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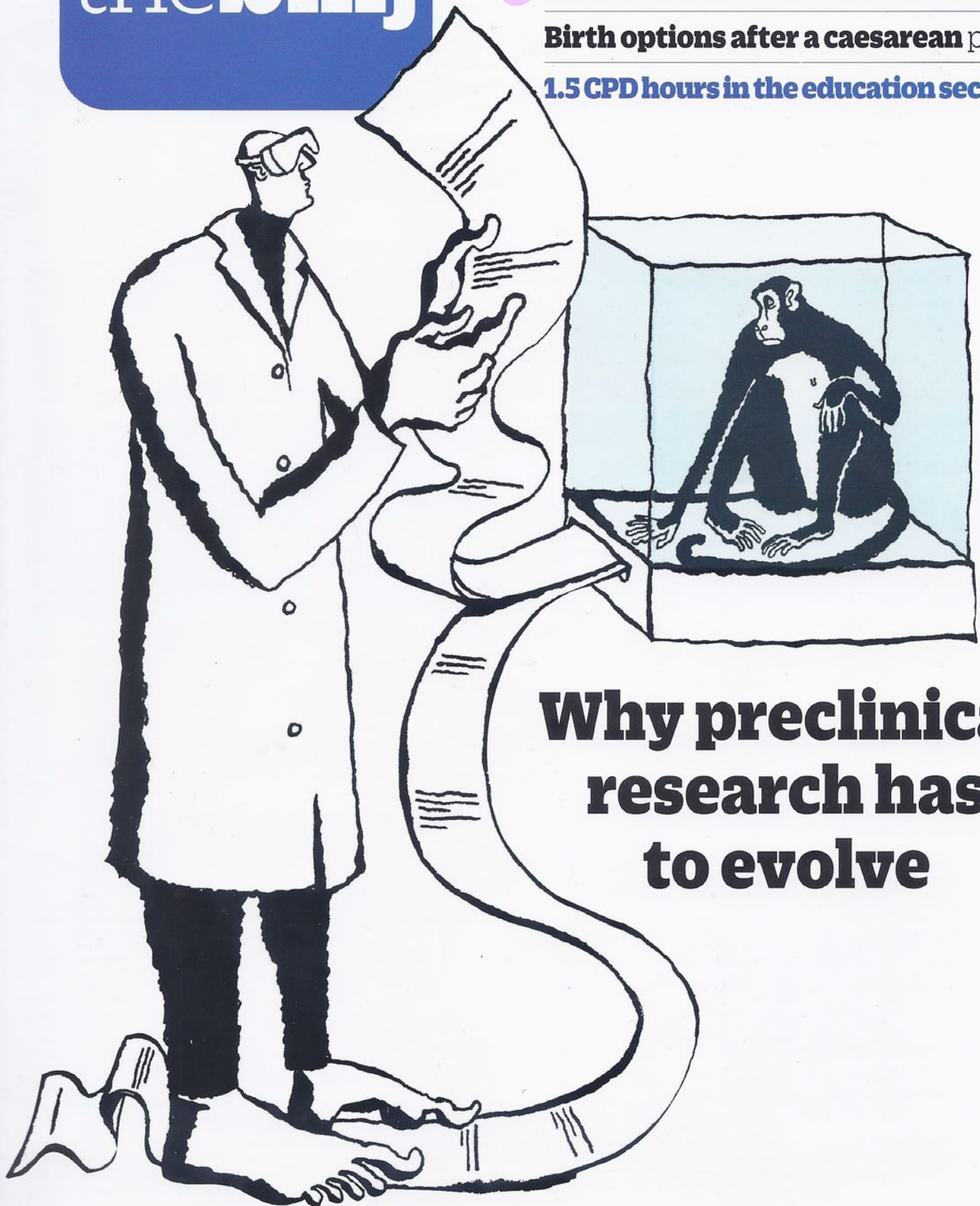
Genes do not hinder weight loss p 60

Breast cancer treatment rethink p 66

Birth options after a caesarean p 76

1.5 CPD hours in the education section

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Why preclinical research has to evolve

ANALYSIS

Neoadjuvant chemotherapy for breast cancer: a rethink

As evidence questioning the treatment's rationale grows, **Jayant Vaidya and colleagues** say the time may have come for a "medical reversal"

Breast cancer is the most common cancer in women worldwide. In 2014, 55 000 women in the UK were given the diagnosis of breast cancer, and 11 000 died.¹ Early breast cancer is traditionally treated with surgery, plus radiotherapy and adjuvant systemic therapy as required.

Neoadjuvant chemotherapy for breast cancer is a strategy that was introduced towards the end of the 20th century with the aim of reducing tumour size. It has four main rationales. First, it should render an otherwise inoperable tumour operable or, second, allow more conservative surgery. Third, starting systemic treatment preoperatively was hoped to lead to improved overall survival in patients with locally advanced cancers, who are at high risk of having distant disease. Finally, unlike adjuvant chemotherapy given in the absence of any measurable disease, neoadjuvant chemotherapy gives us the opportunity to observe the tumour shrink both palpably and on imaging, enabling a rapid assessment of clinical response. This could help test responses *in vivo* to new drug regimens, which could then be used as adjuvant therapies, in so called window of opportunity studies.

KEY MESSAGES

- Neoadjuvant chemotherapy is increasingly used for breast cancer despite higher rates of local recurrence and no evidence of survival benefit, mainly because of the immediate and dramatic pathological responses seen with newer drugs
- The increased pathological response of the primary tumour does not translate into a survival benefit even when given in the adjuvant setting, challenging the paradigm of "window of opportunity" studies
- We must acknowledge that neoadjuvant chemotherapy may not be beneficial to patients and should consider reducing its widespread use

A survey of multidisciplinary teams in Australia, Germany, Italy, the UK, and the US found that 7-27% of new breast cancers are treated with neoadjuvant chemotherapy (Saunders C, Cody H, Kolberg HC, et al, personal communication, 2017). With 1.7 million women receiving diagnoses annually, this translates into 120 000-460 000 women receiving neoadjuvant chemotherapy worldwide.¹

Although data indicate that the first rationale remains valid, the others have not led to the desired outcomes. More conservative surgery after neoadjuvant chemotherapy can result in a higher rate of local recurrence, and, despite the earlier initiation of systemic treatment, no improvement in survival has been seen.²⁻⁴ Furthermore, neoadjuvant chemotherapy may not help test novel chemotherapies—although primary tumour response is a good indicator of prognosis for a particular treatment, it is counterintuitively a poor surrogate marker for the overall survival benefit when evaluating novel chemotherapy regimens. Finally, for 40-80% of patients, even the best neoadjuvant chemotherapy regimens extend the period the cancer remains in the breast and can make surgery more difficult, as the tumour is less easily palpable and the axillary lymph nodes are less distinct. We question the wisdom of the current widespread use of neoadjuvant chemotherapy.

Shrinking tumours to enable surgery

When a patient presents with a breast cancer so large that mastectomy is technically not possible, neoadjuvant chemotherapy may reduce its size, making it possible to do a mastectomy with curative intent. But many such patients also have distant metastases, so surgery is only for symptom control as it can worsen distant disease free

survival⁵; this is a rare indication for neoadjuvant chemotherapy.

Breast conservation, local recurrence, and survival

Data from several randomised clinical trials comparing neoadjuvant with adjuvant chemotherapy have been analysed in three well conducted meta-analyses, comprising about 4500 patients.²⁻⁴ Neoadjuvant chemotherapy did not confer any survival benefit compared with adjuvant chemotherapy, with a summary risk ratio of 1.00 (95% confidence interval 0.90 to 1.12) reported by Mauri et al² and a hazard ratio of 0.98 (0.87 to 1.09) by Miesog et al.³ After neoadjuvant chemotherapy, only 16.6% of patients overall eventually convert from mastectomy to breast conservation, but they carry a statistically significantly higher risk of locoregional recurrence (6% increase in absolute terms).²⁻⁴ If the surgery was less extensive than deemed necessary before neoadjuvant chemotherapy, the rise in risk of local recurrence was much larger. Even with intensive chemotherapy (using paclitaxel and anthracycline), as in one trial included in the meta-analysis, there was only a 29% improvement in breast conservation rate.⁶ The Early Breast Cancer Trialists' Collaborative Group's meta-analysis, with individual patient data from >4500 patients, had similar results: a higher local recurrence with





neoadjuvant chemotherapy.⁴ Doctors must discuss with patients the benefits of breast preservation balanced with the increased risk of local recurrence,²⁻⁴ albeit with no detectable survival detriment.

Neoadjuvant v adjuvant chemotherapy

Neoadjuvant chemotherapy can enable in vivo assessment of tumour response. The fundamental assumptions here are that the characteristics and behaviour of the primary tumour are representative of metastatic deposits and that response to neoadjuvant chemotherapy will predict response to postoperative adjuvant chemotherapy. Data from recent randomised trials challenge these assumptions.

First, a pathological complete response should mean that there are truly no viable residual tumour cells. Traditional histology, however, does not seem to detect all viable cells: randomised trial data show that avoiding surgical excision of the original tumour bed, even with an apparent pathological complete response, leads to higher rates of local recurrence.²⁻⁴

Second, although pathological complete response of the primary tumour has prognostic value in a particular study, it is an unreliable surrogate marker for comparing breast cancer outcomes across treatment regimens. An analysis across trials by

Doctors must discuss with patients the benefits of breast preservation balanced with the increased risk of local recurrence

Cortazar et al found that increases in pathological complete response did not correlate with improvements in overall survival ($R^2=0.24$) (fig 1).¹⁷

Historically, some drugs that improve overall survival have also had higher rates of pathological complete response in the neoadjuvant setting (for example, aromatase inhibitors compared with tamoxifen^{18,19} and trastuzumab compared with no trastuzumab^{20,21}). But this finding is not consistent, and the difference in overall survival is far smaller than the difference in pathological response rates. Randomised trial data for three new targeted therapies, which had dramatically higher pathological complete response rates in the neoadjuvant setting,²²⁻²⁴ found no survival benefit in the adjuvant setting for lapatinib (ALTO trial), bevacizumab (BEATRICE), or pertuzumab (APHINITY).²⁵⁻²⁸ Neoadjuvant pertuzumab, for example, had previously shown a near doubling of rates of pathological complete response (22% v 39%)²⁴ but found no difference in overall survival in the adjuvant setting (fig 2).²⁸

These robust and consistent results should be enough to convince regulators, that they should not provide accelerated approval for drugs based only on achieving a higher rate of pathological complete response, which has the same pitfalls as other surrogate endpoints.²⁹

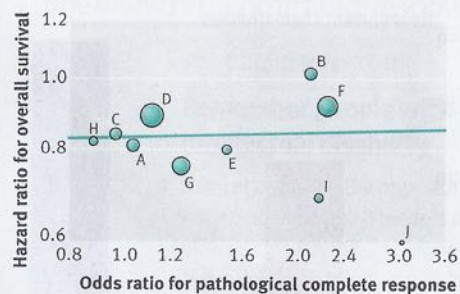


Fig 1 | Correlation between treatment effect on pathological complete response and overall survival. Each circle corresponds to one randomised comparison and the circle's size represents the sample size. A=GeparQuattro (epirubicin plus cyclophosphamide followed by docetaxel then capecitabine versus epirubicin plus cyclophosphamide followed by docetaxel); B=GeparDuo; C=GeparQuattro (epirubicin plus cyclophosphamide followed by docetaxel and capecitabine versus epirubicin plus cyclophosphamide followed by docetaxel); D=EORTC 10994/BIG 1-00; E=PREPARE; F=NSABP B-27; G=responders in GeparTrio; H=non-responders in GeparTrio; I=AGO 1; J=NOAH

The finding that a positive correlation between pathological complete response and overall survival does not always translate into a survival benefit is a major setback for the window of opportunity paradigm of using neoadjuvant chemotherapy for drug discovery.

Third, if the primary tumour mimics the biology of metastatic deposits, then patients with pathological complete response with neoadjuvant chemotherapy might have had a similar response in the adjuvant setting. If so, they may have fared even better, as the disease burden is much lower in the adjuvant setting, and there is no need to worry about the possibility of resistant clones arising in the several months of neoadjuvant chemotherapy.

New targeted therapies increasingly have their first trials in humans in the neoadjuvant setting. If they do not improve pathological complete response, they may be discarded. But this could be a mistake, as these drugs might improve survival only in the adjuvant setting, when the tumour burden is very low. For example, although in the neoadjuvant setting trastuzumab seems to have much less benefit in oestrogen receptor positive than negative tumours,²² its benefit in the adjuvant setting does not seem to depend on oestrogen receptor state.^{30,31} If adjuvant trials had not been published first, we may have

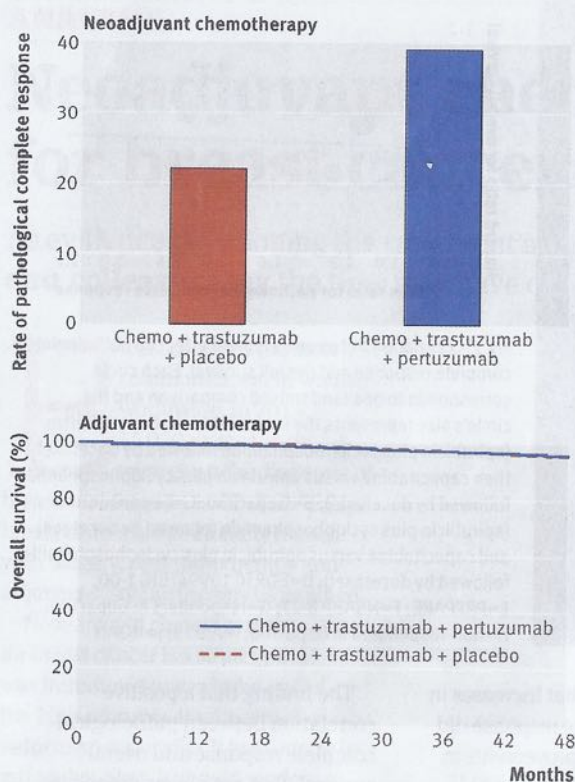


Fig 2 | Sharp contrast between the large improvement in complete pathological response rates in the neoadjuvant setting and the absence of survival benefit in the adjuvant setting.²⁸

excluded oestrogen receptor positive cases in the adjuvant setting, and these patients may have missed the benefits of trastuzumab.

Crucially, the definition of pathological complete response may be wrong. Clearly, the current histopathological assessment after neoadjuvant chemotherapy does not always correlate with the clinical outcomes or biological behaviour of the tissue. Improvements in imaging and pathological technology might help identify occult malignant cells in cases that are now classified as having a complete pathological response.

Length of time that patients harbour a large volume of tumour

Even with the best neoadjuvant chemotherapy regimen the complete pathological response rate (breast plus axilla), is only 39%; 12% of patients have no response and 48% have partial response or stable disease.^{24,32} The definition of stable disease according to RECIST (response evaluation criteria in solid tumours)³³ allows growth up to 20% in the longest diameter, which can represent a 73% increase in volume. Thus, despite the best targeted

treatment given to the appropriate population (dual HER2 blockade with trastuzumab and pertuzumab in HER2 positive cases), 60% of patients overall continue to live with the disease containing aggressive chemoresistant cells, throughout the 5-6 months of neoadjuvant chemotherapy.

Even those who ultimately have a pathological complete response arguably continue to harbour a large volume of tumour for several months before it fully responds. The additional detriment of this delay in surgical excision might not be discernible in older clinical trials, which mainly included patients with high risk disease, but for the smaller and better prognosis tumours that neoadjuvant chemotherapy is now being increasingly used for, it might be more important to avoid this potentially detrimental effect by performing earlier surgery. Importantly, some patients find it psychologically difficult to live with the cancer in their breasts for the duration of neoadjuvant chemotherapy, particularly when it does not respond well, an aspect that has not been considered in any randomised trial.

Neoadjuvant chemotherapy makes surgical removal less precise

The lack of clearly palpable margins of the softer and diffuse remnant tumour after neoadjuvant chemotherapy can reduce the surgical precision of the wide local excision. This rarely expressed difficulty might contribute to higher local recurrence rates.

Furthermore, a negative margin after a wide local excision might not mean much, as the tumour is no longer a contiguous structure but instead consists of multiple viable tumour islands scattered throughout the original volume of tumour tissue. The edges—and therefore margins—of this volume of tissue are very difficult to define, whether by palpation, ultrasonography, mammography, MRI, or even histopathology.

On the other hand, if patients underwent surgery first they would immediately (or after a second surgery if the first left positive margins) be rid of most of the disease, achieving a 100% response rate at the primary site. Operating on a primary tumour that is

clearly palpable is technically much easier simply because the surgeon can define the edges. This is also true for surgical treatment of untreated axilla as lymph nodes are rarely fixed to surrounding structures, and an axillary clearance is easier when they are distinctly palpable, rather than the fibrous tissue of uncertain significance that is encountered after neoadjuvant chemotherapy.

Challenging the paradigm

Neoadjuvant chemotherapy has gained popularity in recent years and is offered to patients with smaller tumours, even when upfront breast conservation is possible, and to those with larger tumours who will still require a later mastectomy. This is mainly because their cancers have certain biological phenotypes that dramatically respond to neoadjuvant chemotherapy; for example, HER2 positive cancers. That such a response will be replicated in the metastatic sites of the tumour has been disproved by randomised trial data.^{17,24} These data should change the conceptual framework of cancer treatment. We should go back to the drawing board and investigate alternative approaches to window of opportunity studies.

The time may have come for a “medical reversal,”³⁴ as new trial data contradict current clinical practice of the widespread use of neoadjuvant chemotherapy even for patients with HER2 positive or triple negative disease. Neoadjuvant chemotherapy should be considered only in patients who are on the borderline of being suitable for breast conservation, in whom a smaller resection might be feasible if there is a response, and if the tumour type is likely to respond. Even in such cases, a shared decision should be taken in which all the advantages, disadvantages, uncertainties, and, importantly, lack of survival benefit, and higher risk of local recurrence are explained to the patient.

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Cite this as: *BMJ* 2018;360:j5913



ANALYSIS

Rethinking neoadjuvant chemotherapy for breast cancer

As evidence questioning the rationale behind neoadjuvant chemotherapy in breast cancer grows, **Jayant Vaidya and colleagues** say we must reconsider the current treatment options

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Key messages

Neoadjuvant chemotherapy is being increasingly used for breast cancer despite higher rates of local recurrence and no evidence of survival benefit, mainly because of the immediate and dramatic pathological responses seen with newer drugs

The increased pathological response of the primary tumour does not translate into a survival benefit even when given in the adjuvant setting, challenging the paradigm of "window of opportunity" studies

We must acknowledge that neoadjuvant chemotherapy may not be beneficial to patients

We should consider reducing the widespread use of neoadjuvant chemotherapy

Breast cancer is the most common cancer in women worldwide. In 2014, 55 000 women in the UK were given the diagnosis of breast cancer, and 11 000 died.¹ Early breast cancer is traditionally treated with surgery, plus radiotherapy and adjuvant systemic therapy as required.

Neoadjuvant chemotherapy for breast cancer is a new strategy that was introduced towards the end of the 20th century with the aim of reducing tumour size. It has four main rationales. Firstly, it should render an otherwise inoperable tumour operable or, secondly, allow more conservative surgery. Thirdly, starting systemic treatment preoperatively was hoped to lead to improved overall survival in patients with locally advanced cancers, who are at high risk of having distant disease. Finally, unlike adjuvant chemotherapy given in the absence of any measurable disease, neoadjuvant chemotherapy gives us the opportunity to observe the tumour shrink both palpably and on imaging, enabling a rapid assessment of clinical response. This could help test responses in vivo to new drug regimens, which could then be

used as adjuvant therapies, in so called window of opportunity studies.

A survey of multidisciplinary teams in Australia, Germany, Italy, the UK, and the US found that 7-27% of new breast cancers are treated with neoadjuvant chemotherapy (Saunders C, Cody H, Kolberg HC, et al, personal communication, 2017). With 1.7 million women receiving diagnoses annually, this translates into 120 000-460 000 women receiving neoadjuvant chemotherapy worldwide.¹

Although data indicate that the first rationale remains valid, the others have not led to the desired outcomes. More conservative surgery after neoadjuvant chemotherapy can result in a higher rate of local recurrence, and, despite the earlier initiation of systemic treatment, no improvement in survival has been seen.²⁻⁴ Furthermore, neoadjuvant chemotherapy may not help test novel chemotherapies—although primary tumour response is a good indicator of prognosis for a particular treatment, it is counterintuitively a poor surrogate marker for the overall survival benefit when evaluating novel chemotherapy regimens. Finally, for 40-80% of patients, even the best neoadjuvant chemotherapy regimens extend the period the cancer remains in the breast and can make surgery more difficult, as the tumour is less easily palpable and the axillary lymph nodes are less distinct. We question the wisdom of the current widespread use of neoadjuvant chemotherapy.

Shrinking tumours to enable surgery

When a patient presents with a breast cancer so large that mastectomy is technically not possible, neoadjuvant chemotherapy may reduce its size, making it possible to do a mastectomy with curative intent. But many such patients also have distant metastases, so surgery is only performed for

symptom control as it can worsen distant disease-free survival⁵; this is a rare indication for neoadjuvant chemotherapy.

Breast conservation, local recurrence, and survival

Data from several randomised clinical trials comparing neoadjuvant with adjuvant chemotherapy have been analysed in three well conducted meta-analyses, comprising about 4500 patients.²⁻⁴ Neoadjuvant chemotherapy did not confer any survival benefit compared with adjuvant chemotherapy, with a summary risk ratio of 1.00 (95% confidence interval 0.90 to 1.12) in Mauri et al² and a hazard ratio of 0.98 (0.87 to 1.09) in Mieog et al.³ After neoadjuvant chemotherapy, only 16.6% patients overall eventually convert from mastectomy to breast conservation, but they carry a statistically significantly higher risk of locoregional recurrence (6% increase in absolute terms).²⁻⁴ If the surgery was less extensive than deemed necessary before neoadjuvant chemotherapy, the rise in risk of local recurrence was much larger. Even with intensive chemotherapy (using paclitaxel and anthracycline), as in one trial included in the meta-analysis, there was only a 29% improvement in breast conservation rate.⁶ The Early Breast Cancer Trialists' Collaborative Group's meta-analysis, with individual patient data from >4500 patients, had similar results: a higher local recurrence with neoadjuvant chemotherapy.⁴ Doctors must discuss with patients the benefits of breast preservation balanced with the increased risk of local recurrence,²⁻⁴ albeit with no detectable survival detriment.

Neoadjuvant versus adjuvant chemotherapy

Neoadjuvant chemotherapy can enable in vivo assessment of tumour response. The fundamental assumptions here are that the characteristics and behaviour of the primary tumour are representative of metastatic deposits and that response to neoadjuvant chemotherapy will predict response to postoperative adjuvant chemotherapy. Data from recent randomised trials challenge these assumptions.

Firstly, a pathological complete response should mean that there are truly no viable residual tumour cells. Traditional histology, however, does not seem to detect all viable cells: randomised trial data show that avoiding surgical excision of the original tumour bed, even with an apparent pathological complete response, leads to higher rates of local recurrence.²⁻⁴

Secondly, although pathological complete response of the primary tumour has prognostic value in a particular study, it is an unreliable surrogate marker for comparing breast cancer outcomes across treatment regimens. An analysis across trials by Cortazar et al found that increases in pathological complete response did not correlate with improvements in overall survival ($R^2=0.24$) (U).¹⁷

Historically, some drugs that improve overall survival have also had higher rates of pathological complete response in the neoadjuvant setting (for example, aromatase inhibitors compared with tamoxifen^{18 19} and trastuzumab compared with no trastuzumab.^{20 21}) But this finding is not consistent, and the difference in overall survival is far smaller than the difference in pathological response rates. Randomised trial data for three new targeted therapies, which had dramatically higher pathological complete response rates in the neoadjuvant setting,²²⁻²⁴ found no survival benefit in the adjuvant setting for lapatinib (ALTTO trial), bevacizumab (BEATRICE), or pertuzumab (APHINITY).²⁵⁻²⁸ Neoadjuvant pertuzumab, for

example, had previously shown a near doubling of rates of pathological complete response (22% v 39%)²⁴ but found no difference in overall survival in the adjuvant setting (U).²⁸

These robust and consistent results should be enough to convince regulators, such as the US Food and Drug Administration, that they should not provide accelerated approval for drugs based only on achieving a higher rate of pathological complete response, which has the same pitfalls as other surrogate endpoints.²⁹

The finding that a positive correlation between pathological complete response and overall survival for a new drug does not always translate into a survival benefit is a major setback for the window of opportunity paradigm of using neoadjuvant chemotherapy for drug discovery.

Thirdly, if the primary tumour mimics the biology of metastatic deposits, then patients with pathological complete response with neoadjuvant chemotherapy might have had a similar response in the adjuvant setting. If so, they may have fared even better, as the disease burden is much lower in the adjuvant setting, and there is no need to worry about the possibility of resistant clones arising in the several months of neoadjuvant chemotherapy.

New targeted therapies increasingly have their first trials in humans in the neoadjuvant setting. If they do not improve pathological complete response, they may be discarded. But this could be a mistake, as these drugs might improve survival only in the adjuvant setting, when the tumour burden is very low. For example, although in the neoadjuvant setting trastuzumab seems to have much less benefit in oestrogen receptor positive than negative tumours,²² its benefit in the adjuvant setting does not seem different between oestrogen receptor positive and negative tumours.^{30 31} If adjuvant trials had not been published first, we may have excluded oestrogen receptor positive cases in the adjuvant setting, and these patients may have missed the benefits of trastuzumab.

Crucially, the definition of pathological complete response may be wrong. Clearly, the current histopathological assessment after neoadjuvant chemotherapy does not always correlate with the clinical outcomes or biological behaviour of the tissue. Improvements in imaging and pathological technology might help identify occult malignant cells in cases that are currently classified as having a complete pathological response.

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for, it might be much more important to avoid this potentially detrimental effect by performing earlier surgery. Importantly, some patients find it psychologically difficult to live with the cancer in their breasts for the duration of neoadjuvant chemotherapy, particularly when it does not respond well, an aspect that has not been considered in any randomised trial.

Neoadjuvant chemotherapy makes surgical removal less precise

The lack of clearly palpable margins of the softer and diffuse remnant tumour after neoadjuvant chemotherapy can reduce the surgical precision of the wide local excision. This rarely expressed difficulty might contribute to higher local recurrence rates. Furthermore, a negative margin after a wide local excision might not mean much, as the tumour is no longer a contiguous structure but instead consists of multiple viable tumour islands scattered throughout the original volume of tumour tissue. The edges—and therefore margins—of this volume of tissue are very difficult to define, whether by palpation, ultrasonography, mammography, MRI, or even histopathology.

On the other hand, if patients underwent surgery first they would immediately (or after a second surgery if the first left positive margins) be rid of most of the disease, achieving a 100% response rate at the primary site. Operating on a primary tumour that is clearly palpable is technically much easier simply because the surgeon's fingers can define the edges. This is also true for surgical treatment of untreated axilla as lymph nodes are rarely fixed to surrounding structures, and an axillary clearance is much easier when they are distinctly palpable, rather than the fibrous tissue of uncertain significance that is encountered after neoadjuvant chemotherapy.

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Contributors: JSV is the guarantor, corresponding author, conceived of the idea, and wrote the initial draft. All other authors contributed to the manuscript and approved the final draft.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: none.

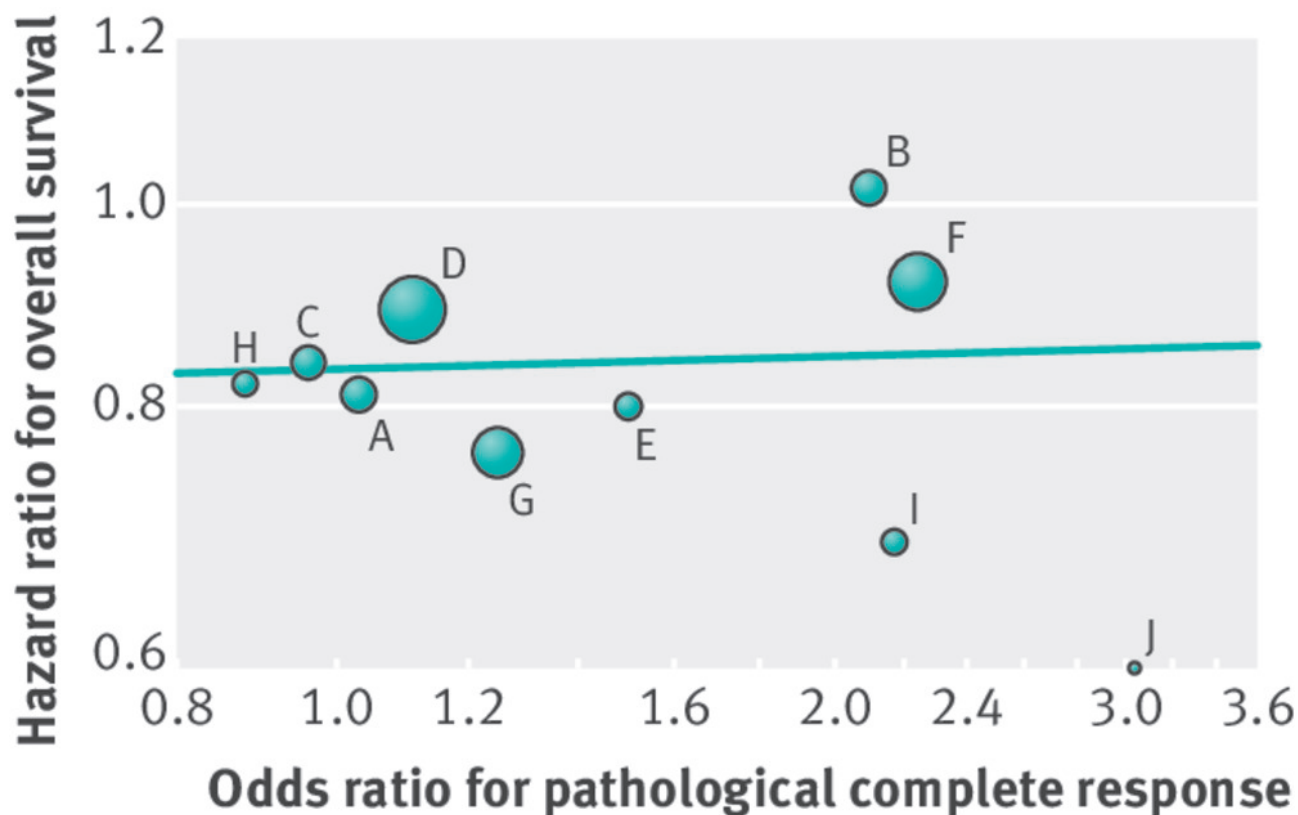
Provenance and peer review: Not commissioned; externally peer reviewed

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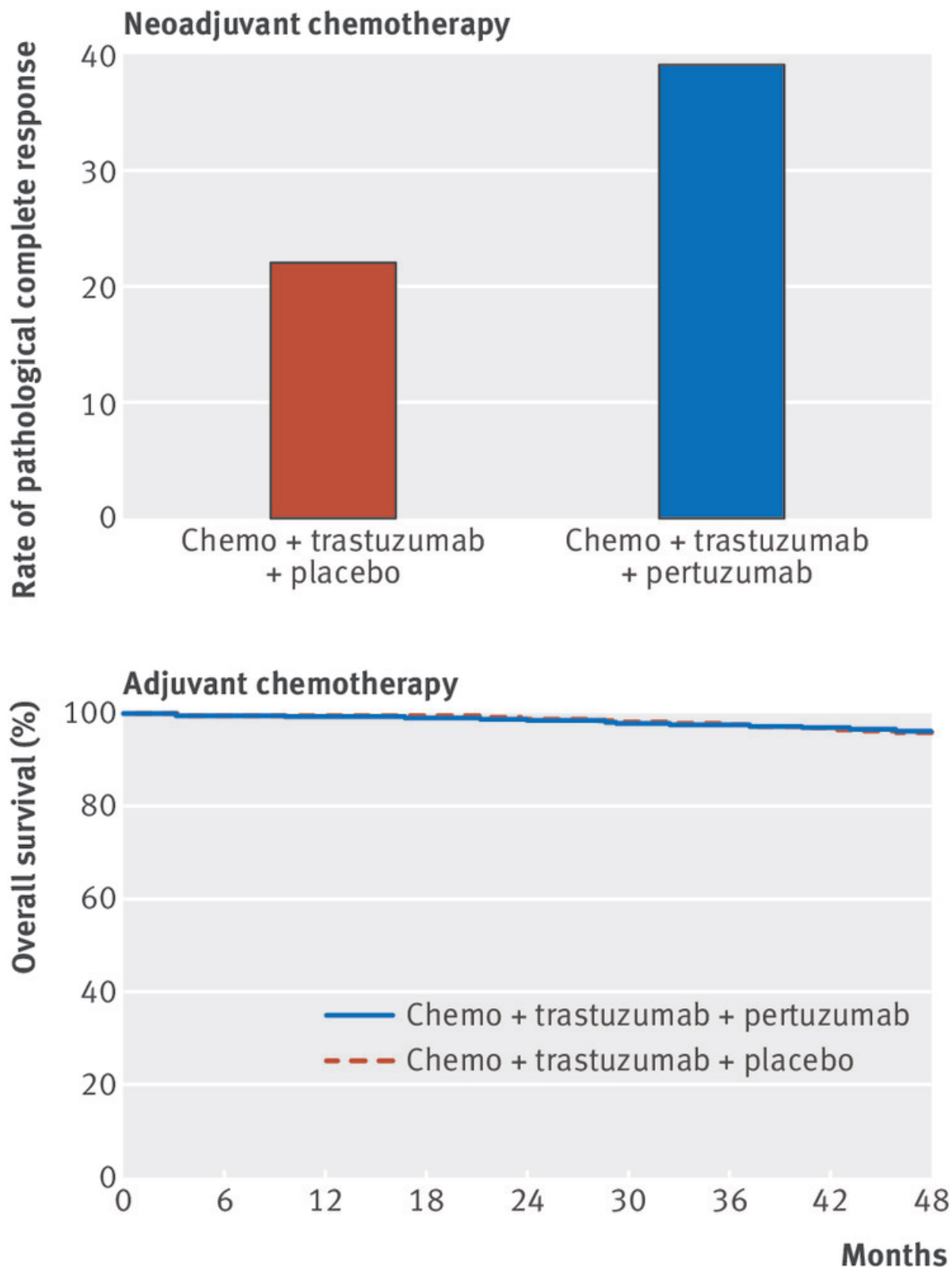
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Figures



Correlation between treatment effect on pathological complete response and overall survival. Each circle corresponds to one randomised comparison and the size of the circle represents the sample size. A=GeparQuattro (epirubicin plus cyclophosphamide followed by docetaxel then capecitabine versus epirubicin plus cyclophosphamide followed by docetaxel)⁷; B=GeparDuo⁸; C=GeparQuattro (epirubicin plus cyclophosphamide followed by docetaxel and capecitabine versus epirubicin plus cyclophosphamide followed by docetaxel)⁷; D=EORTC 10994/BIG 1-00⁹; E=PREPARE^{10,11}; F=NSABP B-27¹²; G=responders in GeparTrio¹³; H=non-responders in GeparTrio¹⁴; I=AGO 1¹⁵; J=NOAH.¹⁶



Sharp contrast between the large improvement in complete pathological response rates in the neoadjuvant setting and the absence of survival benefit in the adjuvant setting.²⁸