economical way to evaluate promising new therapies. However, it is unknown if pathological complete response (pCR) versus no pCR represents the most optimal trial starting point. There are many patients who do not achieve pCR that do not relapse and change in pCR rates has not yet translated well into improvements of the harder end points of disease-free and overall survival in the larger adjuvant studies. It is likely that additional biomarkers such as circulating cell-free DNA and immune infiltration in the residual disease will help us refine this end point [14, 15].

In essence, gains continue to be made in the management of breast cancer resulting in improved survival and better selection of patients for therapies. The continued development of more potent and specific targeted therapies, combined with sensitive imaging methods and accurate prognostic biomarkers, will ultimately result in the diagnosis of breast cancer being a less fearful one.

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Does adjuvant therapy reduce postmetastatic survival?

Adjuvant therapy can eradicate tumors in a stage of microdissemination which would be incurable after manifestation of overt metastases. The curative effect of this treatment, especially in breast and colorectal cancer, is undisputed. But it is also known that many of the adjuvantly pretreated tumors will relapse. Therefore, it is unavoidable that adjuvant therapy also involves selection: the sensitive tumors are cured and the relapsing tumors are resistant, at least in this phase of microdissemination, where mechanisms of resistance may be different from those in overt metastases. If we then treat these tumors after overt dissemination, we call that the 'first-line' treatment, although in reality this is 'second line' after adjuvant therapy. It is known that second-line therapy is less effective than first line [1]. Thus, we have two reasons why in adjuvantly pretreated patients a shorter postmetastatic survival must be expected.

Ten years ago, this journal published a consensus statement that characterized adjuvant chemotherapy as an unfavorable prognostic factor for metastatic breast cancer [2]. In this statement, it was also mentioned that increased use of anthracyclines and taxanes as adjuvant and neoadjuvant treatment has restricted their use in patients with relapse. However, for studies in this field, typical methodical problems exist. Most of these publications are retrospective evaluations of adjuvant studies, sometimes including antihormonal or

anti-*HER2* treatment, with rate and time of relapse as end points. Thereafter, therapy is usually individualized to new and more effective drugs that may have been approved during a study and which may prolong postmetastatic survival. Furthermore, adjuvant therapy depends on the initial tumor stage, which also influences postmetastatic survival [3]. Thus, a complete presentation and evaluation of all relevant data is almost impossible.

In 1981, the Milan group described [4] that in breast cancer the sites of relapse after 6 or 12 cycles of CMF adjuvant increased in liver and CNS and decreased in bone. This was later confirmed, with a higher number of patients, by the Munich group [5].

An analysis of the results after adjuvant CMF and postrelapse treatment with anthracyclines was published by Bonneterre et al. [6]. In 477 relapsing patients, risk was not balanced, with higher initial lymph node involvement in the group with (87%) than without (34%) adjuvant CMF, which was considered among other factors in a multivariate analysis. Overall response rate after relapse was 31.2% in patients with adjuvant treatment and 48% in those without ($P = 0.03$), time to treatment failure was 182 versus 268 days ($P = 0.007$), and survival after relapse 410 versus 560 days ($P = 0.008$). Overall survival after initial diagnosis was not significantly different.

The largest study so far was published by Pierga et al. [7] who analyzed data on 1430 patients with metastasized breast cancer. This included studies of first-line therapy with anthracyclines after overt metastases between 1977 and 1992. Adjuvant therapy had been given to 446 patients based on assessment of their risk for recurrence. One hundred and sixty-five patients received 5-FU, doxorubicin and cyclophosphamide (FAC), 92 CMF, 98 cyclophosphamide, melphalan and methotrexate, and 64 other combination without anthracyclines; 27 had chemotherapy of an unspecified type. Mean disease-free interval was almost identical: 42 months in the adjuvant versus 43 months in the non-adjuvant group. The frequency of bone, liver and CNS metastases were not significantly different. In the multivariate analysis, prior adjuvant chemotherapy was associated with a lower response rate (56% versus 66%; $P < 0.0001$), a lower median survival after recurrence (19 versus 26 months; $P < 0.0001$) and a lower overall survival from initial diagnosis (61 versus 70 months). In this study, adjuvant anthracycline-based chemotherapy had no greater adverse effect on postmetastatic survival than CMF. However, in the study of Alba et al. [8] adjuvant anthracycline-containing therapies resulted in a significantly poorer outcome in metastatic disease than anthracycline-free schedules.

Hölzel et al. of the Munich Cancer Registry published in 2017 [5] data on 60 227 breast cancer patients diagnosed between 1978 and 2013. This registry has fairly complete pathological and clinical data including time and site of metastases, but no details about systemic treatment. The time from 1978 to 2013 was divided into four periods, which were separately analyzed. During these periods, 5-year relative survival increased from 80.3% to 93.6%, with an adjusted hazard ratio of 0.54 ($P < 0.0001$). Adjuvant therapies changed the pattern of metastases: the percentage of liver and CNS metastases more than doubled, the rate of lung metastases remained stable, and the rate of bone metastases decreased by half. Metastasis-free survival was prolonged with a hazard ratio of 0.75 ($P < 0.0001$), but postmetastatic survival declined, with a hazard ratio of 1.36 ($P < 0.0001$).

Several groups described a particularly attenuated effect of palliative treatment after adjuvant therapy with taxanes. Miller et al. [9] found with paclitaxel monotherapy in the first line after dissemination a progression-free survival of 6.5 months without previous adjuvant treatment ($n = 237$), after a taxane-free adjuvant treatment of a surprising 7.7 months ($n = 328$) and after a taxane-containing adjuvant treatment of only 3.0 months' duration ($n = 108$). Progression-free survival increased in all groups when paclitaxel was combined with bevacizumab, in the latter group from 3.0 to 12 months; however, this did not translate in a longer postmetastatic survival for the whole bevacizumab group.

We published data in 2013 from a cancer research registry (Projektgruppe Internistische Onkologie) with real life data [10]. Relative postmetastatic survival of breast cancer patients after adjuvant therapy with taxanes was about one-third shorter than after adjuvant therapy without taxanes ($P = 0.000025$). This analysis was univariate and any influence of other factors cannot be excluded. But our findings are identical with those of Seidman et al. [11], who compared two different docetaxel-containing regimens in patients with disseminated breast cancer. The inclusion of adjuvant taxanes in the final analysis was not planned from the beginning; therefore, this treatment was not completely documented. In the multivariate analysis, not including initial tumor stage, patients without this documentation were considered to have received no prior adjuvant taxane. The hazard ratio for postmetastatic survival without adjuvant taxanes was 0.686 ($P < 0.001$) compared with patients who received this treatment. Complete documentation of the adjuvant taxane therapy would have increased this difference.

Another approach for calculating the effect of adjuvant therapy on survival after dissemination is a comparison of outcomes in metastatic breast cancer after relapse versus *de novo* metastatic presentation, because survival in the latter group is not influenced by adjuvant treatment. In a recent paper Malmgren et al. [12] found, for de novo metastasized breast cancer patients, in three cohorts from 1990 to 2010, an increase of the 5-year disease-specific survival from 28% to a surprising 55% ($P = 0.008$), while in the same time this measure dropped from 23% to 13% ($P = 0.065$) for patients with metastatic disease after relapse. A 78% of the latter group was pretreated with adjuvant chemotherapy. Brain metastases at initial diagnosis were more common in relapsed (8%) than in *de novo* metastasized patients (1%) (no *P* value given). The advent of effective targeted therapy for hormone receptor-positive disease, *HER2* positive-disease and taxane therapy in the adjuvant/neoadjuvant setting coincided with improved *de novo* metastasized survival and a decline in incidence of relapse. In a similar study of den Brok et al. [13], more than 60% of patients with relapsed breast cancer had received some form of systemic adjuvant therapy. Overall survival of *de novo* metastasized patients was higher than for relapsed patients (29 versus 17 months, $P < 0.0001$) and each subgroup had a gain of survival which was 11 months for HR+/*HER2*− ($P < 0.0001$), 14 months for *HER2*+ ($P < 0.0001$), and 3 months for triple negative cancer ($P = 0.02$). In the study of Hölzel et al. [14], 4756 patients had distant metastases at diagnosis. In four periods from 1978–2013, the 5-year survival rate improved from 17.4% to 24.7%, while the pattern of metastases did not change.

Table 1. Adjuvant therapies change characteristics of metastases and postmetastatic course

Tumor	Type of adjuvant therapy	Effect on metastases	Effect on therapy after dissemination
Breast cancer	Chemotherapy (general)	Percentage of metastases higher in liver and CNS, but lower in bone [4, 5]	Reduced response rate Reduced time to treatment failure Reduced postmetastatic survival
Breast cancer	Chemotherapy including taxanes		Further shortened postmetastatic survival
Breast cancer	Hormonal therapy	Loss of estrogen receptor in ∼30%	Shorter postmetastatic survival
Breast cancer	Immunotherapy with trastuzumab	Higher rate of cerebral metastases	Reduced effect of trastuzumab
Colon cancer	5FU-based chemotherapy		Shorter postmetastatic survival
Colon cancer	Chemotherapy including oxaliplatin	More mutations in liver metastases	Further shortened disease free and overall survival [23–25]
Different primaries	Previous chemotherapy (not specific adjuvant)		Reduced effect of stereotactic radiotherapy

If statements are controvers among the cited authors, the supporting references are given in brackets.

Karagiannis et al. [15] reported that neoadjuvant chemotherapy induces breast cancer metastasis through a 'tumor microenvironment of metastasis' (TMEM)-mediated mechanism. Chemotherapy increases the density and activity of TMEM sites and promotes distant metastasis. Once again, taxanes and angiogenesis seem to play a special role within these mechanisms, which is reminiscent of the above-mentioned results of Miller et al. [9]. From the clinical point of view, adjuvant and neoadjuvant chemotherapy have in breast cancer almost identical results with only an increased local relapse rate after 15 years of 21.4% for neoadjuvant versus 15.9% for adjuvant chemotherapy ($P = 0.0001$), and this difference may be an effect of local treatment rather than of tumor biology [16]. Therefore, it looks possible that many of the mechanisms explored by Karagiannis for neoadjuvant therapy are also relevant for adjuvant treatment.

Hormone receptors at diagnosis and after relapse were examined by Lindström et al. [17]. The estrogen receptor was positive in 47.1% ($n = 216$) both in the primary and metastasis. Depending on the type of adjuvant therapy, tumors with initially positive estrogen receptors became receptor negative after chemo-hormonal therapy in 34.3%, after hormonal therapy in 29% and without adjuvant therapy in 11.5%. Initial nondemonstrable estrogen receptors turned positive in these groups in 4.0%, 4.3% and 12.6% of metastases. Women with ER-positive primary tumors that changed to ER-negative tumors had a significant 48% increased risk of death (hazard ratio 1.48; 95% CI 1.08–2.05) compared with women with stable ER-positive tumors.

An effect of adjuvant tamoxifen on subsequent hormone therapy in metastatic breast cancer was also confirmed in a recent paper by Mehta et al. [18]. In this study, patients were treated in the first line after relapse with anastrozole alone versus anastrozole plus fulvestrant. Overall survival among women who had not received adjuvant tamoxifen was longer with the combination therapy versus anastrozole alone (median 52.2 versus 40.3 months; HR 0.73; 95% CI 0.58–0.92). Among women who had received tamoxifen previously, overall survival was similar in the two groups (median 48.2 versus 43.5 months; HR 0.97; 95% CI 0.74–1.27). Thus, the adjuvant estrogen antagonist tamoxifen reduced the effect of the palliative therapy with the estrogen antagonist fulvestrant.

Trastuzumab is established in the adjuvant therapy of *HER2* positive breast cancer, but the rate of brain metastases increases after adjuvant treatment with this antibody [19]. Furthermore, patients relapsing after adjuvant therapy with trastuzumab had a significantly poorer outcome after retreatment with this antibody than trastuzumab-naïve controls [20].

In colon cancer, Moertel et al. [21] described, after adjuvant 5-FU and levamisole, a postmetastatic survival of 11 months compared with 15 months in controls without adjuvant therapy. In his 2008 analysis of the ACCENT dataset, O'Connell et al. [22] found a longer survival following recurrence in patients initially treated with surgery alone versus with 5-FU-based adjuvant therapy ($P = 0.0005$) and with initial stage II versus III disease ($P < 0.0001$). All relationships were maintained in multivariate models. Thus, as in breast cancer, no adjuvant therapy and lower initial tumor stage were independent predictors of longer postmetastatic survival.

For studying the effect of adjuvant oxaliplatin in colorectal cancer patients, Andreou et al. [23] identified 341 patients who underwent hepatectomy for metachronous liver metastases after a disease-free interval ≥12 months. Adjuvant treatment of primary colorectal cancer was FOLFOX in 77 patients, 5-FU in 169 patients, and no chemotherapy in 95 patients. A node-positive primary was comparable between FOLFOX and 5-FU but lower in the no-chemotherapy group ($P < 0.0001$). Mass-spectroscopy genotyping for somatic gene mutations in liver metastases was carried out in a subset of 129 patients. On multivariate analysis, adjuvant FOLFOX was associated with worse DFS ($P < 0.0001$) and OS ($P < 0.0001$). Mutation analysis revealed ≥1 mutations in 57% of patients (27/47) after FOLFOX, 29% (12/41) after 5-FU, and 32% (13/41) after no chemotherapy ($P = 0.011$).

When comparing adjuvant treatment with leucovorin/5-FU with or without oxaliplatin in colon cancer, the NSABP C-07 [24] and MOSAIC trial [25] suggested that adjuvant oxaliplatin reduces post-relapse survival, e.g. from 24 to 21 months [25]. However, in a pooled analysis of four similar studies, Schmoll et al. [26] were not able to reproduce this assumption. But they mentioned that differences in post-relapse therapy could not be excluded, and a more frequent use of bevacizumab and *EGFR*-inhibitors in the oxaliplatin groups seems possible. Thus,

in colon cancer, a reduction of postmetastatic survival after adjuvant oxaliplatin is also probable.

Cytostatic pretreatment is also harmful before radiotherapy. Klement et al. reported that previous chemotherapy reduced the effect of stereotactic irradiation of lung [27] and liver metastases [28] from different primaries.

A summary of these findings is given in Table 1.

The data given in this article must not be misunderstood as a critique of adjuvant therapy. It has been shown that the gain in years of life due to adjuvant treatment of breast cancer is ∼20× greater than the loss of survival in the subgroup of patients who develop metastases [29]. But there are several reasons why we should further study this effect: it reduces survival in a subgroup of patients, it is underreported in the literature, and it is difficult to search in public data bases because an adequate search term is lacking. Consequently, we suggest the acronym ATRESS for 'Adjuvant Therapy-RElated Shortening of Survival', which particularly includes survival after overt metastases [30]. This effect arises in a pivotal situation of malignant growth: adjuvant therapy has already demonstrated that cancer cells are vulnerable in this phase. Now we should try to understand how cancer cells become resistant and grow despite adjuvant treatment. Studies of postmetastatic survival as well as examinations of surgical specimens after neoadjuvant therapy [15] are a good approach for this learning process and could eventually help us to circumvent these resistance mechanisms and to increase cure rate.

Key words: ATRESS, breast cancer, colon cancer, adjuvant and postmetastatic survival

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Extending the interval to surgery in rectal cancer and filling the time with chemotherapy—how much is enough?

Randomised trials in rectal cancer are difficult to perform. It is therefore crucial that we gain as much information as possible from every trial completed—even a negative trial. In this issue of *Annals of Oncology*, the updated results of the polish two trial are presented with a median follow-up of 7 years [1]. The initial report [2] showed that the addition of FOLFOX neoadjuvant chemotherapy (NACT) following 5 × 5 Gy short-course preoperative radiotherapy (SCPRT) compared with chemoradiation (CRT) did not significantly improve early surgical outcomes such as R0 resection (the primary end point). It did have lower toxicity and did not impact adversely on postoperative surgical morbidity and mortality. Somewhat counterintuitively, the disease-free survival (DFS) rates were almost identical at 53% versus 52% (HR =0.96, 95% CI 0.75–1.24, P =0.85) and the cumulative incidence of distant metastases were similar (30% versus 27%, P =0.26), yet an improved overall survival was reported favouring 5 ×5 Gy and FOLFOX consolidation chemotherapy.

The updated report [1] shows no difference in OS at 8 years, which was 49% in both arms. There was no difference in local failure and distant metastases (HR =1.08, 95% CI 0.70–1.23, P = 0.60, 35% versus 32% and HR =1.10, 95% CI 0.68–1.23, P = 0.54, 36% versus 34%), respectively. The rate of late complications was also similar (P = 0.66), with grade 3+ being 11% versus 9% in the SCPRT consolidation chemotherapy group versus the chemoradiation group, respectively. Regarding non-cancer deaths, the survival curves overlap throughout the entire observation period (P = 0.81).

The eligibility of fixed or T4 tumours in the present trial would normally be considered as 'ugly' tumours even though MRI was not mandated. Hence, it is not unreasonable to consider that these patients would in general have a worse prognosis and might well have benefitted from up-front NACT. However, this study now appears to show that patients with rectal cancer treated with three cycles of neoadjuvant FOLFOX chemotherapy (even if high risk) do not seem to benefit from it in the long term.

The finding that there is no longer an advantage in OS will disappoint many who were looking for some immune mechanisms specific to the 5 ×5 Gy fractionation to explain the disconnect between DFS and OS. These hopes were based on a small study which showed a transient reduction in myeloid-derived suppressor cells and Tregs following SCPRT [3].

Other phase III trials have used or are using a similar design to the Polish 2 trial. RAPIDO [4] compared 5 ×5 Gy and consolidation chemotherapy with CAPOX to CRT (NCT01558921), similar to the STELLAR trial [5] (NCT02533271). The results of these trials, when available, may clarify further the optimal duration of NACT after 5 ×5 Gy, since four cycles of CAPOX (12 weeks) are administered in the STELLAR trial and six cycles of CAPOX (18 weeks) in the RAPIDO trial. In contrast to the Polish 2 trial, these latter trials aim to assess the concept of total neoadjuvant treatment (TNT) by adding chemotherapy to impact on systemic disease. The primary end point is 3-year DFS in both trials. There is also a Korean trial [ESCORT (NCT03676517)], which is currently recruiting and uses SCPRT and two cycles of consolidation XELOX for 6 weeks, with pCR as the primary end point.

The previous results of Polish 2, published in 2016, begged the question as to whether 3-year-DFS is a good surrogate for 5-year overall survival in rectal cancer after CRT and consolidation chemotherapy. In colon cancer, the Adjuvant Colon Cancer Endpoints (ACCENT) Group confirmed that 3-year DFS is an appropriate surrogate end point for OS in colon cancer with a median of 5-years of follow-up [6] and subsequently continues to support this surrogacy of DFS for OS, but suggested it was stronger for patients with stage III than stage II disease [7]. Recent updated analyses from the ACCENT database using results of eight randomised adjuvant trials confirm that 3-year-DFS remains a validated surrogate end point for 5-year OS in colorectal cancer even with oxaliplatin. The correlation was strengthened with more than 6 years of follow-up for OS [8]. Hence, the present results of the Polish 2 trial will please investigators of those trials above with their primary end point set as 3-year-DFS.

In the USA, 4 months of neoadjuvant FOLFOX is considered a standard preoperative treatment of patients with rectal cancer considered to be high-risk [9] and eight cycles is used in the NRG-GI002 Clinical Trial Platform. This is based on the high pCR rates achieved with increasing sequential courses of FOLFOX following CRT within the Timing of Rectal Cancer Response to Chemoradiation study [10].

The results of the IDEA collaboration in colon cancer suggest that for both stage III (T1-3, N1) and high-risk stage II colon