of patients in the study. Although 27% of patients in the Swedish and 30% of patients in the Dutch trial had upper-third tumours, neither study was designed or powered to look at local recurrence following preoperative RT for T3/4 upper-third lesions, and neither study showed any benefit in this group of patients. MRI is indisputably the gold standard for preoperative T staging, as confirmed by the 2006 Mercury trial; but, in common with CT and ERUS, it is a poor predictor of N stage. Guillem in 2008 reported 188 patients who underwent preoperative combined modality therapy followed by surgery for T3N0 disease; 22% had involved lymph nodes, suggesting substantial understaging.

A second problem lies in the importance of the circumferential resection margin (CRM). For low rectal cancers, a positive CRM is associated with a 10-fold increase in LR and the same probably holds true for posterior (i.e. non-peritonealised) tumours above the peritoneal reflection. Although the incidence of LR becomes progressively lower from lower- to middle- to upper-third it retains its relation to a positive CRM (Bernstein, Br J Surg 2009). As the authors point out, however, a transmural tumour may be T3 below the reflection, but T4 if anterior and above it. In peritonealised tumours, it is not possible to achieve a more radical resection and the benefits of preoperative RT are doubtful. There is no discussion in this paper of the potential morbidity of RT in peritonealised tumours, particularly collateral small bowel damage. However, since the morbidity of postoperative RT is likely to be substantially worse, it is difficult to disagree with the authors' view that preoperative RT in upper-third tumours should be individualised to patients with bulky nodes or tumour adherent to the pelvic side wall. – JRN

Preoperative Radiation Therapy for Upper Rectal Cancer T3,4/Nx: Selectivity Essential.
Popek S, Tsikitis V, Hazard L, Cohen A.
CLINICAL COLORECTAL CANCER
2012;11(2):88-92.

Clinical Decision Aids in Colon Cancer: A Comparison of Two Predictive Nomograms

This interesting study from Dublin employed 2 nomograms, both available online, designed to predict outcome and risk of recurrence following surgery for early rectal cancer. The first, "Adjuvant!", uses clinical parameters to predict the risk of relapse and the possible benefit of adjuvant therapy in reducing this risk. It also considers the reduction in impact of adjuvant therapy due to non-tumour related comorbidities and their resultant "natural" mortality. This is expressed as an additional biological age of +10, +20 or +30 years, giving a more realistic estimate than chronological age alone. The second nomogram, from the Memorial Sloane Kettering Cancer Centre, is based on their patient database and uses tumour site, preoperative CEA assay, lymphovascular and perineural invasion to predict risk of recurrence. Predicted five-year survival rates and risk of relapse were calculated in a cohort of 205 patients who underwent curative surgery without neoadjuvant treatment, with no known metastatic or residual disease. The authors immediately hit a problem in that 71 patients did not have a preoperative CEA level, a pattern I suspect would be widely replicated throughout the UK. Of the remaining 134

patients, 64 were alive with no recurrence at a median follow-up of just under five years. Sixty-five patients had died (35 of recurrent disease) and five patients were alive with recurrence. As a result of clever (and, to this reviewer, frankly incomprehensible) statistical analysis of the predicted and actual survival curves, the authors concluded that there was good correlation between the predicted and true recurrence rates. In addition, there was a statistically higher disease free five-year survival in patients who received adjuvant chemotherapy (65% vs 47%, p=0.046), which should give encouragement, if any is needed, to medical oncologists everywhere. – JRN

Clinical Decision Aids in Colon Cancer: A Comparison of Two Predictive Nomograms.
Collins I, Kelleher F, Stuart C, Collins M, Kennedy J.
CLINICAL COLORECTAL CANCER
2012;11(2):138-42.

International Journal of Cancer

The use of TRAIL death receptor DR5 DNA vaccination to induce apoptotic cell death in triple negative breast cancer

Apoptosis through extrinsic pathway is mediated via ligand binding of death receptors. Of the five known TRAIL (TNF-related apoptosis-inducing ligand) receptors, death receptor 4(DR4) and death receptor 5 (DR5) are agonist receptors that transmit death signals. In humans, DR4 and DR5 are expressed in both solid tumours and hematological malignancies. In contrast, in mice, only the DR5 receptor is identified. Triple negative breast cancer (TNBC or basal-like sub-type) does not express ER, PR and HER2 receptors and hence cannot be treated with hormone or molecular based therapies. However, TNBCs appear sensitive to extrinsic apoptosis. In this paper, an experimental study is described in which BALB/c and severe combined immune-deficient (SCID) mice aged six to eight weeks were electrovaccinated with DR5 DNA to raise DR5 specific antibodies and T cells. The immune serum thereafter was applied at dilutions of 0.5-2% in vitro to TNBC cells which were also TRAIL sensitive. The findings showed apoptotic cell death induced by anti-DR5 antibody evidenced by cleavage of PARP and caspase-3 in vitro, and blocked tumour growth of SUM159 TNBC cells in SCID mice. The findings support DR5 as a promising vaccine target controlling TNBC and other DR-5 positive tumours.

Reviewer's opinion: This is an interesting translational study that highlights use of DR-5 receptor agonists as that induce tumour apoptosis. Using modified TRAIL isoforms that bind specifically to DR4 and DR5, apoptotic signalling through DR5 is superior to DR4, thereby making it the preferred target for solid tumour treatment. As TNBCs show a rich expression of DR5 receptors, induction of pro-apoptotic antibody which is DR5 receptor agonist can therefore be advantageous in treating these cancers. Furthermore, as the anti-tumour effects of the DR5 agonist can be enhanced in presence of chemotherapeutic agents, future studies can focus on the synergy between DR5 vaccine and conventional therapies to broaden the scope of patients that may benefitted with the combination treatment. – TH

Induction of proapoptotic antibodies to triple-negative breast cancer by vaccination with TRAIL death receptor DR5 DNA.
Piechocki MP, Wu GS, Jones RF, Jacob JB, Gibson H, Ethier SP, Abrams J, Yagita H, Venuprasad K, Wei WZ.
INTERNATIONAL JOURNAL OF CANCER
2012;Dec 1;131(11):2562-72.

Neuro-Oncology

Population effects of temozolomide

The Stupp regime, consisting of concomitant radiotherapy and temozolomide (TMZ) is the current 'gold standard' therapy for glioblastoma with median overall survival in this study of 14.6 months. However, patients may have better outcomes in RCT's due to their strict entrance criteria and patient selection. In this Norwegian study, the authors report the effect of the introduction of TMZ on survival. 1157 patients with GBM were identified. Median OS was 8.3 months pre-'Stupp' and 10.1 months post-TMZ introduction (P<0.001), in keeping with available RCT outcomes. Both groups showed a very poor OS when no treatment was given (2.8m vs 2.1m P=0.08). Men and younger patients were offered more advanced therapy, and those receiving TMZ were given higher radiation doses. However, age was not a factor in TMZ effect or radiotherapy dose. Median OS for the control, radiotherapy alone and concomitant groups were 2.5, 9 and 16.2 months, respectively.

Reviewer's opinion: This study highlights outcomes following treatment with the Stupp regime. It is reassuring that the findings of this population study are in keeping with the published RCTs, which is further evidence that this regime should remain the gold standard. – SB

A population based study on the effect of temozolomide in the treatment of glioblastoma multiforme.
Ronning P, Helseth E, Meling T, Johannsen TB.
NEURO-ONCOLOGY
2012;14(9):1178-84.

Glioma associated microglia/macrophages

Microglia are important for immune surveillance in the CNS; however, their role in the tumour environment remains unclear. Tumour associated microglia may aid tumour growth and progression, and are an emerging target for novel glioma therapies. CD38, an enzyme and cell surface receptor, has a role in microglial activation and may be a potential target. In this study, the authors used a syngeneic model, implanting GL261 glioma cells into the brains of both wild type (WT) and CD38-deficient mice (CD38-). T1-weighted MRI at 21 days post-injection showed significantly reduced tumour volume in the CD38- group compared to WT (p=0.001). Furthermore, analysis of mouse survival showed that CD38- group was more favourable (OS 30.5 vs 27 days, P=0.0003). Tumour sections stained for GFAP (astrocyte marker), CD3, CD4 (T cell markers), CD11b and Iba-1 (microglial markers) had similar staining patterns within both groups. However, there was a lower density of staining for F4/80 and MMP-12 within the tumours of the CD38- group. Immunoblot analysis of active MMP-12 showed a significant reduction in the amount of MMP-12 present in the CD38- group compared to WT (65% reduction P=0.039).

Reviewer's opinion: This study assessed the role of microglia in glioma growth in an in vivo syngeneic model and showed that CD38 deficiency may reduce glioma expansion. It would be interesting to assess this finding in primary specimens. Targeting the microenvironment alongside the tumour cells themselves may hold the key to improved survival rates in the future. – SB

CD38 deficiency in the tumour microenvironment attenuates glioma progression and modulates features of tumour associated microglia/macrophages.
Levy A, Blacher E, Vaknine H, Lund F, Stein R and Mayo L.
NEURO-ONCOLOGY
2012;14(8):1037-49.