SELECTED ABSTRACTS

Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis.

Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, Rooney PS, Susnerwala S, Blower A, Saunders MP, Wilson MS, Scott N, O'Dwyer ST.

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Background

Induction of a clinical complete response with chemoradiotherapy, followed by observation via a watch-and-wait approach, has emerged as a management option for patients with rectal cancer. We aimed to address the shortage of evidence regarding the safety of the watch-and-wait approach by comparing oncological outcomes between patients managed by watch-and-wait who achieved a clinical complete response and those who had surgical resection (standard care).

Methods

The study "Oncological outcomes after clinical complete response in patients with rectal cancer" (OnCoRe) was a propensity-score matched cohort analysis study, that included patients of all ages diagnosed with rectal adenocarcinoma without distant metastases who had received preoperative chemoradiotherapy (45 Gy in 25 daily fractions with concurrent fluoropyrimidine-based chemotherapy) at a tertiary cancer centre in Manchester, UK, between January 14, 2011, and April 15, 2013. Patients who had a clinical complete response were offered management with the watch-and-wait approach, and patients who did not have a complete clinical response were offered surgical resection if eligible. We also included patients with a clinical complete response managed by watch-and-wait between March 10, 2005, and January 21, 2015, across three neighbouring UK regional cancer centres, whose details were obtained through a registry. For comparative analyses, we derived one-to-one paired cohorts of watch-and-wait versus surgical resection using propensity-score matching (including T stage, age and performance status). The primary endpoint was non-regrowth disease-free survival from the date that chemoradiotherapy was started, and secondary endpoints were overall survival, and colostomy-free survival. We used a conservative p value of less than 0.01 to indicate statistical significance in the comparative analyses.

Findings

259 patients were included in our Manchester tertiary cancer centre cohort, 228 of whom underwent surgical resection at referring hospitals and 31 of whom had a clinical complete response, managed by watch-and-wait. A further 98 patients were added to the watch-and-wait group via the registry. Of the 129 patients managed by watch-and-wait (median follow-up 33 months [IQR 19 – 43]), 44 (34%) had local re-growths (3-year actuarial rate 38% [95% CI 30 – 48]); 36 (88%) of 41 patients with non-metastatic local re-growths were salvaged. In the matched analyses (109 patients in each treatment group), no differences in 3-year non-regrowth disease-free survival were noted between watch-and-wait and surgical resection (88% [95% CI 75 – 94] with watch and- wait vs 78% [63 – 87] with surgical resection; time varying p = 0·043). Similarly, no difference in 3-year overall survival was noted (96% [88 – 98] vs 87% [77 – 93]; time varying p = 0.024). By contrast, patients managed by watch-and-wait had significantly better 3-year colostomy-free survival than did those who had surgical resection (74% [95% CI 64 – 82] vs 47% [37 – 57]; hazard ratio 0·445 [95% CI 0.31 – 0.63; p<0.0001), with a 26% (95% CI 13 – 39) absolute difference in patients who avoided permanent colostomy at 3 years between treatment groups.

Interpretation

A substantial proportion of patients with rectal cancer managed by watch-and-wait avoided major surgery and averted permanent colostomy without loss of oncological safety at 3 years. These findings should inform decision making at the outset of chemoradiotherapy.

Commentary

Dr Wasantha Wijenayake,
Senior Lecturer in Surgery,
General Sir John Kotelawala Defence University,
Sri Lanka.

Neo-adjuvant chemoradiation is employed to achieve diverse objectives in the management of rectal cancer: to control local recurrence, to enable preservation of the anal sphincter and to downgrade and downsize tumour so as to enable surgical reaction with a clear circumferential resection margin.

In a proportion of patients, chemoradiation may result in complete resolution of the tumour. While the original work was undertaken in Brazil, this report from the United Kingdom provides further evidence in favour of pre-operative chemoradiation.

In this study the authors followed up 129 patients who had a clinical complete response for a median of 33 months. Previous studies have shown the incidence of local recurrence to be highest within the first 24 months. By the time of

analysis of the data, only 34% (44 patients) had local regrowth and 66% (85 patients) had the benefit of not having to undergo major surgical intervention.

At the time of diagnosis of 44 local regrowths; 41 (93%) did not have distal metastasis and 88% (36) of 41 had salvage surgery without affecting their 3 year non-regrowth disease-free survival compared to the group of patients who had surgical resection (78%).

Comparison of two non-homogenous groups to comment on survival is a shortcoming of the study. Furthermore, it becomes clear that some complete responders may have had a survival advantage if surgical resection was performed, and it is best reserved for young, fit patients.

Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, Budrukkar A, Mittra I, Gupta S.
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doi: 10.1016/S1470-2045(15)00135-7.

Summary

This study from Tata Memorial Centre, Mumbai, India, compared the effect of locoregional treatment with no such treatment on outcome in women presenting with primary metastatic breast cancer. Study participants were randomly assigned to receive locoregional treatment directed at their primary breast tumour and axillary lymph nodes, or no locoregional treatment. Patients with resectable primary tumour in the breast that could be treated with endocrine therapy were randomly assigned upfront, while those with an unresectable primary tumour were planned for chemotherapy before randomisation. Patients who had chemotherapy before randomisation, and had an objective tumour response after 6 – 8 cycles of chemotherapy, were then randomised. Of 716 women presenting between 2005 and 2013 with primary metastatic breast cancer, 350 were randomised: 173 to locoregional treatment and 177 to no locoregional treatment. At a median 23 - month follow-up, 235 deaths had been reported (locoregional treatment n = 118, no-locoregional treatment n = 117). Median overall survival was 19.2 months (95% CI, 16. 0 - 22.5) in the locoregional treatment group and 20.5 months (17.0 - 24.0) in the no-locoregional treatment group (hazard ratio [HR] 1.04; 95% CI, 0.81 - 1.34; p = 0.79); corresponding 2-year overall survival was 41.9% (95% CI, 33.9 - 49.7) and 43.0% (35.2 - 50.8), respectively.

Commentary

Sanjeewa Seneviratne,
Senior Lecturer and Consultant Surgeon,
Department of Surgery,
Faculty of Medicine Colombo,
Sri Lanka.

This study demonstrated no effect of locoregional treatment of the primary tumour on overall survival in patients with metastatic breast cancer at initial presentation, who had responded to front-line chemotherapy. Of note, targeted therapies (hormones or trastuzumab) were only received by a small minority of eligible patients. It is possible that the use of such agents may have further improved survival, potentially enabling a benefit from locoregional treatment, particularly in those with small volume metastatic disease. In those with significant volume disease or metastatic disease however, these results seriously question whether resection of the primary offers any meaningful benefit and indirectly question the place of radiation therapy for this group. At this point, only those with significantly symptomatic local disease should be considered for local therapy in the setting of significant metastatic disease.

Optimal Surgical Management for Occult Breast Carcinoma: A Meta-analysis

Macedo FI, Eid JJ, Flynn J, Jacobs MJ, Mittal VK.
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Background

Occult breast cancer (OBC) represents a rare clinical entity and poses a therapeutic dilemma. Due to limited experience, no optimal treatment approaches have yet been established.

Methods

A meta-analysis was performed using MEDLINE and EMBASE databases to identify all studies investigating the surgical options for OBC: (1) axillary lymph node dissection (ALND) with radiotherapy (XRT); (2) ALND with mastectomy; and (3) ALND alone. Comparative studies including nonoperative management (observation or XRT alone) were excluded. The primary endpoints were locoregional recurrence, distant metastasis, and mortality rates.

Results

The literature search yielded 42 publications. Seven studies met the inclusion criteria comprising 241 patients. Among these patients, 94 (39 %) underwent ALND with XRT, 112 (46.5 %) underwent mastectomy, and 35 (14.5 %) underwent ALND alone. Mean follow-up was 61.8 ± 16.2 months (range 5–396 months). Locoregional recurrence (12.7 vs. 9.8 %), distant metastasis (7.2 vs. 12.7 %), and mortality rates (9.5 vs. 17.9 %) were similar between ALND with XRT and mastectomy. ALND with XRT was superior to ALND alone

regarding locoregional recurrence (12.7 vs. 34.3 %, p < 0.01) and there was a trend toward improved mortality rates (9.5 vs. 31.4 %, p = 0.09).

Conclusions

There was no difference in survival outcomes between mastectomy and ALND with XRT of patients with OBC. Radiotherapy improves locoregional recurrence and, possibly mortality rates of patients undergoing ALND. Based on this meta-analysis, combined ALND and radiation therapy may appear as the optimal surgical approach in these patients.

Commentary

Naomal MA Perera,
Consultant Oncological Surgeon,
Lanka Hospitals, Colombo, Sri Lanka.

Occult Breast Cancer (OBC) is a rare form of breast cancer presentation reported in less than 1% of the literature. OBC is defined as axillary carcinoma metastases (ACM) arising in the absence of clinically, radiologically or pathologically identifiable breast tumour. The authors claim this to be the first meta-analysis on the management of OBC. Historically and the current common practice in Sri Lanka is to perform a Modified Radical Mastectomy (MRM). At present, the National Comprehensive Cancer Network (NCCN) guidelines on management of OBC recommends MRM with axillary lymph node dissection (ALND) or whole breast radiation therapy (XRT) with ALND. Further favours the use of adjuvant doxorubicin-based chemotherapy especially for those with more than three positive nodes.

The authors have concluded the meta-analysis with finding no difference in the control of locoregional disease, distant metastases and overall survival benefit between MRM and XRT on breast following an ALND, and hence the combined ALND and radiation to the breast do appear as the optimal surgical approach in these patients.

Before the invention of advanced breast imaging technology, the cornerstone of primary breast tumour diagnosis was clinical examination with mammography. The low sensitivity diagnostic capabilities of small breast carcinomas prompted to take precautions then, and offered MRM for all OBC with axillary nodal disease. With the refinement of breast ultrasonography, digital mammography and MRI, sensitivity of detecting subcentimetric tumours within the breast has increased.

Presently the breast imaging technologies in Sri Lanka has advanced moreover in detecting subcentimetric lesions in the breast. Thus ALND with whole breast irradiation with or without adjuvant chemotherapy could be offered for OBC patients as the optimum care at local institutions practicing a multidisciplinary approach.

Loss of kidney function in patients with critical limb ischemia treated endovascularly or surgically

Sigterman TA, Bolt LJ, Krasznai AG, Snoeijs MG, Heijboer R, Schurink GH, Bouwman LH.
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Background

Acute kidney injury after the administration of contrast material during endovascular procedures for peripheral arterial disease generally recovers with supportive treatment. However, long-term effects of endovascular procedures for critical limb ischemia on renal function remain to be investigated.

Methods

This retrospective observational cohort study included all patients who newly presented to the vascular surgery outpatient clinic with Rutherford class 4 to class 6 peripheral arterial disease and who were treated with either endovascular or surgical interventions. Changes in estimated glomerular filtration rate (eGFR) after 1 year were compared between the two types of intervention. Multivariate linear regression analysis was done to correct for potential confounders.

Results

One year after treatment, eGFR was reduced by 15.0 mL/min (95% confidence interval [CI], 13.1-17.0; P < .001) after endovascular interventions (n = 209) and by 7.6 mL/min (95% CI, 5.1-10.0; P < .001) after surgical therapy (n = 81). Although eGFR rates decreased in both groups, loss of renal function was significantly greater in patients after endovascular interventions (P < .001). Furthermore, 77% of patients receiving endovascular interventions experienced fast renal decline (defined as >4 mL/min loss of eGFR within 1 year) compared with 54% of patients treated surgically (P < .001). After correction for potential confounders, endovascular intervention was associated with 7.4 mL/min (95% CI, 5.4-9.3; P < .001) greater loss of renal function compared with patients treated surgically.

Conclusions

Endovascular procedures for critical limb ischemia are associated with clinically relevant permanent long-term loss of kidney function. This loss of renal function is greater than in comparable patients who were treated with open surgery.

Commentary

Nalaka Gunawansa
Consultant Vascular Surgeon,
National Hospital of Sri Lanka,
Colombo, Sri Lanka.

This is a very interesting study given the ongoing debate about the comparison of endovascular versus open surgical revascularization for critical limb ischaemia.

Majority of these patients who undergo revascularization for critical limb ischaemia in the current context are long standing diabetics. Furthermore, they are usually in the age group of 50-80 years. Given the advanced age and long standing diabetes, these patients anyway have a tendency of developing renal dysfunction. This study clearly shows that there is significant deterioration of renal function among those treated endovascularly as opposed to open surgery at 1 year. This becomes even more significant considering that those treated by endovascular means are more than likely to require repeat contrast imaging and re-intervention in the subsequent years. Hence, careful consideration of underlying renal function is needed when deciding on the best approach to managing critical limb ischaemia.